University of Strathclyde

Department of Pure and Applied Chemistry

STUDIES ON ORGANIC ELECTRON DONORS AND THEIR APPLICATIONS IN CHEMISTRY

BY

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A thesis submitted to the Department of Pure and Applied Chemistry, University of Strathclyde, in part fulfilment of the regulations for the Degree of Doctor of Philosophy in Chemistry.

2017

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: Date:

Acknowledgment

First, I would like to thank Professor John A. Murphy for giving me the opportunity to do my PhD in his group. His guidance, knowledge and discussions have been a major help for my studies. The projects have been highly challenging but Professor Murphy always helped to make them an interesting and enjoyable experience.

I would like to thank all the Murphy group members I had the pleasure to work with: Dr Sheng-Ze Zhou, Dr Eswararao Doni and Dr Graeme Coulthard for their help in the lab and interesting discussions, whether it was about research results or everyday life. I also thank Dr Steven O'Sullivan, Dr Greg Anderson, Dr Anthony McDonagh, Katie Emery, Mark Allison, Allan Young, Giuseppe Nocera, Andrew Smith, Jude Norman Arokianathar, Simon Rohrbach, Joshua Barham and Samuel Dalton, for making my PhD life enjoyable and for all the nice times we had inside and outside the lab; my PhD would not have been the same without the times we played squash and football.

I extend my thanks to Dr Kenneth Down, my supervisor from GlaxoSmithKline in Stevenage.

I would like to thank Dr Tell Tuttle for allowing me to work in his computational chemistry lab and for his help and guidance when I was getting my hands dirty with computations. I also want to thank the other members of the Tuttle group: Dr. Daniel A. Cannon, a true Arsenal fan, Dr. Ivan Ramos Sasselli, his wedding in Spain with Paula González was one of the best times I ever had, Dr. Enrico Angioni, "weirdo" would be a nice nickname for him, Dr. Ines Pimentel Moreira, the names need to be in that order otherwise she gets angry, and Gary Scott, a true Scottish man. I also extend my thanks to some people who shared the office with us: Ana Sousa, even if she yells at me for no reason, and Dr. Maria Paola Conte, who speaks better French than she thinks.

I would like to thank all the personnel of the University of Strathclyde who were involved in the wellbeing of my PhD in particular: Dr Glenn Burley for his useful comments during my 1st and 2nd year exams, Dr John Parkinson and Craig Irving for NMR analysis, Pat Keating for mass spectrometry and Gavin Bain for all the times he was here to fix something in the lab. Also, I would like to thank the EPSRC National Mass Spectrometry Service Centre in Swansea for high resolution mass spectroscopy.

I would like to thank the University of Strathclyde and GlaxoSmithKline for funding my PhD.

I extend my thanks to the following people who have been part of my PhD life, and usually for the best: Davide Cappelluti, even if he still blames me for a bad decision during a Monopoly game, Laura Pala, she is always a fully charged battery even when she is tired, Miguel Franco, “poor Miguel”, Andreia Silva, for making the best drawing of the Eiffel Tower I have ever seen, and Nuno Covas, although he prefers to be called “Antonio” or is it the other way around?

Finally, I would like to thank my parents Brigitte and Jean François, my grandparents, Denise and Georges, and my brothers, Victorien and Justin. Your love and moral support were a constant help to go through my PhD while being abroad and far from home. I would also like to thank my friends from France with whom it is always a great pleasure to celebrate the New Year.

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Abbreviations

°C	Degree Celsius
δ	Chemical Shift
AcOH	Acetic Acid
Adoc	Adamantyloxycarbonyl
AIBN	Azo*bis*isobutyronitrile
APCI	Atmospheric Pressure Chemical Ionisation
ASAP	Atmospheric Solids Analysis Probe
BHAS	Base-promoted Homolytic Aromatic Substitution
Boc	*tert*-Butyloxycarbonyl
bs	Broad singlet
cal	Calories
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
d	Doublet
DBB	Di-*tert*-butylbiphenyl
DCM	Dichloromethane
DET	Double Electron Transfer
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DKP	Diketopiperazine
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane
DMEDA	*N*,*N*'-dimethylethylenediamine
DMEU	1,3-dimethyl-2-imidazolidinone
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl Sulfoxide

Abbreviations

eq.	Equivalent(s)
ESI	Electron Spray Ionisation
ET	Electron Transfer
Et	Ethyl
GC	Gas Chromatography
g	Gram(s)
h	Hour(s)
HMDS	Bis(trimethylsilyl)amine
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infrared
J	Coupling constant
LUMO	Lowest Unoccupied Molecular Orbital
m	multiplet
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole
mol	Mole
Mes	Mesitylene
M. Pt.	Melting Point
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NSI	Nanospray Ionization
Ph	Phenyl
ppm	Parts per million
q	Quartet
quin	Quintet

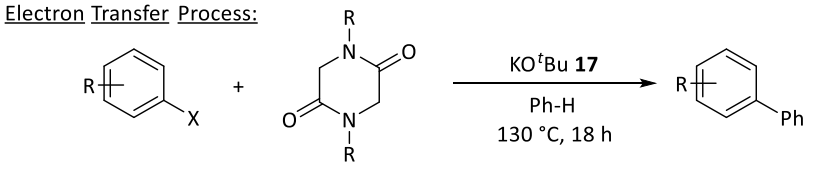
Abbreviations

s	Singlet
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
^{t}Bu	*tert*-Butyl
t	Triplet
TDAE	Tetrakis(dimethylamino)ethylene
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMDSO	Tetramethyldisiloxane
Ts	*p*-Toluenesulfonyl
TTF	Tetrathiafulvalene
UV	Ultra-violet
V	Volt
vs.	Versus

Abstract

Electron transfer reactions using organic donors have been and are still successfully applied in the Murphy group to perform reductions usually requiring heavy metals. This thesis focuses on several organic electron donors used to: (i) promote the cross-coupling reaction between aryl halides and benzene, which was also studied with computational experiments, (ii) cleave carbon-oxygen bonds and (iii) reduce nitrobenzenes and azobenzenes. In addition, computational analysis of controversial literature proposals for a radical/electron transfer mechanism for ring-forming reactions of alkoxide allenes and amide allenes is reported and supports an anionic rather than a radical process.

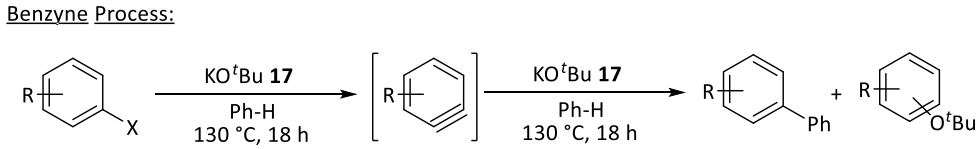
Chapter Two highlights the ability of diketopiperazines **1**-**4** to promote the cross-coupling reactions of aryl halides **5-16** with benzene in the presence of potassium *tert*-butoxide **17** to form biaryls **18**-**24** via electron transfer.



5 R = H, X = I
6 R = *o*-OMe, X = I
7 R = *m*-OMe, X = I
8 R = *p*-OMe, X = I
9 R = *o*-Me, X = I
10 R = *m*-Me, X = I
11 R = *p*-Me, X = I
12 R = H, X = Br
13 R = *o*-OMe, X = Br
14 R = *m*-OMe, X = Br
15 R = *p*-OMe, X = Br
16 R = *p*-Me, X = Br

1 R = Ph
2 R = Bn
3 R = $(CH_2)_2Ph$
4 R = $(CH_2)_3Ph$

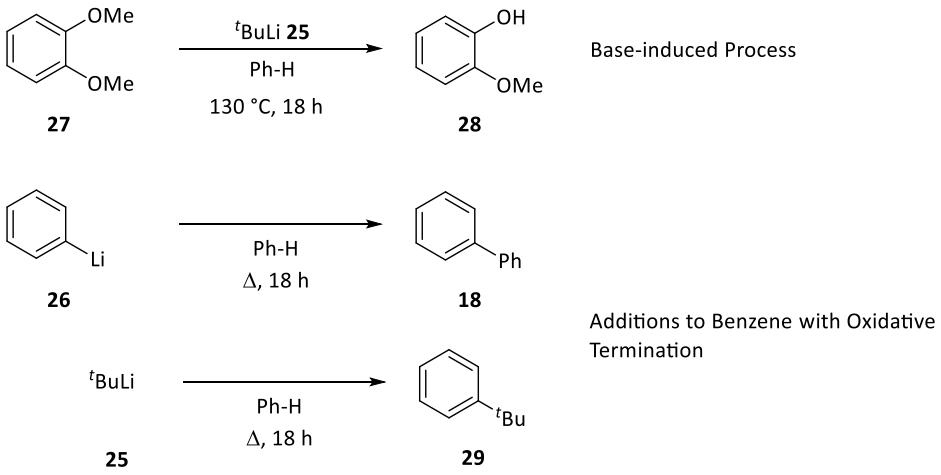
18 R = H
19 R = *o*-OMe
20 R = *m*-OMe
21 R = *p*-OMe
22 R = *o*-Me
23 R = *m*-Me
24 R = *p*-Me



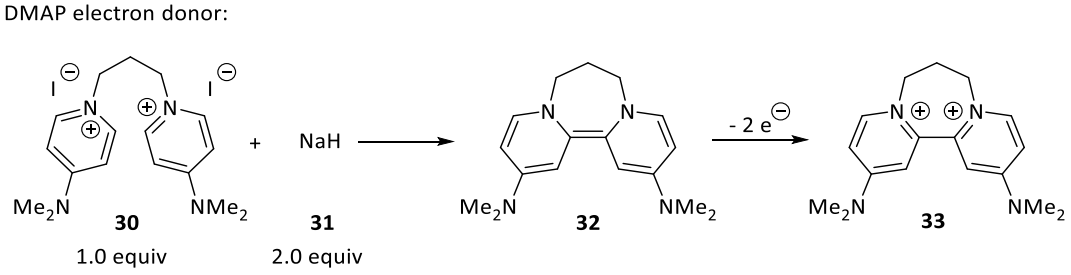
It also investigates the different outcomes of the reaction when a diketopiperazine is used or not, providing evidence for formation of a benzyne intermediate which can

lead to both the coupling product with benzene (when aryl iodides are used) and to *tert*-butoxybenzenes.

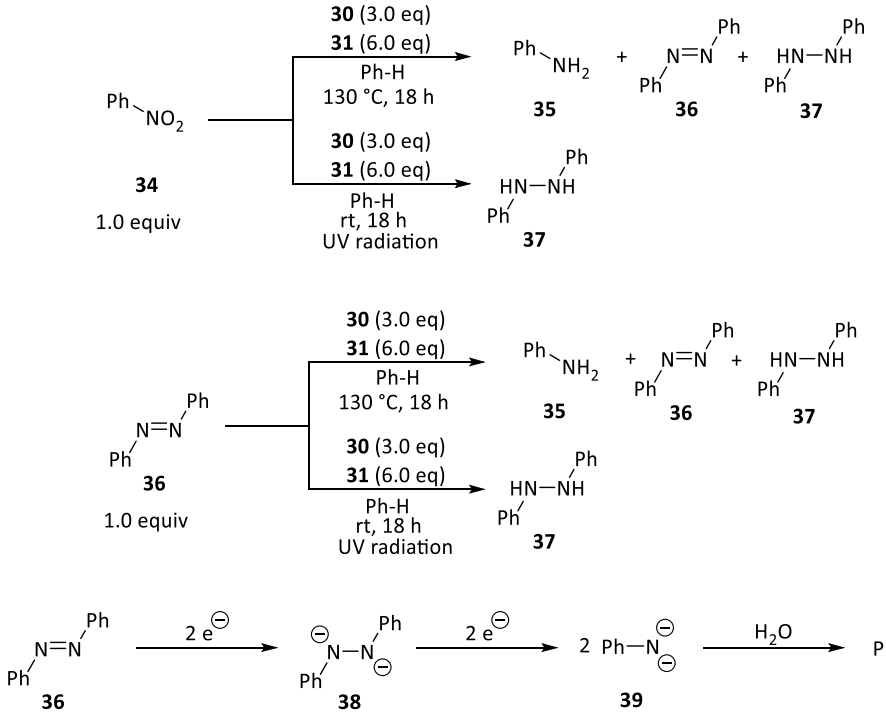
Chapter Three explores electron transfer reactions that lead to alkyl aryl ether deprotection. It highlights that *tert*-butyllithium **25** performs this deprotection and shows the series of reactions that led to evidence of an anionic addition of phenyllithium **26** to benzene and also of *tert*-butyllithium **25** to benzene.



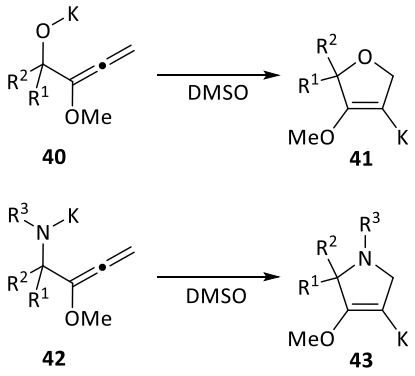
Chapter Four focuses on a 4-DMAP-derived organic electron donor **32**, commonly referred to as "DMAP donor", that reduces nitrobenzene **34** and azobenzene **36**, amongst others, under UV activation or thermal conditions, via successive single electron transfers. This chapter also discusses the unlikely possibility of an electron transfer from the DMAP donor **32** to the 1,2-diphenylhydrazine dianion **38** leading to the formation of aniline dianion **39**. More rational mechanistic considerations involving the reduced diphenylhydrazine and dication **33** will be described to explain the formation of aniline **35**.



Abstract



Chapter Five is a computational study of the 5-*endo*-*trig* cyclisation of alkoxide-allenes and amide-allenes, discussing the process involved (electron transfer or direct intramolecular anionic cyclisation) and comparing it with the, non-experimentally observed, 4-*exo*-*dig* cyclisation.



Chapter Six provides the detailed experimental procedures and data for the compounds that were synthesised and reported in this thesis.

Chapter 1: Introduction to Electron Donors and Their Use in Organic Chemistry

Oxidation and reduction reactions are the pillars of the natural environment. They are involved in many biological processes, such as cellular respiration, where nutrients (sugar, amino acids and fatty acids) are metabolised, which mostly involves redox reactions; batteries use an electric current resulting from oxidation-reduction reactions; and metals, like iron, can be oxidized by oxygen leading to corrosion.

This chapter introduces different ways that reduction reactions that involve electron transfer can be undertaken in organic chemistry.

Section 1.1 focuses on electron transfer reactions from metals and metal complexes, including alkali metals and lanthanides.

Section 1.2 discusses the development and applications of neutral organic electron donors in their ground-state and under UV-light activation.

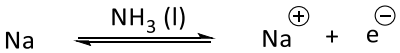
Section 1.3 highlights transition metal-free cross-coupling reactions using a combination of an organic additive and base to generate an organic electron donor *in situ*, which is used to initiate the coupling reactions of aryl halides with arenes.

1.1 Metals and metal complexes as electron donors

Electron transfer chemistry is mainly dominated by metals and metal-based reagents as these species were firstly found to be able to perform reductions. This section highlights several metal-based electron transfer reactions.

1.1.1 Alkali metals

One of the most commonly known reduction reactions is the Birch reduction using a dissolved alkali metal in ammonia.[1] Following the first report of sodium, in liquid ammonia, behaving as a solution of metal cations and solvated electrons in equilibrium with metal sodium,[2] it was expected that it was possible to give an electron to several chemical species in order to reduce them.



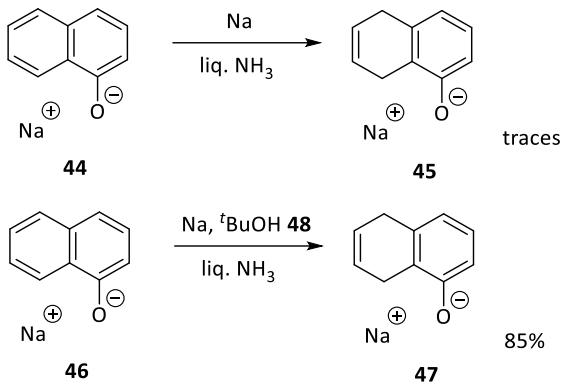
Scheme 1

Indeed, alkali metals such as lithium, sodium and potassium readily give away one electron as this gives them the electron configuration of a noble gas. Their strong ability to lose one electron makes them the strongest reducing agents as their determined reduction potentials also show.[3]

Alkali Metal	Standard Reduction Potential (V)
Li	-3.04
Na	-2.71
K	-2.93

Table 1: Standard reduction potentials of alkali metals.[3]

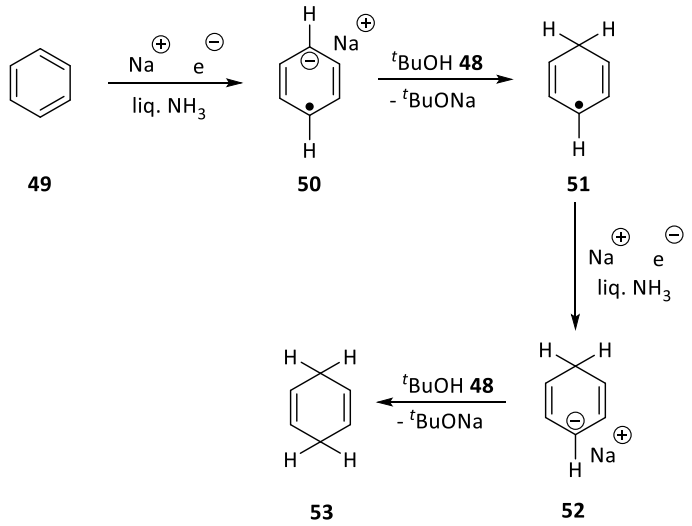
Birch focused on the comparison between a reduction reaction involving only a dissolved alkali metal in liquid ammonia and a reduction reaction involving a ready proton source (such as an alcohol) alongside a dissolved alkali metal in liquid ammonia. Experiments on sodium 1-naphthoxide **44** clearly showed the role of an alcohol, here *tert*-butyl alcohol **48**, on the reaction (Scheme 2).



44 **45** **46** **47**

Scheme 2

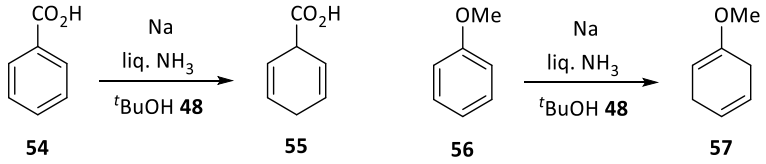
Further work from Birch[4-5-6] led to a mechanistic proposal for the Birch reduction (Scheme 3 with benzene **49** as an example). The dissolution of the alkali metal, here sodium, in liquid ammonia leads to the presence of solvated electrons. One of these electrons is transferred to benzene **49** to form a radical anion **50**.[7] This radical anion is protonated by the proton source (proven to be the rate-limiting step[8]), here *tert*-butanol **48**, to form the radical species **51** which receives another electron to form the delocalised anion **52** which is protonated by the proton source **48** to produce the reduction product, here cyclohexa-1,4-diene **53**.



49 **50** **51** **52** **53**

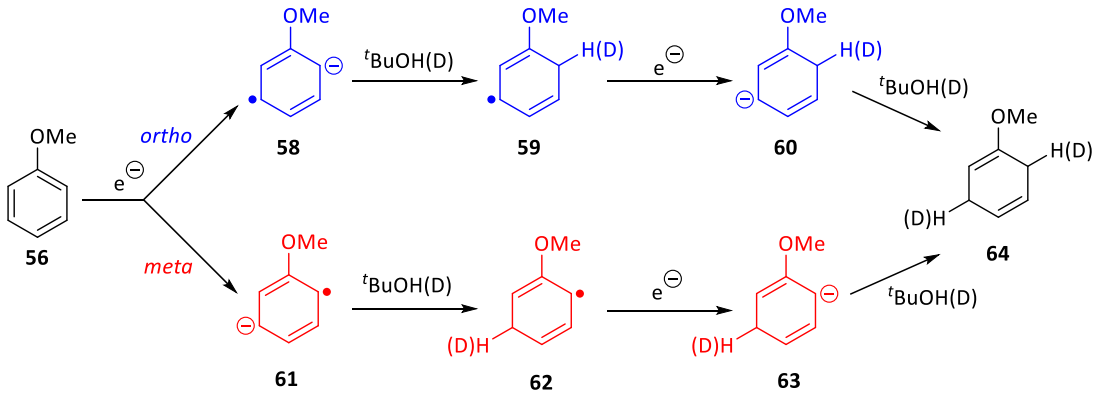
Scheme 3

In the case of benzene **49**, there is no problem of regioselectivity. However, Birch reduction was found to be regioselective in the case of substituted benzenes. The regioselectivity depends on the electronic effect of the substituent (Scheme 4).



Scheme 4

In the case of benzoic acid **54**, the withdrawing mesomeric effect of the carboxyl group leads to an *ipso*, *para* reduction while the donating effect of the methoxy group of anisole **56** leads to an *ortho*, *meta* reduction. There has been a huge interest in the mechanistic pathway involved in these reductions, particularly for the reduction of anisole **56**. The question lies on where does the first protonation happens. There are two possibilities commonly referred to as *ortho* and *meta* pathways (Scheme 5).

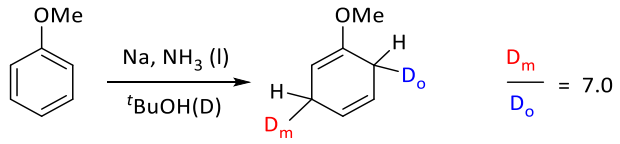


Scheme 5

Birch initially proposed[6] the *meta* position of radical anion **61** to have the highest electron density since the *ortho* and *para* positions would be avoided by the added electron due to the donating mesomeric effect of the methoxy group. However, Hückel calculations made by Zimmerman suggested that the *ortho* protonation of the radical anion **58** was the preferential process as this was the site of the highest electron density.[9] Later again, Birch concluded that protonation of the radical anion

could happen at both *meta* and *ortho* positions meaning that both mechanistic pathways were followed during the reaction.[10]

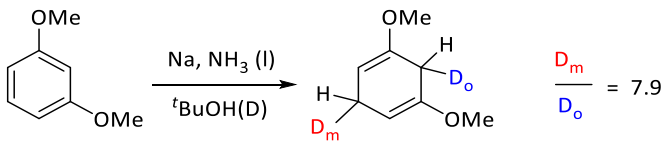
In order to bring experimental proof on the selectivity of the mechanism of the Birch reduction, Zimmerman studied the Birch reduction of anisole **56** using *tert*-butyl alcohol enriched in deuterium (as represented in Scheme 5).[11] His research relied on the idea that the isotope selectivity will be greater for radical anion **58** than for carbanion **60** as a radical anion is less reactive and thus more selective than a carbanion.[12] In other words, it was expected that of the two possible sites, the position with the less deuterium content would be the carbon protonated in the radical anion protonation step. Consequently, the carbon containing the more deuterium would be the carbanion site, more reactive thus less selective. This strategy paid off and revealed a strong selectivity of the *ortho* position as the site of initial protonation since the ratio of *meta*- to *ortho*-deuterium content was found to be about 7.0 meaning that the protonation of the radical anion is happening preferentially at the *ortho* position (Scheme 6).[13]



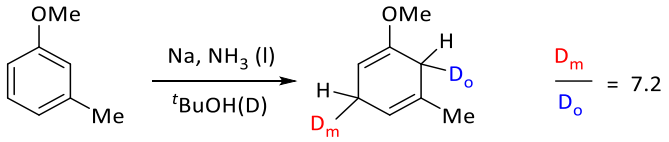
56 **64**

Scheme 6

This mechanism was found to be general as other examples with 1,3-dimethoxybenzene **65** and with 3-methoxytoluene **67** showed the same selectivity (Scheme 7).



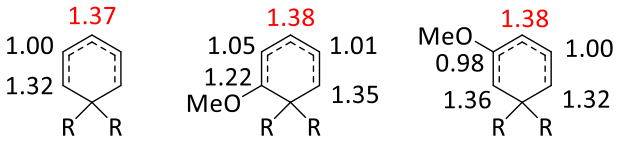
65 **66**



67 **68**

Scheme 7

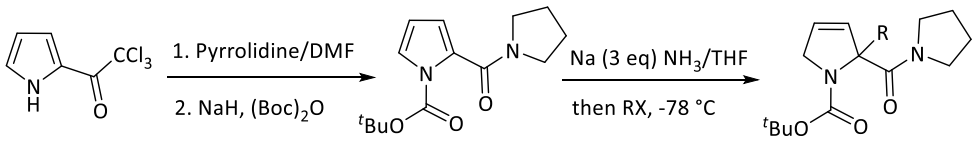
The final step of the Birch reduction has also been studied by Zimmerman looking to understand why the final products of a Birch reduction have unconjugated 1,4-cyclohexadienyl structures which are less thermodynamically favoured than conjugated 1,3-cyclohexadienyl structures.[9, 14] In other words, it was wondered why the protonation happened on the central carbon. Hückel calculations showed in several cases that the central carbon has the highest electron density and thus central protonation is expected and is experimentally observed (Scheme 8).



Electron density of the carbons of aryl anions formed under Birch conditions

Scheme 8

Although the mechanistic study of the Birch reduction has been a major topic of debate, its use has been of strong interest in organic chemistry. Donohoe extended the use of the Birch reduction to partial reduction of heterocycles such as electron-deficient pyrroles.[15,16] While the Birch reduction of pyrrole and derivatives was found to be inefficient,[17] Donohoe found that electron-withdrawing substituents on the pyrrole, especially on the nitrogen, allowed the reduction of the heterocycle to be undertaken under Birch conditions (see Scheme 9).



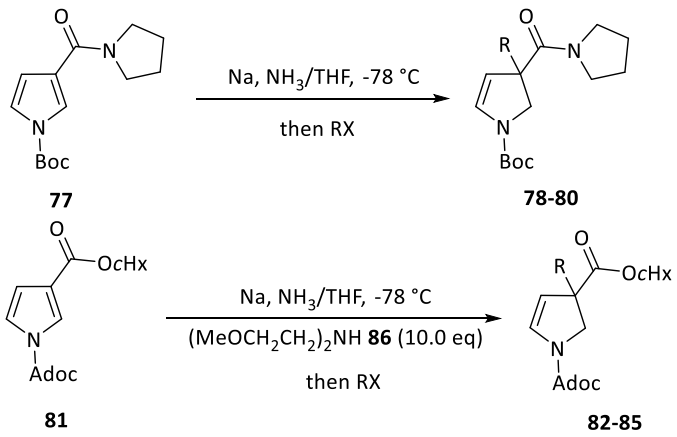
69 **70** (74%) **71-76**

Scheme 9

Entry	RX	R	Yield (%)	Product
1	MeI	Me	85	**71**
2	BnBr	Bn	72	**72**
3	EtI	Et	81	**73**
4	BuI	Bu	86	**74**
5	^{i}BuI	^{i}Bu	73	**75**
6	NH_4Cl	H	71	**76**

Table 2: Birch reduction of electron-deficient pyrroles to 3-pyrrolines.

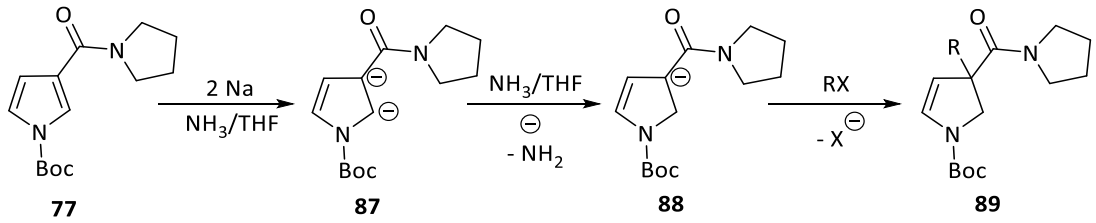
Donohoe also described the Birch reduction of electron-deficient 3-substituted pyrroles into 2-pyrrolines.[18] This reduction was accomplished with an excess of sodium metal (3-5 equivalents) in a mixture of liquid ammonia and THF and, surprisingly, without use of an alcohol as proton source (see scheme 10 and table 3). Since this reduction was accomplished without use of an alcohol as proton source, it was proposed by Donohoe that the reduction proceeds *via* formation of a dianion **87** resulting from the addition of two electrons to the pyrrole. This dianion can be protonated by ammonia to form the enolate **88** which reacts with the alkyl halide to form the substituted 2-pyrroline **89** (see scheme 11).



Scheme 10

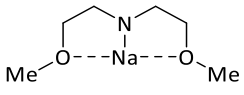
Entry	Pyrrole	RX	Yield (%)	Product
1	**77**	MeI	70	**78**
2	**77**	BnBr	69	**79**
3	**77**	^{i}BuI	58	**80**
4	**81**	MeI	72	**82**
5	**81**	BnBr	53	**83**
6	**81**	^{i}BuI	73	**84**
7	**81**	H	74	**85**

Table 3: Birch reduction of 3-substituted pyrroles.



Scheme 11

Scheme 10 shows use of bis(2-methoxyethyl)amine **86** in excess in the reduction of **81**. This amine was used to avoid the deprotection of the pyrrole or pyrroline by loss of the Adoc protecting group. Donohoe proposed that this amine would be preferentially deprotonated to ammonia and would lead to a stabilised anion **90** due to chelation (see Scheme 12). Avoiding the deprotonation of ammonia, and thus the formation of the highly reactive NH_2^- anion, ensured that the protecting group would not be removed.

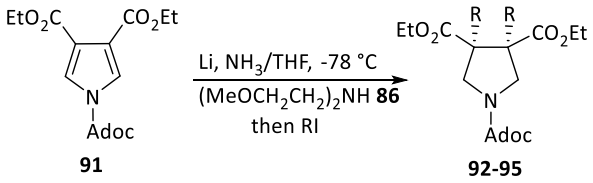


90

Scheme 12

Donohoe extended his work to disubstituted pyrroles and found that 3,4-disubstituted pyrroles underwent a double reductive alkylation to form pyrrolidines

with adjacent quaternary centres with good stereoselectivity.[19] For this reduction, the metal used was lithium rather than sodium. The reaction of the reduced heteroaromatic ring with an alkyl halide led to stereoselective 3,4-disubstituted pyrrolidines (see Scheme 13 and Table 4).

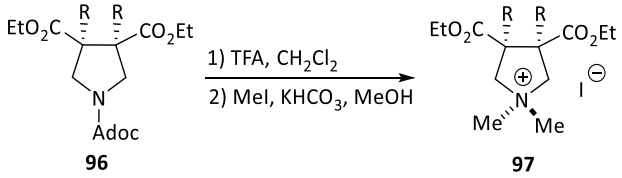


Scheme 13

Entry	RX	*cis/trans*	Yield (%)	Product
1	MeI	≥20:1	77	**92**
2	EtI	≥10:1	82	**93**
3	^{i}BuI	≥10:1	79	**94**
4	Allyl-I	≥10:1	70	**95**

Table 4: Birch reduction of **91**.

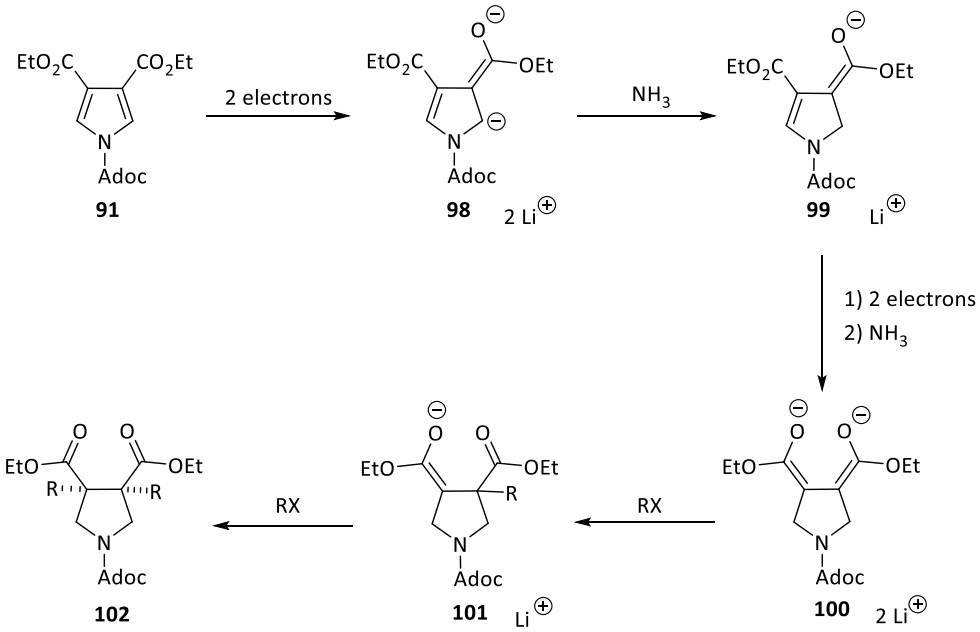
The formation of products **92**-**95** was not enough to determine the stereoselectivity of the reaction by NMR. Donohoe and his group had to further react these products to form quaternary ammonium salts (a general case is described in Scheme 14).



Scheme 14

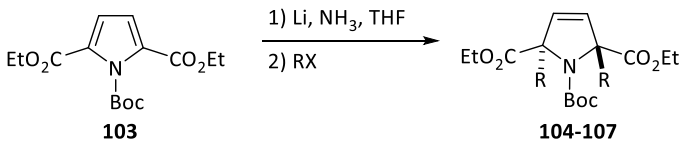
These quaternary ammonium salts allowed Donohoe to identify two (3H) different N-CH_3 singlets which meant that the two *N*-methyl groups resonated at different chemical shifts, and therefore that the stereochemistry of salts **97** and therefore products **92**-**95** was *cis*, as a *trans* stereochemistry would make the *N*-methyl groups

homotopic, thus resonating at the same chemical shift. The mechanism Donohoe proposed for this reaction suggested that **91** could receive 2 electrons and form dianion **98**. This dianion could deprotonate ammonia [or bis(2-methoxyethyl)amine **86**] and form enolate **99**. Due to the presence of a second ester group on the ring, **99** could be further reduced by addition of two electrons and protonation would give dienolate **100** which can be alkylated twice to afford the *cis*-3,4-disubstituted pyrrolidines **102** (see Scheme 15).



Scheme 15

Under similar conditions, Donohoe also reduced 2,5-disubstituted pyrroles which afforded doubly alkylated pyrrolines, preferentially the *trans* diastereoisomer (see scheme 16 and table 5).[20]

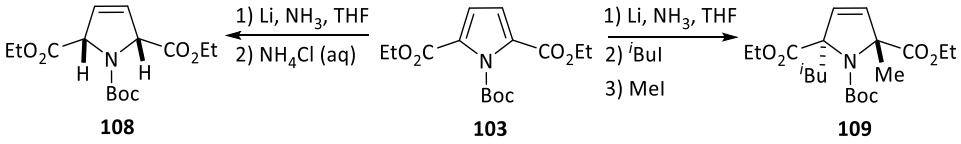


Scheme 16

Entry	RX	Yield (%)	Product
1	MeI	85	**104**
2	EtI	87	**105**
3	BnBr	71	**106**
4	Allyl-Br	81	**107**

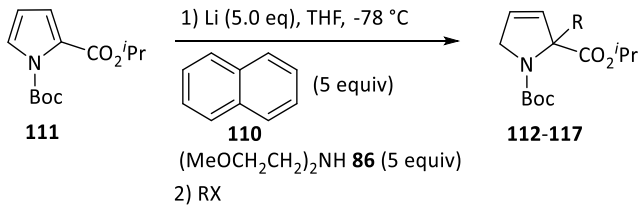
Table 5: Birch reduction of **103**.

Interestingly, it was possible to synthesise an unsymmetrical isomer **109** as the alkyl groups to be attached to C-2 and C-5 did not need to be the same. Also, using ammonium chloride as a protonating agent led to formation of the dehydroproline **108** with a bias for the *cis* isomer (see scheme 17).



Scheme 17

In parallel with these reductions, Donohoe found that an electron shuttle, such as naphthalene **110**, could be used in THF with lithium metal to perform similar partial Birch reductions, without requirement of liquid ammonia, which would make the experimental process easier.[21] The reduction of several heteroaromatics, such as pyrrole **111**, gave good results for the formation of substituted pyrrolines (see Scheme 18 and Table 6).

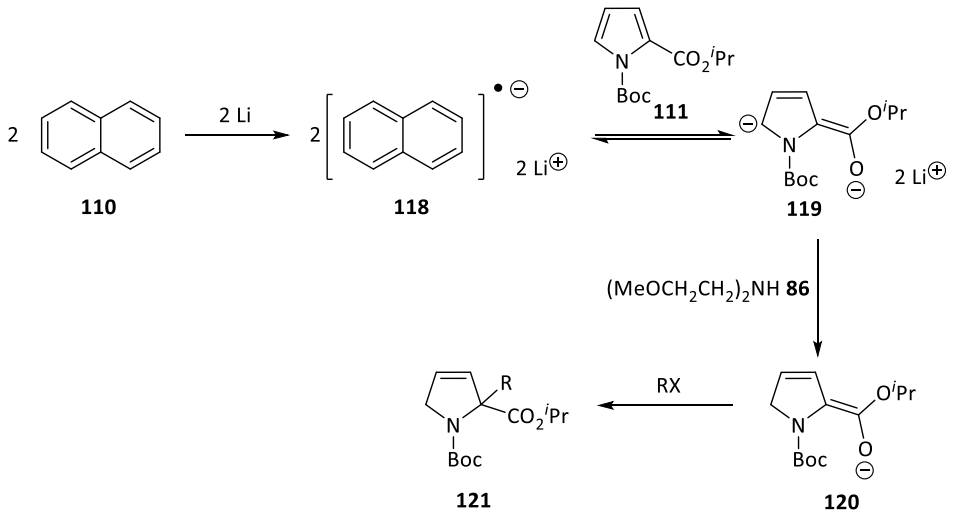


Scheme 18

Entry	RX	R	Yield (%)	Product
1	MeI	Me	62	**112**
2	EtI	Et	57	**113**
3	BnBr	Bn	59	**114**
4	Allyl-Br	Allyl	78	**115**
5	BuBr	H	57	**116**
6	PhCHO	PhCHOH	50	**117**

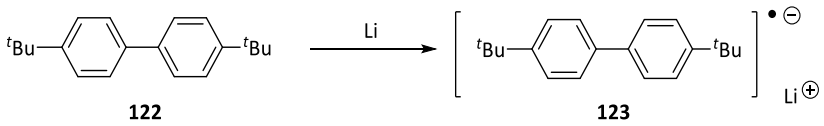
Table 6: Birch reduction of **111** using an electron shuttle.

The role of naphthalene **110** as an electron shuttle was deduced by formation of its green radical anion **118**. It was proposed that this radical anion could give away one electron to pyrrole **111**, thus two equivalents of **118** would lead to formation of dianion **119** which could deprotonate amine **86** leading to enolate **120** which would finally react with an electrophile to afford the reduction product **121** (see Scheme 19).



Scheme 19

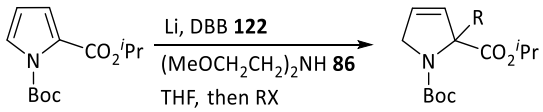
Naphthalene **110** as an electron shuttle was progressively replaced by di-*tert*-butylbiphenyl[22] (DBB) **122** (see Scheme 20) as it resulted in an improvement in yield of the reduction of aromatic compounds by lithium.[23]



122 **123**

Scheme 20

Using DBB **122** to replace naphthalene **110** was also beneficial as it led to cleaner reactions and allowed isolation of **127** as a pure product, which was not possible when naphthalene **110** was used (see Table 7 and Scheme 21). The hindered structure of DBB **122** is likely the reason for its greater efficiency than naphthalene **110** as it disfavours the radical coupling of the DBB radical anion **123** with other radicals present in solution. Also, DBB **122** has a more negative reduction potential than naphthalene and thus, the DBB radical anion **123** will be a stronger reducing agent.[24-25]



111 **124-128**

Scheme 21

Entry	RX	R	Ammonia (%)	Naphthalene 110 (%)	DBB 122 (%)	Product
1	BnBr	Bn	87	59	80	**124**
2	MeI	Me	87	62	74	**125**
3	BuBr	H	-	57	62	**126**
4	PhSSPh	SPh	93	-	52	**127**
5	PhCHO	PhCHOH	91	50	70	**128**

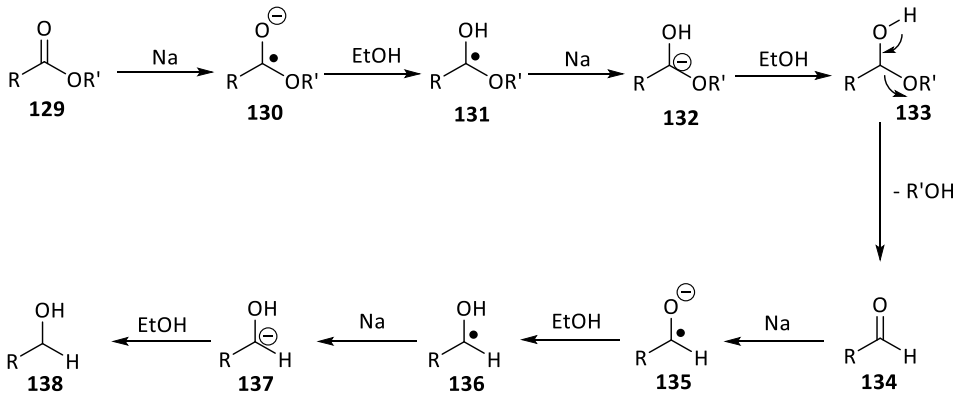
Table 7: Comparison of yields between ammonia and ammonia-free (naphthalene and DBB) conditions of the reduction of **111**.

The Birch reduction has clearly been of major interest in organic chemistry and is a perfect example of the reductive strength of alkali metals. These metals can also be

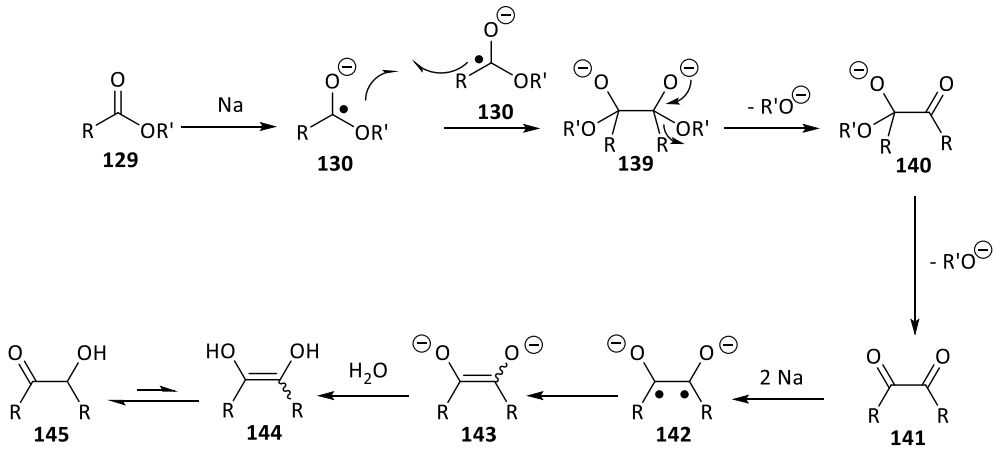
involved in the reduction of various chemical functions such as esters and ketones in protic solvent, a reaction known as the Bouveault-Blanc reaction[26] (see Scheme 22). It was found that the use of an aprotic solvent stopped the reaction from happening as expected when an ester was used, as there were no protons available for protonation, thereby leading to acyloin products[27] (see Scheme 22).

With a protic solvent, such as ethanol, ester **129** receives one electron from the alkali metal, here sodium, to afford radical anion **130** which can be protonated by ethanol to form radical **131** This radical receives one more electron from sodium to form anion **132**, which affords hemiacetal **133**. Loss of an alcohol leads to aldehyde **134** which can react with sodium and ethanol the same way to finally afford alcohol **138**.

Protic solvent:



Aprotic solvent:



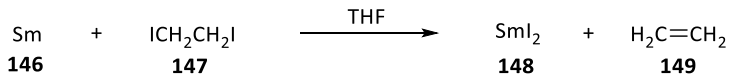
Scheme 22

When the solvent is aprotic, 2 molecules of the radical anion **130** couple to generate dianion **139** which leads to diketone **141** after loss of two alkoxides. This diketone receives two more electrons to afford biradical dianion **142** leading to an enediolate **143** which can be protonated by water to afford enol **144** and thus its keto form, **145**, by keto-enol equilibrium.

The Birch conditions can be used with several aromatics and heteroaromatics as well as other chemical functional groups. However, its use requires difficult conditions as sodium is particularly reactive and must be used under inert conditions and liquid ammonia requires a low temperature to be maintained during the total procedure as it is very volatile. Over the years, other alternatives were found to perform electron transfer reactions.

1.1.2 Lanthanides

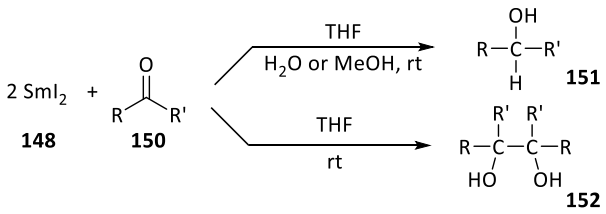
Lanthanides and, more particularly, lanthanide (II) reagents have been of major interest in organic chemistry. Samarium diiodide (SmI_2 **148**) has attracted most interest since Kagan *et al.* found an easy way to synthesise it in solution in THF and used it as a single electron donor.[28] The process involves a smooth reaction of the samarium metal **146** with 1,2-diiodoethane **147** in THF at room temperature under inert atmosphere and anhydrous conditions to yield samarium diiodide **148** with quantitative yield (see Scheme 23).



Scheme 23

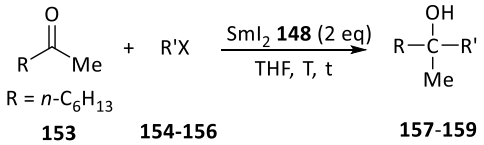
The formation of this samarium (II) complex was the beginning of an extensive use of lanthanide (II) complexes in organic chemistry, while the use of lanthanides was mostly for inorganic chemistry prior to Kagan's work. For example, it was found that

samarium diiodide (II) **148** could reduce carbonyl groups[28] and couple them (see Scheme 24). [29-30]



Scheme 24

It was also found that a one-pot Barbier reaction[31] was possible when using two equivalents of SmI_2 **148** (see Scheme 25 and Table 8).



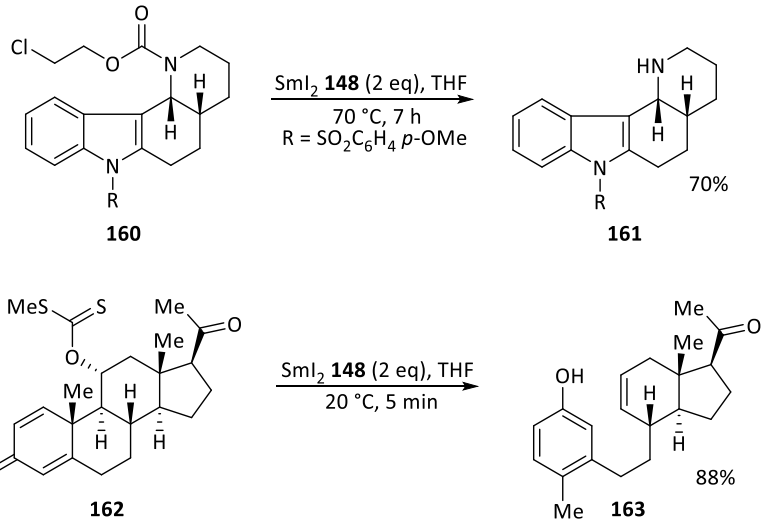
Scheme 25

Entry	R'	T (°C)	t (h)	Yield (%)	Product
1	Me	65	8	75	**157**
2	*n*-Bu	65	8	76	**158**
3	Allyl	rt	0,25	71	**159**

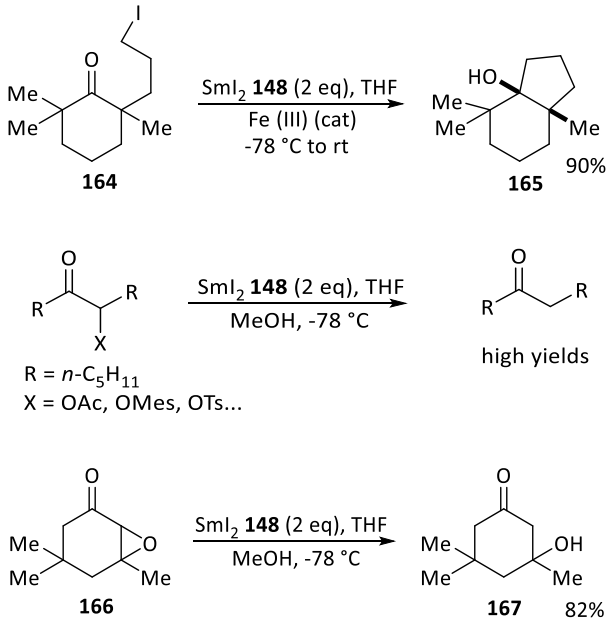
Table 8: Samarium Barbier reaction.

Magnus *et al.* used SmI_2 **148** to fragment bonds that they could not fragment with other reducing agents (see Scheme 26),[32-33-34] and Molander *et al.* extended the scope of the samarium Barbier reaction with its intramolecular version[35] and found an easy cleavage of C-heteroatom bonds when the bond is vicinal to a carbonyl group (see Scheme 26).[36-37]

Magnus:

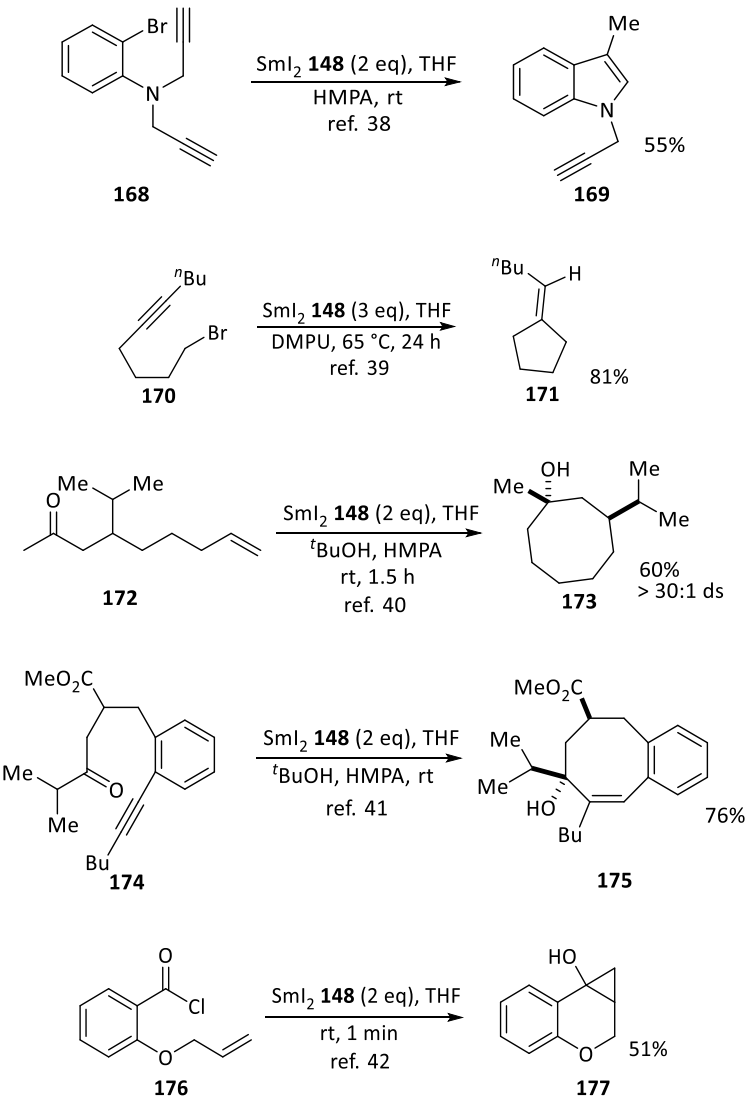


Molander:



Scheme 26

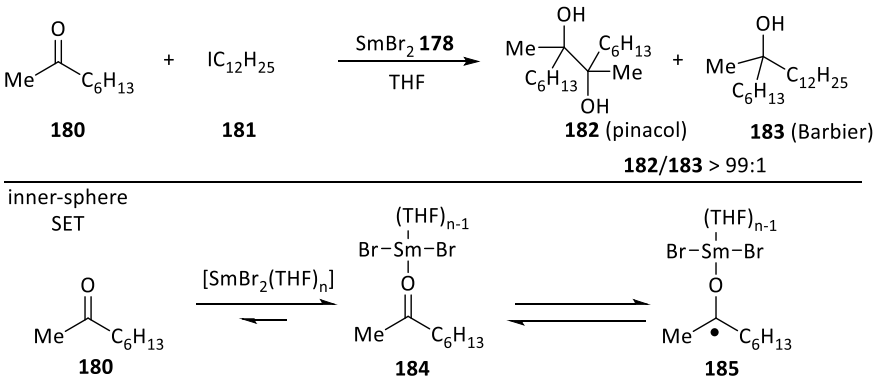
Samarium diiodide **148** can also be used for cyclisation reactions and many varied types of cyclisation have been investigated and reported in the literature (see Scheme 27): cyclisation via aryl radicals,[38] alkyl radicals,[39] ketyl radical,[40-41] and acyl radical.[42]



Scheme 27

While samarium diiodide **148** was the beginning of the interest for samarium (II) complexes in organic chemistry, other samarium (II)-based reagents have been used and found to be generally more powerful reducing agents. The six major samarium (II)-based reagents other than SmI_2 are samarium (II) bromide ($SmBr_2$) **178**, samarium (II) chloride ($SmCl_2$) **179**, samarium (II) iodide/water complex (SmI_2/H_2O), samarium (II) amides, samarium (II) alkoxides and samarium (II) cyclopentadienyl complexes. Samarium (II) bromide **178** is not only a stronger reducing agent than samarium (II) iodide **148** ($SmBr_2$: -1.55 V vs SCE in THF; SmI_2: -0.98 V vs SCE in THF)[43], it also leads to strong selectivity in various reductions.

For example, Flowers *et al.* found that the C-C bond-forming reaction of reactive alkyl iodides with ketones in presence of $SmBr_2$ **178** selectively formed the pinacol coupling product rather than the Barbier product (see Scheme 28) while the same reaction in presence of SmI_2 **148** or $SmCl_2$ **179** afforded a mixture of the two products. Mechanistic studies proposed that the reduction of the ketone with $SmBr_2$ **178** proceeds via an inner-sphere electron transfer.



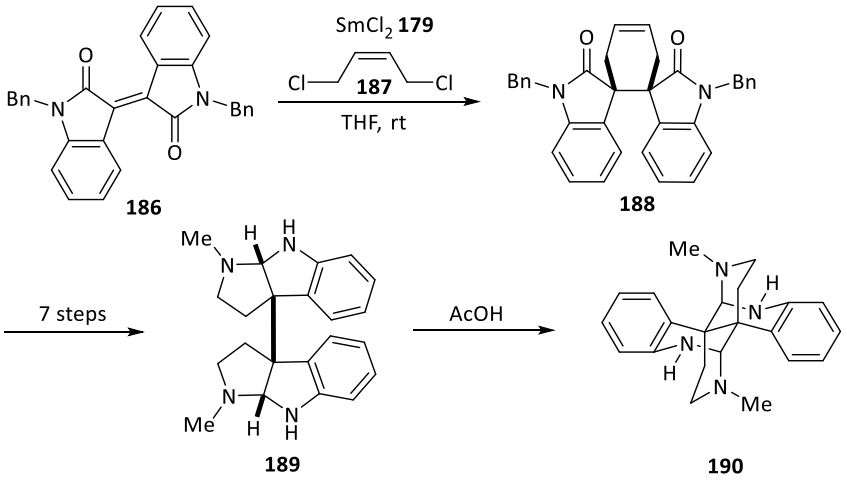
Scheme 28

On the other hand, the samarium (II) complex SmI_2/HMPA[44] (SmI_2/HMPA: -1.75 V vs SCE in THF, the complex is formed with six molecules of HMPA for one of SmI_2)[45] used instead of $SmBr_2$ **178** in the same reaction afforded the Barbier product **183** exclusively and mechanistic studies suggest an outer-sphere single electron transfer process.

Samarium (II) chloride **179** is an even stronger reducing agent than the other samarium (II) complexes seen so far ($SmCl_2$: -1.78 V vs SCE in THF).[44] Its strong reducing ability has made it a very interesting promoter of difficult electron-transfer reactions. Link and Overman used $SmCl_2$ **179** in the reductive dialkylation of isoindigo **186** with *cis*-1,4-dichloro-2-butene **187** (see Scheme 29).[46] The product of this reaction was obtained with excellent control over stereoselectivity and was further used in the total synthesis of *meso*-chimonanthine **189** and *meso*-calycanthine **190**.

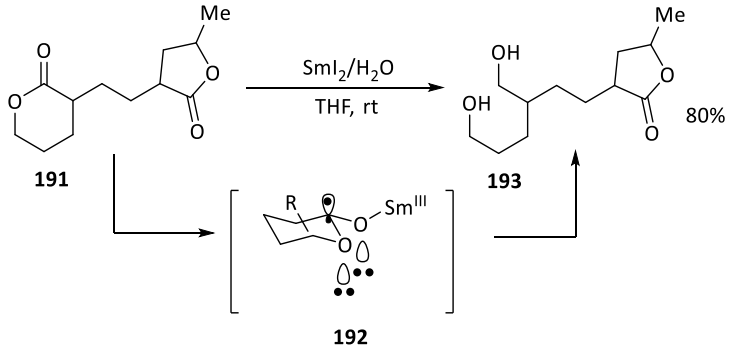
This stereocontrol was proposed to be the result of chelation of both carbonyl groups to the samarium.[47] Alternative samarium (II) complexes such as SmI_2 and SmI_2/HMPA

were not able to establish the same stereocontrol and led to a mixture of products showing the strong potential of $SmCl_2$ for challenging natural product synthesis.



Scheme 29

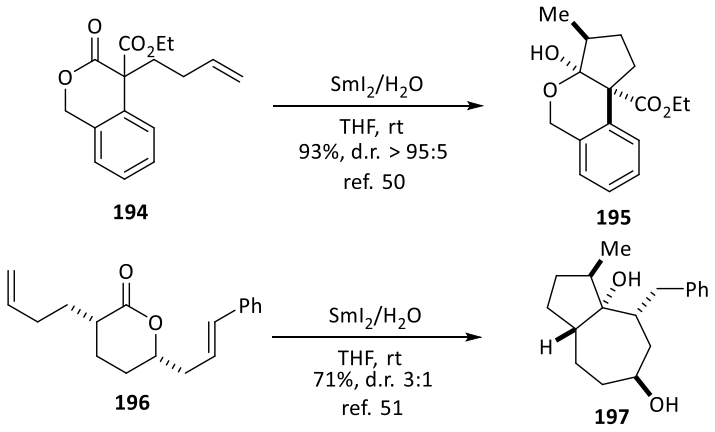
The samarium (ii) iodide/water complex (SmI_2/H_2O) was also found to be a better reducing agent than SmI_2 **148** itself (SmI_2/H_2O: -1.9 V vs $Ag/AgNO_3$ in THF; SmI_2: -1.33 V vs $Ag/AgNO_3$ in THF).[48] While it was thought that ester carbonyl groups could not be reduced by SmI_2 **148**, Procter and Szostak found that SmI_2/H_2O could reduce unactivated cyclic esters (see Scheme 30). Interestingly, this samarium (II) complex reduced selectively lactones over esters and also showed ring-size selectivity as only six-membered lactones were converted into the corresponding diol.



Scheme 30

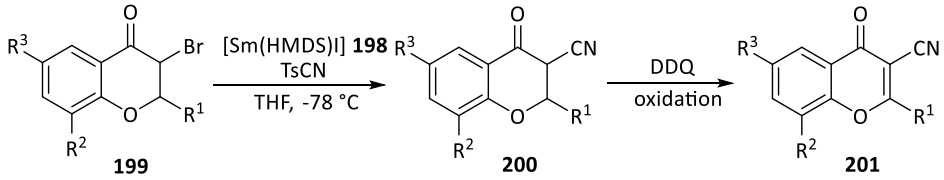
The selectivity of the reaction was rationalised by the formation of the ketyl radical anion intermediate **192**, which is stabilised by an anomeric effect that is more

pronounced in six-membered ring systems than five-membered ring systems.[49] The radical anion intermediate formed during the reduction of six-membered lactones has been used in intramolecular coupling reactions with alkenes.[50] This led to cascade cyclisation processes which allowed access to five- and seven-membered oxygenated scaffolds and azulene motifs with good yields and diastereoselectivity (see Scheme 31).[51]



Scheme 31

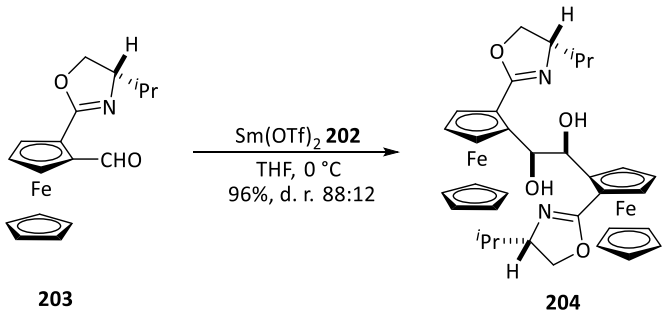
Several samarium (II) amide complexes have also been studied and found to be also better reducing agents than SmI_2 ([Sm(HMDS)$_2$]: -2.1 V vs Ag/AgNO$_3$; [SmI_2(HMPA)]: -2.35 V vs Ag/AgNO$_3$).[52] The heteroleptic [Sm(HMDS)I] complex **198** was reported by Hilmersson as an excellent reagent for the α-functionalization of chromanones (see Scheme 32).[53]



Scheme 32

Samarium (II) alkoxides and particularly samarium (II) triflate Sm(OTf)$_2$ **202** have also been widely used in organic chemistry.[54-55] The redox potential of Sm(OTf)$_2$ **202** has yet to be found but this complex has been shown to be able to promote similar reactions to SmI_2 **148** and, in some cases, enhances the diastereoselectivity and the

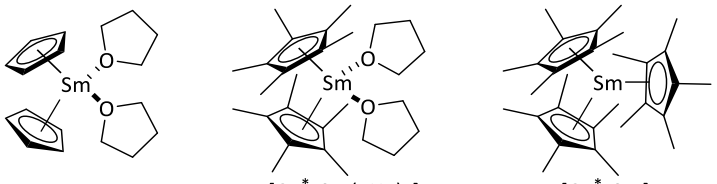
yield of reductions compared with SmI_2 **148**. Samarium (II) triflate **202** has been used by Fukuzawa *et al.* in the pinacol coupling of planar chiral ferrocenes with good stereoselectivity (see Scheme 33).[56] The strong selectivity was explained by the steric hindrance of the triflate anion in the transition state.



203 **204**

Scheme 33

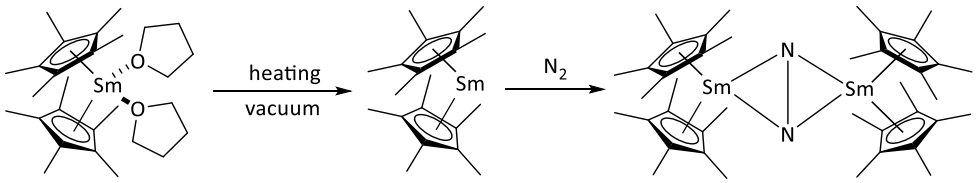
Samarium (II) cyclopentadienyl complexes are known to be the strongest samarium (II)-based reductants ($[Cp^*_2Sm]$: -2.44 V vs SCE in DMF;[57] $[Cp_2Sm]$: -2.66 V vs $[Cp_2Fe]^+/[Cp_2Fe]$ in THF).[58] Various complex structures were found (see Scheme 34). The use of $[Cp_2SM]$ **205** has remained unexplored since it has a poor solubility in most common organic solvents. However, $[Cp^*_2Sm]$ **206** is soluble in a range of organic solvents. When heating under vacuum, Evans *et al.* found that the decamethylsamarocene **206** gave the desolvated complex **207** (see Scheme 35).[59]



$[Cp_2Sm(THF)_2]$ **205** $[Cp^*_2Sm(THF)_2]$ **206** $[Cp^*_3Sm]$ **207**

Scheme 34

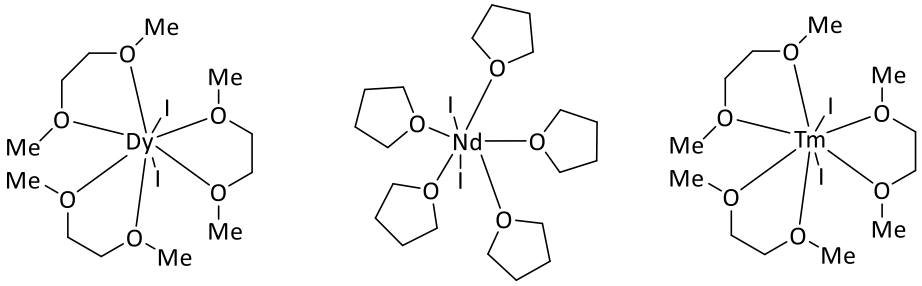
This desolvated complex **206** was found to be the first lanthanide complex capable of dinitrogen activation.[60]



206 **208** **209**

Scheme 35

To conclude this part on lanthanides, which focused only on samarium, we can mention a few more lanthanide (II) complexes used in organic chemistry: dysprosium (II) $[DyI_2(DME)_3]$,[61] neodymium (II) iodide $[NdI_2(THF)_5]$[62] and thulium (II) iodide $[TmI_2(DME)_3]$[63] (see Scheme 36) are some of the many lanthanide (II) complexes that allow difficult reduction reactions to be performed in an efficient and elegant way. Also, samarium (II) has been recently used in water alongside triethylamine to reduce nitriles into primary amines[64] and with lithium bromide to perform dearomatizing radical cyclisations[65] showing that the use of samarium (II) complexes is likely to afford new efficient reactions in the future and will remain a tool to overcome challenging reactions.



ref 61. ref 62. ref 63.

Scheme 36

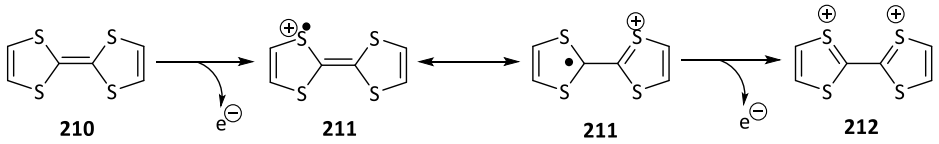
1.2 Neutral Organic Electron Donors and Their Applications

For many years, electron transfer reactions were made by low valent metals and metal complexes as reported in part 1.1. The requirement for alternatives has arisen

in order to decrease both the economic and the environmental impacts of metal-based electron transfer reactions. Neutral-organic electron donors have been found to be capable of undertaking challenging reduction reactions under mild conditions and have become a strong alternative for metal-based reactants.

1.2.1 Early findings in organic electron-transfer reagents

In 1970, Wudl synthesised tetrathiafulvalene (TTF) **210**, an air-stable organic compound containing four sulfur atoms which can increase the electron density of the C=C double bond, making it particularly electron-rich.[66] TTF was used for its electron donor properties in generating new types of semiconductors.[67] It was only several years later that the use of TTF in organic chemistry was found and used by the Murphy group.[68-69] The driving force for the electron transfer to occur from TTF is the gain in stability by aromatisation after loss of one and two electrons (see Scheme 37). The first oxidation leads to radical cation **211** and the second oxidation leads to dication **212** both being aromatic species. These electron transfer reactions are assisted by solvation of the species in polar solvents. The two oxidation potentials for the electron donations were found to be +0.34 V for the first electron and +0.81 V for the second (vs. SCE in benzonitrile).[70]

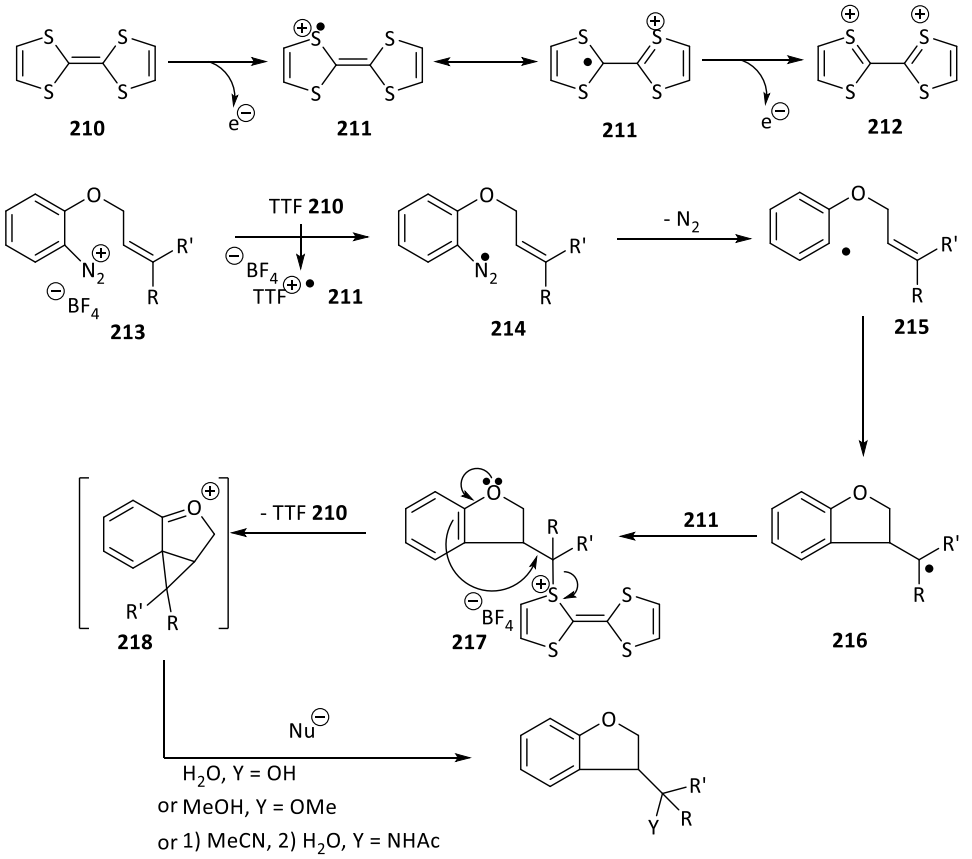


Scheme 37

One of the early reactions that the Murphy group performed involved electron-deficient diazonium salts and led to the first ever reported radical-polar crossover reaction based on tetrathiafulvalene (see Scheme 38).[68]

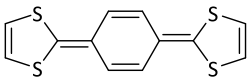
In this reaction, TTF gives one electron to the arenediazonium salt **213**, forming an unstable arenediazenyl radical **214** which loses nitrogen gas to form aryl radical **215**.

This aryl radical undergoes a 5-*exo*-*trig* cyclisation and produces a more stable alkyl radical **216**. The radical is then trapped by TTF radical cation **211** which affords sulfonium salt **217**, a polar intermediate. TTF **210** is then expelled from **217** by delocalisation of electrons to generate the cation intermediate **218** which, after attack by several nucleophiles, can afford the corresponding substituted dihydrobenzofurans.

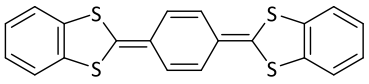


Scheme 38

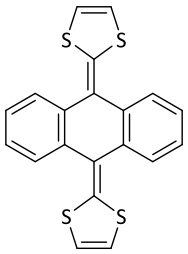
Other electron donors with a structure similar to TTF **210** have been synthesised (see Scheme 39) and some of them were found to be even better reducing agents.[71-72] For example, the first oxidation potential of **220** was found to be -0.11 V and its second oxidation potential to be -0.04 V (vs SCE in MeCN).[71]



219



220

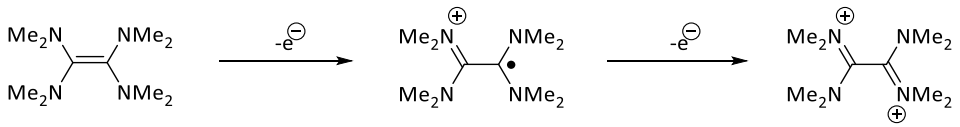


221

Scheme 39

However, these other species were difficult to synthesise. In addition, TTF **210** was found to be limited in its reductive powers as it was ineffective in the reduction of aryl and alkyl halides.[73]

This led to the investigation of even more powerful organic electron donors by increasing the π-electron density of the donor. A solution was found by replacing the sulfur atoms by nitrogen atoms. The commercially available 1,1,2,2-tetrakis(dimethylamino)ethylene (TDAE) **222** can act as an electron donor by giving away up to two electrons (see Scheme 40). Its oxidation potentials have been determined: -0.78 V and -0.61 (vs SCE in MeCN) showing that TDAE **222** is indeed a better reducing agent than TTF **210**, as expected.[74]

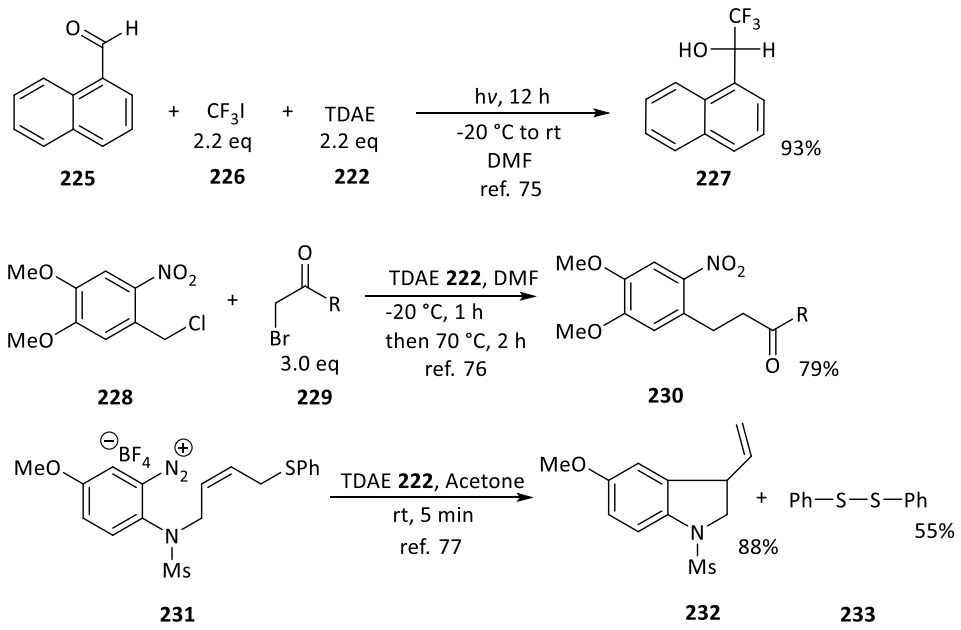


222 **223** **224**

Scheme 40

TDAE **222** was engaged in several reduction reactions and found to be a good reducing agent for various species such as trifluoromethyl iodide **226**,[75] *o*-nitrobenzyl chlorides[76] and also arenediazonium salts (see Scheme 41).[77] However, TDAE **222** was still not a powerful enough reducing agent to cause reduction of unactivated aryl and alkyl halides. Still, these first organic electron donors were showing the pattern that should be followed for the elaboration of new electron donors, in particular the presence of nitrogen atoms to increase the electron density on a C=C double bond

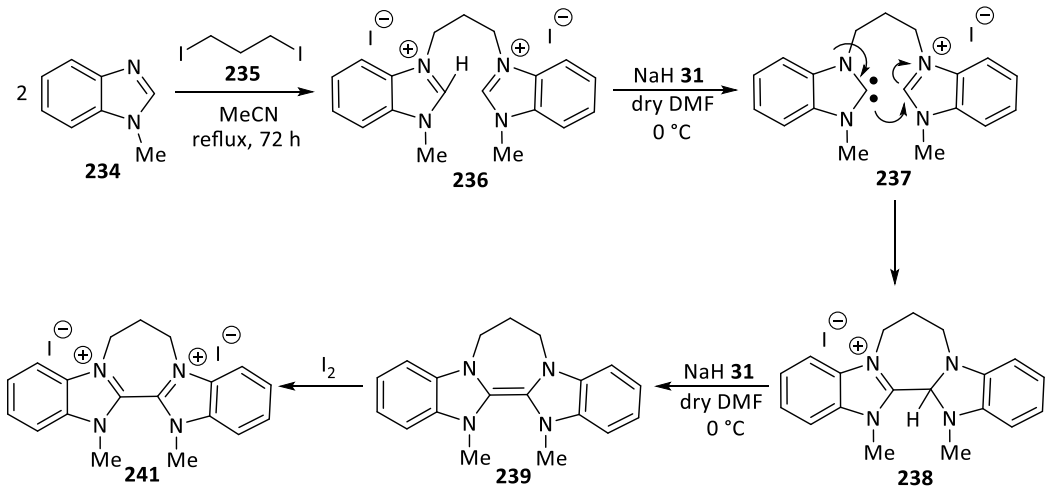
and provision of additional driving force by aromatisation once the electron donor species has lost one and two electrons.



Scheme 41

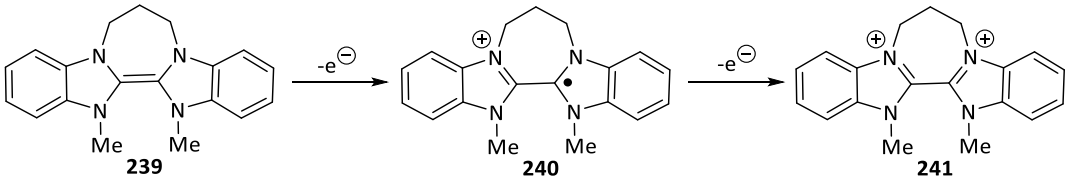
1.2.2 Neutral Organic Super Electron Donors

Shi and Thummel published in 1995 a synthetic route for bridged derivatives of 2,2'-bibenzimidazolinylidenes.[78] One of the benzimidazole-derived species **239** created a strong interest for the Murphy group as its structure was in accordance with the requirements of neutral organic electron donors. The synthesis of **239** began with the alkylation of two molecules of *N*-methylbenzimidazole **234** by 1,3-diiodopropane **235**, to give **236**. Deprotonation of salt **236** by a strong base such as sodium hydride **31** leads to carbene **237** which can attack the other benzimidazolium group to form cation **238**. Further deprotonation of cation **238** forms the doubly-bridged species **239** which was initially characterised by quenching with iodine to form disalt **241** (see Scheme 42).



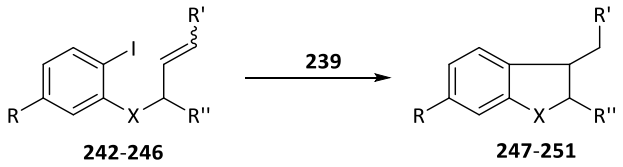
Scheme 42

As for the previous organic electron donors discussed earlier, **239** is electron-rich thanks to the four nitrogen atoms increasing the electron density of the central C=C double-bond by their donating effect. Thus, **239** can give away up to two electrons as this leads to stabilized radical cation **240** and dication **241** (see Scheme 43). The oxidation potentials were found for **239** and are -0.82 V for the first oxidation and -0.75 V for the second (vs SCE in DMF).[79] Since this species was published, no study had been made on its reductive reactivity toward organic substrates.



Scheme 43

The Murphy group investigated the ability of **239** to reduce aryl halides and found excellent reactivity with aryl iodides that had been chosen so the aryl radical formed would lead to an intramolecular cyclisation to form indolines (see Scheme 44 and Table 9).[80]



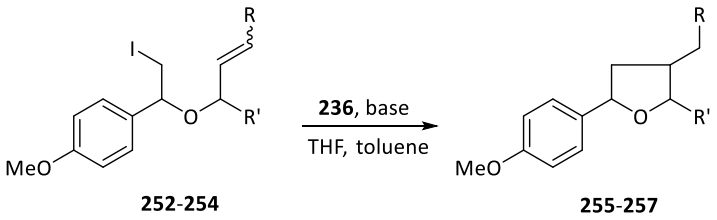
242-246 **247-251**

Scheme 44

Entry	Substrate	X	R	R'	R''	Product	Yield (%)
1	**242**	NMs	H	H	H	**247**	80
2	**243**	NMs	H	Me	H	**248**	88
3	**244**	NMs	OMe	H	H	**249**	87
4	**245**	NMs	H	$(CH_2)_3$	$(CH_2)_3$	**250**	89
5	**246**	O	H	H	H	**251**	65

Table 9: Aryl iodides reduction by **239**.

Similarly, aliphatic iodides were reacted with **239** (formed *in situ* by reaction with salt **236** and a base) and afforded excellent yields of the cyclised products (see Scheme 45 and Table 10).



252-254 **255-257**

Scheme 45

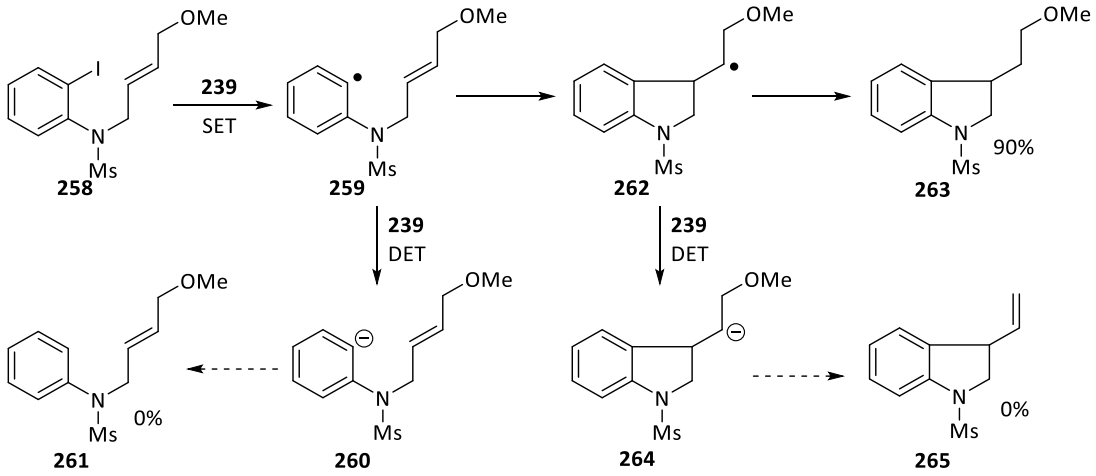
Entry	Substrate	R	R'	Product	Yield (%)
1	**252**	H	H	**255**	83
2	**253**	Me	H	**256**	83
3	**254**	$(CH_2)_3$	$(CH_2)_3$	**257**	88

Table 10: Alkyl iodide reduction by **239**.

The question that arose with these experiments was about the mechanistic pathway followed during the reduction and, more particularly, whether the reaction involved a single (SET) or double electron transfer (DET). To bring light to the mechanistic pathway, substrate **258** was chosen as it possesses a potential anionic leaving group (see Scheme 46).

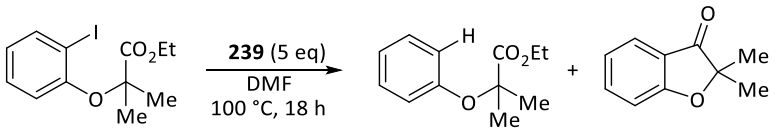
In theory, a double electron transfer pathway could form two different products, depending on whether the second electron is transferred before cyclisation (product **261**) or after (product **265**) if it transferred at all. If there is only one electron being transferred to the substrate, then only one product could be formed (product **263**). Since only **263** was formed during the reaction, it was concluded that the mechanistic pathway involves a single electron transfer.

To identify the source of hydrogen allowing a radical such as **262** to form **263** by hydrogen abstraction, similar reactions were carried out in deuterated DMF but no deuterium labelling was found on the reaction products suggesting that the solvent was not the source of hydrogen. It was suggested that the ionic species resulting from loss of electrons by the donor (**240** and **241**) or the donor **239** itself might be the source of hydrogen atoms. It is also interesting to note that the hydrogen abstraction does not happen with radical **259** but only after cyclisation.



Scheme 46

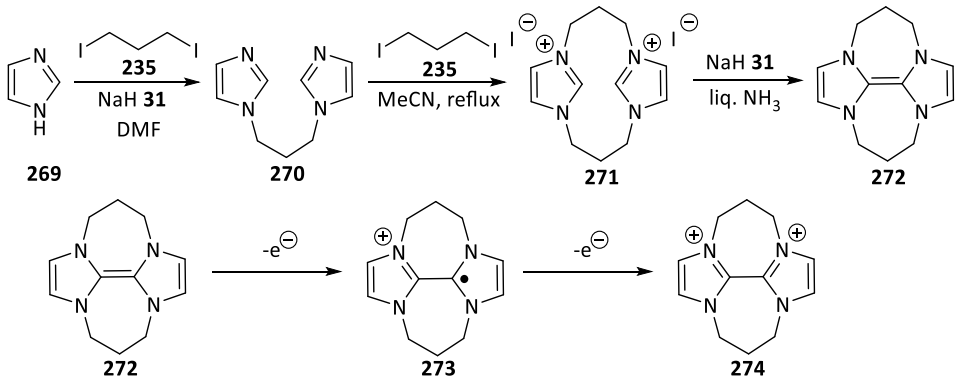
Another experiment confirmed the ability of **239** to give away only one electron in these reactions (see Scheme 47). If the substrate **266** could receive two electrons and thus form an aryl anion, it should be expected to cyclise by reaction on the ester moiety. Since the corresponding product **268** was not found and only the SET product **267** was provided, a DET process was ruled out.



266 **267** (83%) **268** (0%)

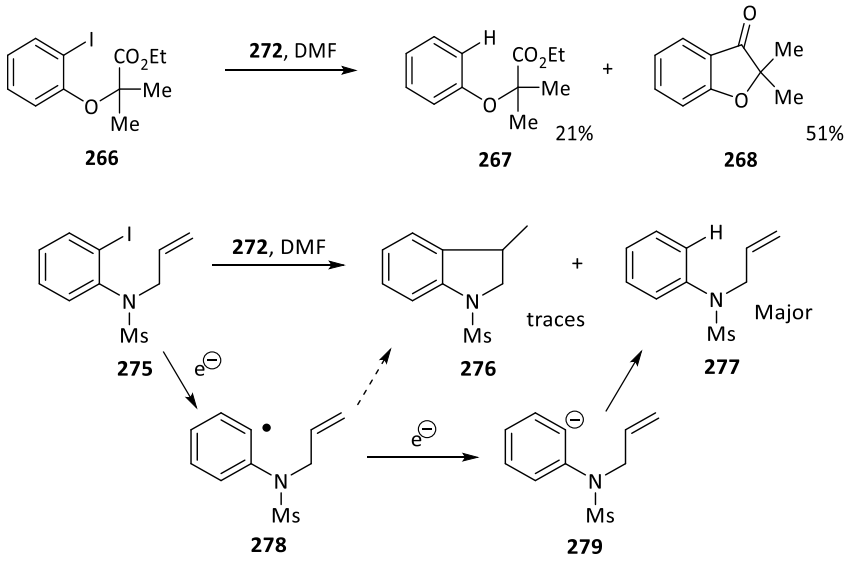
Scheme 47

Now that a neutral organic electron donor was found to be able to reduce aryl and alkyl iodides via SET, investigations turned to new donors which would be able to undergo DET and also to reduce aryl and alkyl bromides which remained too challenging substrates for **239**.[81] An imidazole-derived neutral organic super-electron-donor **272** (see Scheme 48) was reported by the Murphy group,[82] although this compound had been firstly synthesised by Chen but not investigated as an electron donor to organic molecules.[83] The first and second oxidation potential of this electron donor (-1.37 V and -1.18 V vs SCE in MeCN)[82] showed that it should be more powerful than **237** and perhaps powerful enough to undergo DET. The synthesis of **272** is based on a similar strategy to that of **239**: alkylation of two molecules of imidazole **269** with 1,3-diiodopropane **235** affording "singly-bridged" **270** followed by another alkylation with 1,3-diiodopropane **235** leading to "doubly-bridged" salt **271**. This salt then reacts with a strong base, here NaH **31**, in liquid ammonia to afford the electron donor **272**, following the same pathway as described earlier in Scheme 42. Upon oxidation, **272** gains stability by aromatisation (see Scheme 48).



Scheme 48

This electron donor was tested with aryl iodide **266** to check its reactivity (see Scheme 49).

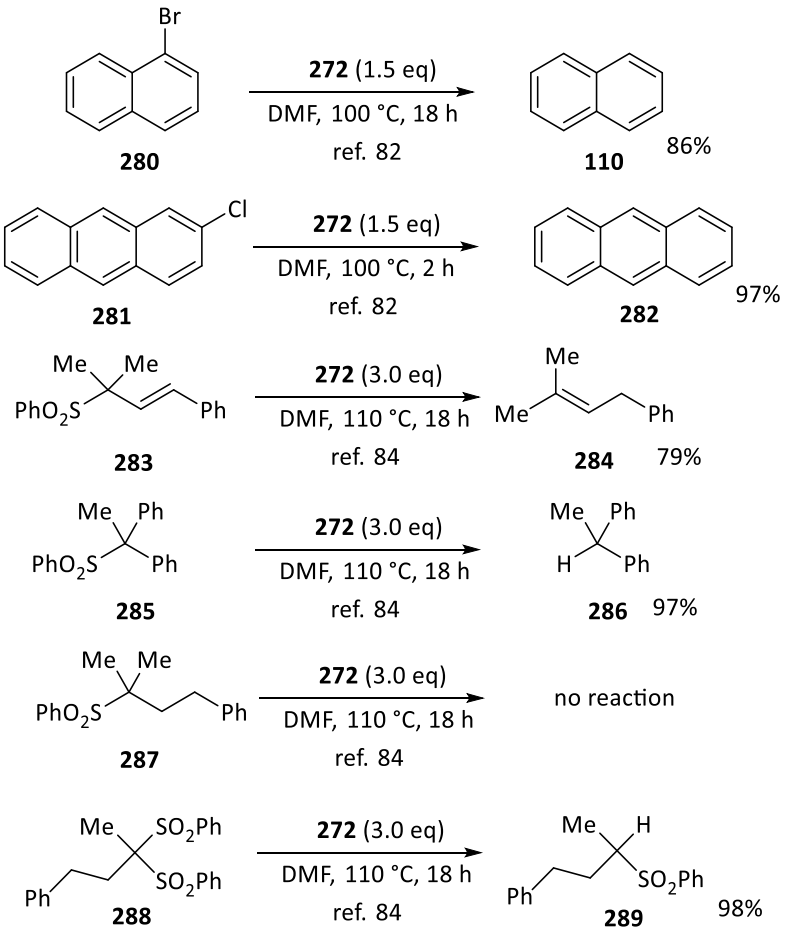


Scheme 49

The deiodination was successful but the reaction led to a mixture of uncyclized product **267** and indanone product (cyclised) **268**. The indanone formation was good evidence for the formation of an aryl anion intermediate, resulting from a DET, which would cyclise quickly onto an ester. The deiodination product **267** could arise from a hydrogen abstraction after formation of an aryl radical, resulting from SET or from a proton abstraction after formation of an aryl anion. However, substrate **275** tested under the same conditions led almost exclusively to the uncyclized product **277** which strongly suggests formation of an aryl anion as the aryl radical would have led to

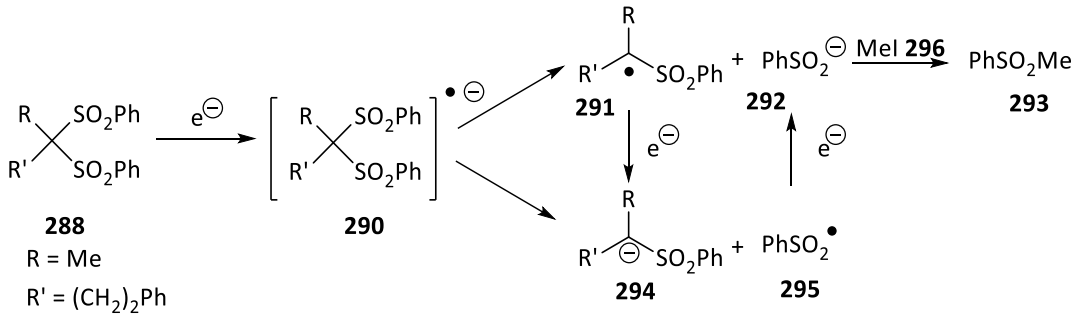
cyclisation. These results suggest that the second electron transfer forming aryl anion **279** from aryl radical **278** is a faster process than the radical cyclisation that can happen from radical **278** to form cyclised product **276**.

The "doubly bridged" electron donor **272** proved to be strong enough to undergo double electron transfer reactions to aryl iodides and it was then deployed in reductions of various aryl halides and was also found to be capable of cleaving some aryl sulfones (see Scheme 50)[84] which had been previously achieved by use of alkali metals (Birch conditions) or use of samarium (II) complexes.[85] Cleavages of sulfones **283** and **285** were successful and afforded high yields of hydrocarbons **284** and **286** after quenching with water. However, the unactivated sulfone **287** was not cleaved by action of doubly-bridged electron donor **272**, which showed that its action was limited to sufficiently activated sulfones.



Scheme 50

Interestingly, donor **272** was able to cleave geminal disulfones, such as **288**, with excellent yields, which was a particularly interesting breakthrough as these disulfones are widely used in organic chemistry.[86] The proposed mechanistic pathway (see Scheme 51) involves an electron transfer to an arenesulfonyl group leading to radical anion **290** followed by fragmentation which can afford two pairs of species: radical **291** and anion **292** or anion **294** and radical **295**; transfer of one more electron leads to the pair of anions **292** and **294**. The formation of anion **292** was confirmed by addition of an excess of iodomethane **296** at the end of the reaction which led to formation of phenyl methylsulfone **293** in high yield.

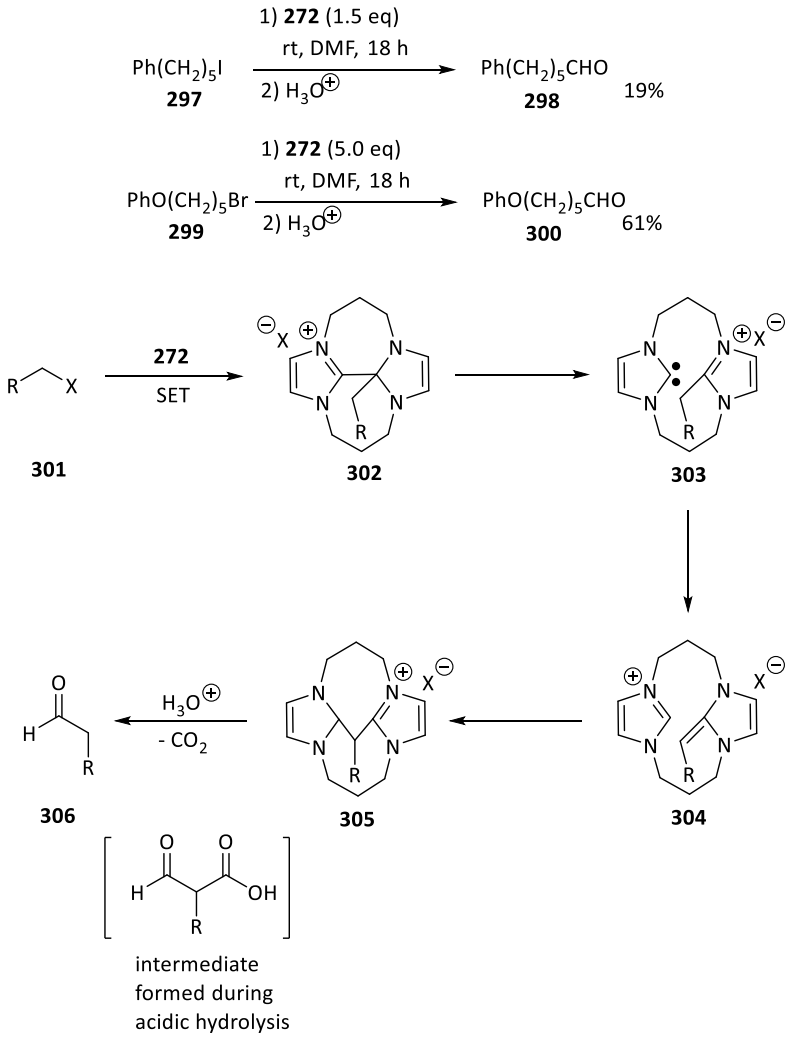


Scheme 51

The doubly-bridged neutral organic super electron donor **272** being so successful with aryl halides, investigations were conducted to check the possibility of this donor to convert alkyl halides to the corresponding alkyl anions.[87]

It is important to know that the chemistry described here that can lead to aryl and alkyl anions is different than the chemistry of Grignard reagents as they feature a polarized carbon-metal bond while the carbanions formed by organic super electron donors are naked anions thus more unstable and thus are more challenging to form. Scheme 52 shows reductions of alkyl iodide **297** and alkyl bromide **299** by donor **272** in DMF. In both cases, traces of aldehydes **298** and **300** were found. The yields of the aldehydes were increased by prolonged acidic work-up suggesting that the aldehydes were complexed by another species or that they were being liberated from a protected form. Interestingly, NMR analysis showed one extra carbon on the products compared with the alkyl halide reactants. Changing the solvent from DMF

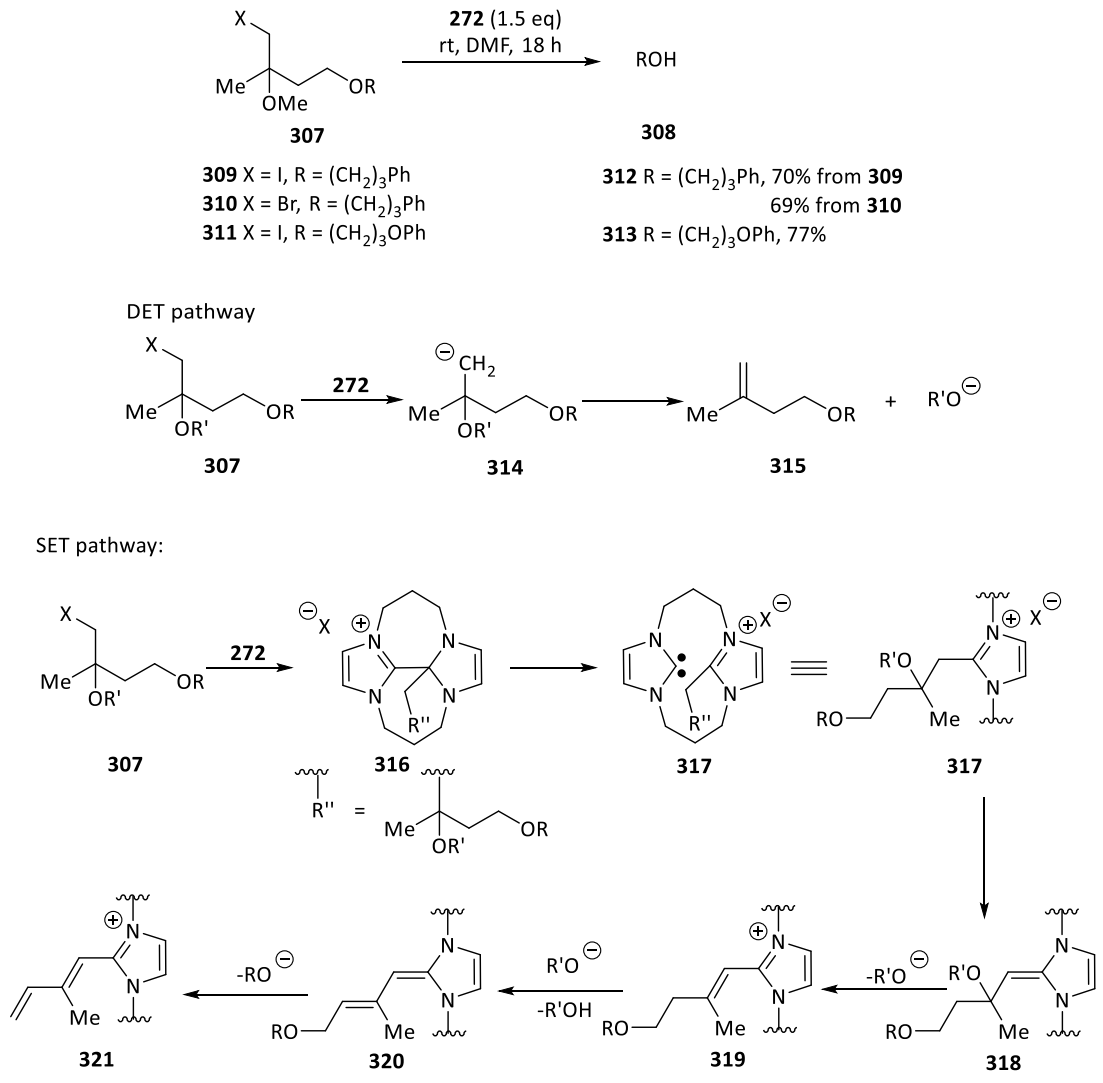
to DMA did not change the outcome of the reaction which suggested that the extra carbon was coming from the donor itself rather than from DMF (see Scheme 52 for proposed mechanism).



Scheme 52

To shine a light on the mechanistic pathway and the source of the extra carbon, some alkyl halides were designed as probes (see Scheme 53 for their reduction and mechanistic explanation with compound **307** used as a general case). There were two ways these substrates could react: by DET which would lead to formation of homoallylic ether **315** which did not react further under these conditions (checked by a blank reaction), or via a radical pathway (SET). The double electron transfer pathway can be quickly ruled out as the formation of the homoallylic ether **315**

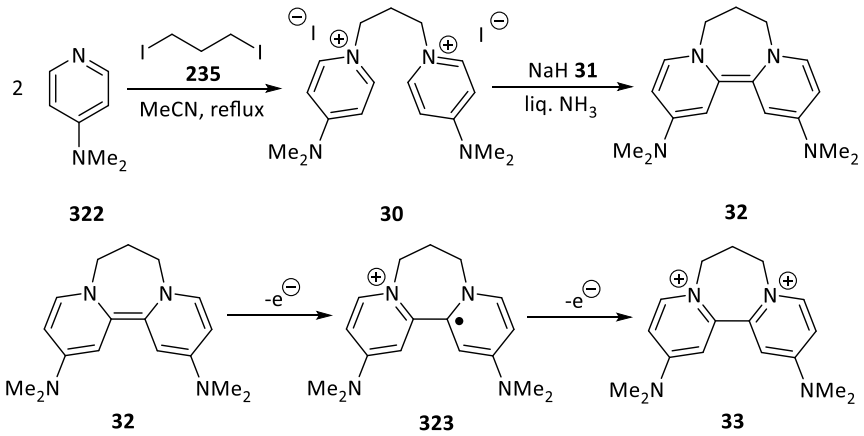
cannot allow formation of alcohol ROH which has been isolated and identified in all reactions. The single electron transfer pathway is in accordance not only with the formation of the expected alcohols but also highlights the trapping of the alkyl radical, obtained after alkyl halide **307** has received one electron, by the radical cation **273** (shown in Scheme 48 on page 40).



Scheme 53

The species **316** resulting from radical coupling can form intermediate **318** which will lead to salt **319** after loss of an alkoxide R'O$^-$. Proton transfer made by this alkoxide affords conjugated diene **320** which can expel the other alkoxide R'O$^-$, which upon protonation, will afford ROH found experimentally.

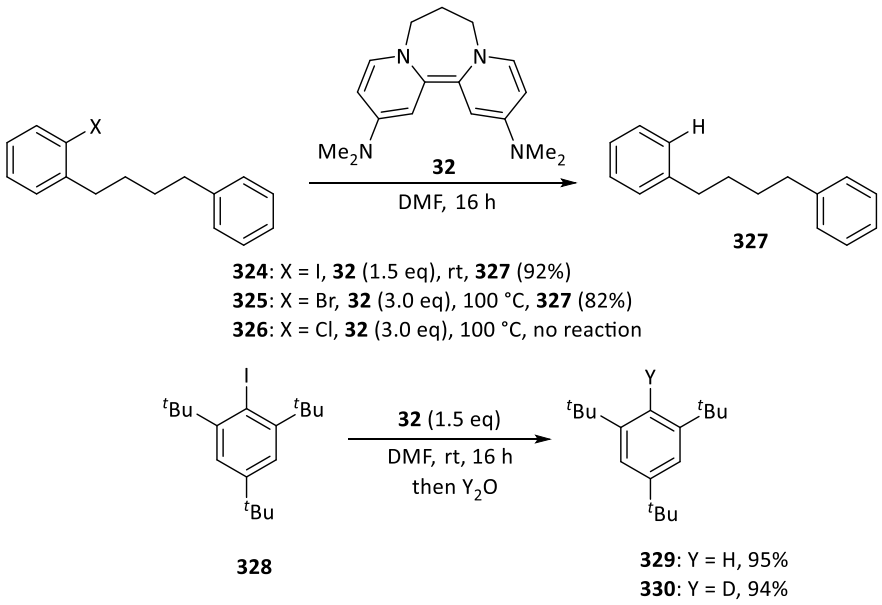
The uses and interesting outcomes of the doubly-bridged electron donor **272** are undeniable. However, it was particularly difficult to accomplish the synthesis of its precursor salt **271** as the reaction was very time-consuming and led to undesirable side-products.[88] For this reason, the Murphy group considered a more easily accessible electron donor being as strong or stronger than **272**. In 2008, Garnier *et al.* published a new neutral organic super electron donor **30** derived from 4-dimethylaminopyridine **322** (DMAP).[89] The synthesis of this donor was straightforward and was achieved in two simple steps: alkylation of two molecules of DMAP **322** with 1,3-diiodopropane **235** to get the precursor salt and deprotonation by a strong base in liquid ammonia to afford the donor **32** which was isolated as a dark purple solid (see Scheme 54). This donor **32**, usually called "DMAP donor", is similar to the two-previous organic super electron donors **239** and **272** reported earlier, in reacting by giving away electrons and gaining stability upon aromatisation (see Scheme 54). Cyclic voltammetry of DMAP donor **32** showed a single reversible two-electron peak at -1.24 V (vs SCE in DMF)[89] meaning that this donor was as strong as **272**.



Scheme 54

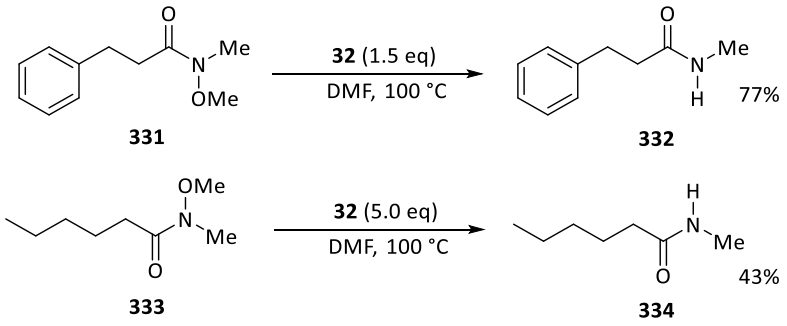
Dication **33** was initially characterized by quenching donor **32** with iodine and recording its X-ray structure.[90] The reactivity of the DMAP donor **32** was tested with several aryl halides and quickly confirmed the ability of aryl halides to receive two electrons from this donor (see Scheme 55). Reductions of aryl iodide **324** and aryl bromide **325** were easily performed by DMAP donor **32** but the aryl chloride **326**

remained a too challenging substrate, affording no reduction product. 1,3,5-Tri-*tert*-butyl-2-iodobenzene **328** was also tested twice and the reaction was quenched once with water; the other time with deuterated water (D_2O). The use of D_2O led to efficient deuterium incorporation confirming the presence of an aryl anion intermediate resulting from a double electron transfer process.



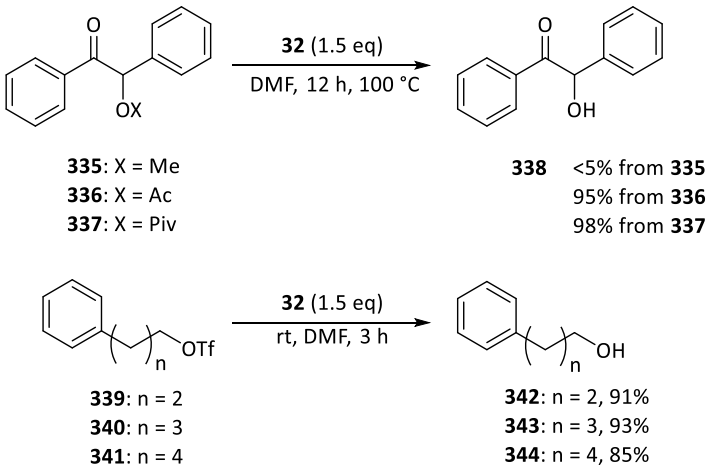
Scheme 55

Also, DMAP donor **32** was shown to follow the same pathway as described in Scheme 53, meaning that radical cation **323** can trap an alkyl radical by C-C coupling.[91] The scope of reduction reactions that could be undertaken by neutral organic super electron donors was extended to Weinreb amides to investigate the cleavage of N-O bonds (see Scheme 56).[92] The efficiency of the cleavage quickly appeared to be dependent on the structure of side-chain of the amide. While the arene-containing structure of substrate **331** led to an efficient cleavage with only 1.5 equivalents of DMAP donor **32**, the alkyl structure of substrate **333** led to a lower yield even with the use of 5.0 equivalents of DMAP donor **32**. Computational studies of substrate **331** showed that the LUMO was localized on the arene unit suggesting that an initial electron transfer would be made to the arene followed by an intramolecular electron transfer to the Weinreb amide group. In other words, arene-containing substrates could provide an enhancement of reactivity toward electron transfer.



Scheme 56

A few more substrates were found to undergo efficient reduction when reacting with DMAP donor **32**. Acyloin derivatives (C-O bond cleavage)[93] and alkyl triflates (S-O bond cleavage)[94] afforded very good results (see Scheme 57) although the acyloin derivatives required a good anionic leaving group (substrates **336** and **337**) to be cleaved efficiently.



Scheme 57

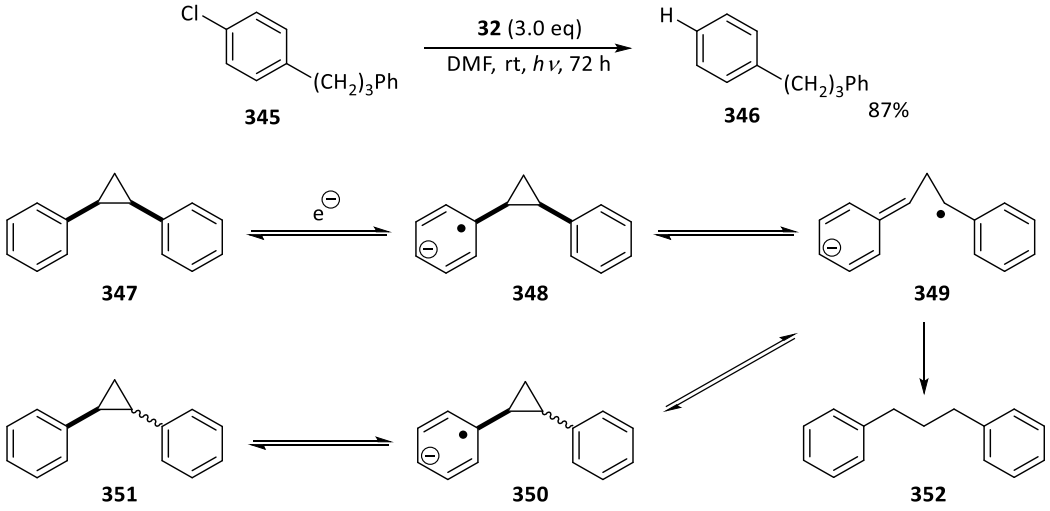
Reduction of triflates **339**-**341** led to formation of the alcohols **342**-**344**. To check that this formation of the alcohol was not due to a nucleophilic attack of the DMF solvent, ^{18}O-labeled DMF was used but led to unlabelled alcohol, meaning that there was no involvement of the oxygen from DMF. The process involved an electron transfer to the triflate group leading to S-O bond scission. The finding of DMAP donor **32** enriched the scope of substrates that neutral organic super electron donor could

reduce. A new area of investigation was opened once these donors were tested under photoactivation.

1.2.3 Photoactivated Neutral Organic Super Electron Donors

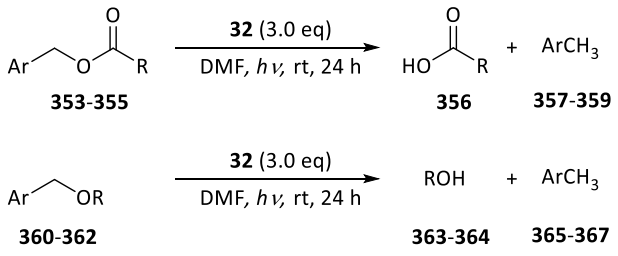
The strong colour of the three electron donors, yellow for **239** and **272** and purple for **32**, led the Murphy group to wonder if excitation by visible light or near-UV light could promote one electron of the HOMO to the LUMO of these donors, making this electron strongly reducing towards new substrates. It was already clear that aryl iodides and, under stronger conditions, aryl bromides were good substrates for reduction with these donors in the ground state, but aryl chlorides remained non-reactive substrates.

Aryl chloride **345** was tested with DMAP donor under photoactivation and afforded reduction product **346** in excellent yield (see Scheme 57).[95] Investigations were made on the Birch reduction of an arene with photoactivated DMAP donor **32**. However, as discussed earlier in this review, Birch reductions require a proton transfer (usually from *tert*-butanol **48**) and organic electron donors such as DMAP donor **32** are basic and would likely be incompatible with a proton transfer. This was the reason why *cis*-diphenylcyclopropane **347** was chosen as this particular species would afford a proper indication of reaction even if back-electron transfer occurs (see Scheme 58). Indeed, if an electron were given to **347**, this would form radical anion **348** still with a *cis*-configuration. Opening of the cyclopropane ring would afford radical anion **349** which could then undergo a reversible ring-closure reaction leading to a *cis*-/*trans*-mixture of diphenylcyclopropane radical anion **350** which would lose one electron to give a *cis*-/*trans*- mixture of diphenylcyclopropane **351**. This was the outcome of the experimental procedure, bringing proof that an electron transfers from photoactivated DMAP donor **32** to benzene rings.



Scheme 58

During experiments with a longer reaction time, the intermediate distal radical anion **349** was reductively trapped to afford 1,3-diphenylpropane **352**. The scope was then extended to benzylic ethers and esters.[96] The cleavage of benzylic esters afforded very good yields of corresponding carboxylic acids (see Scheme 59 and Table 11) but almost no products derived from the benzylic portion of the substrates were found. It was proposed that the benzylic radical resulting from the cleavage of the C-O bond was trapped by a radical cation (such as **323** when DMAP donor **32** was used (as represented in Scheme 45 on page 45)). The cleavage of benzylic ethers was also successful although the yields of the recovered alcohols were a bit lower but, interestingly, more products derived from the benzylic portion of the substrate were recovered.



Scheme 59

Entry	Benzyl Ester	Ar	R	Carboxylic Acid (%)	$ArCH_3$ (%)
1	**353**	2-(MeO)C_6H_4	^{t}Bu	**356** (90)	**357** (0)
2	**354**	4-(MeO)C_6H_4	^{t}Bu	**356** (83)	**358** (0)
3	**355**	4-(CF_3)C_6H_4	^{t}Bu	**356** (88)	**359** (trace)
Entry	**Benzyl Ether**	**Ar**	**R'**	**Alcohol (%)**	**$ArCH_3$ (%)**
4	**360**	2-(MeO)C_6H_4	$C_{10}H_{21}$	**363** (71)	**365** (20)
5	**361**	3,5-$(MeO)_2C_6H_3$	$C_{10}H_{21}$	**364** (60)	**366** (27)
6	**362**	3,4,5-$(MeO)_3C_6H_2$	$C_{11}H_{23}$	**365** (51)	**367** (20)

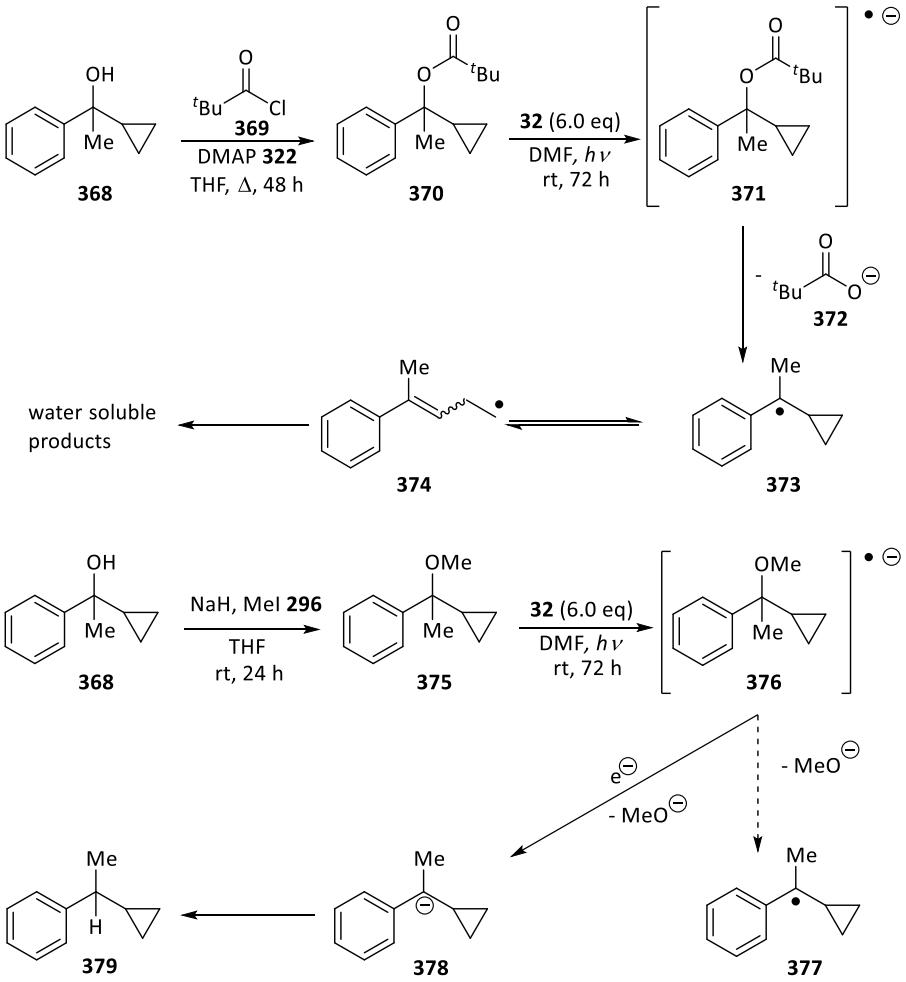
Table 11: Reductive cleavage of benzylic esters and ethers.

This raised the question of whether the reaction pathway involved in the reduction of benzylic ethers was a DET while the pathway involved in the reduction of benzylic esters was a SET.

To identify the process involved in the reduction of both benzylic esters and ethers, two compounds: benzylic ester **370** and benzylic ether **375** were synthesised from alcohol **368** and treated with DMAP donor **32** under photoactivation under the same conditions (see Scheme 60).

On one hand, the reaction of ester **370** with DMAP donor **32** should lead to radical anion **371** which will cleave to release pivalate **372** and radical **373** which should lead to a cyclopropane ring opening to afford radical **374**. In theory, both radicals **373** and **374** should be trapped by radical cation **323** leading to water-soluble products which would then not be found in the organic phase after work-up. On the other hand, the reaction of ether **375** with DMAP donor **32** would form radical anion **376** and then, either it would cleave to release methoxide and radical **377** which would be trapped by radical cation **323**, or radical anion **376** would undergo a concerted pathway where it would receive a second electron and release methoxide to form carbanion **378** which would protonate during work-up and afford cyclopropane **379**.

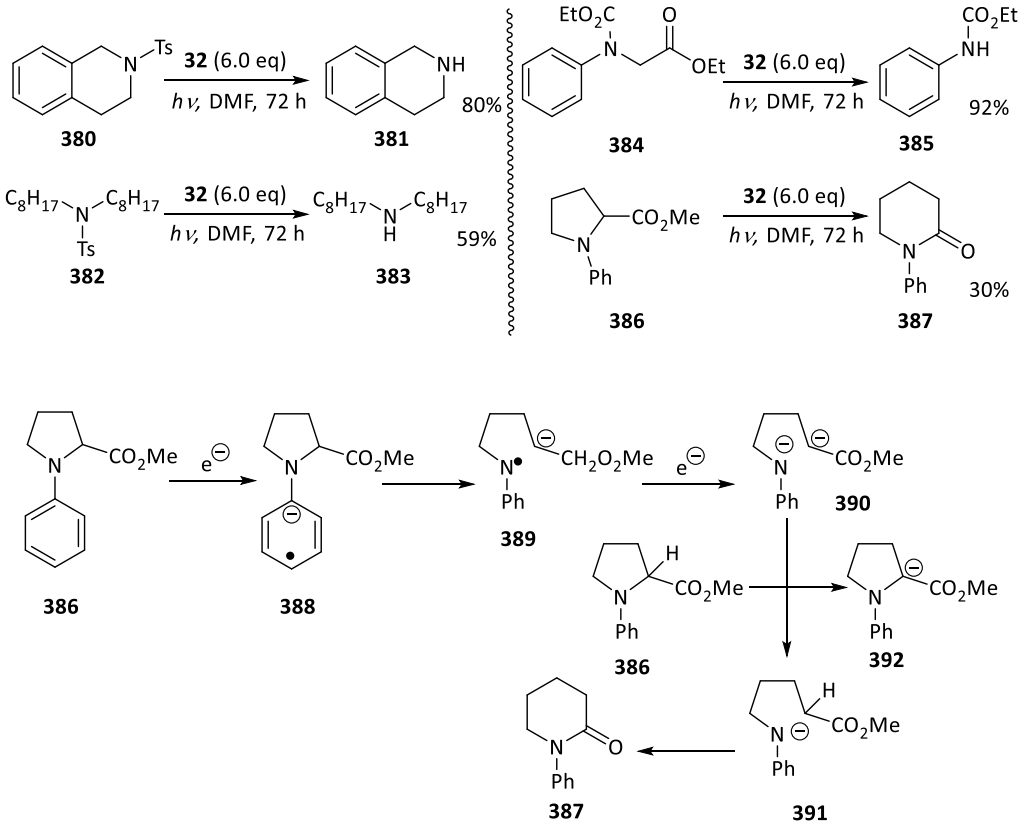
The outcome of the experimental reactions was in accordance with a SET for the reduction of ester **370**, as only pivalic acid (85%) was recovered, and a DET for the reduction of ether **375** as cyclopropane **379** (29%) was isolated together with some unreacted ether **375** (45%).



Scheme 60

Several other substrates were found to be reduced by DMAP donor **32** under photoactivation.[97] *N*,*N*-dialkylaresulfonamides were untouched by ground-state electron donors but then were found to be effectively reduced by photoactivated DMAP donor **32** (see Scheme 61). The cleavage of the benzylic C-N bond in various substrates was also investigated. It was particularly interesting to observe transformation of *N*-phenylproline **386** to *N*-phenylpyridone **387** even if the yield was lower (30%). It was proposed that initial reduction of **386** would form radical anion

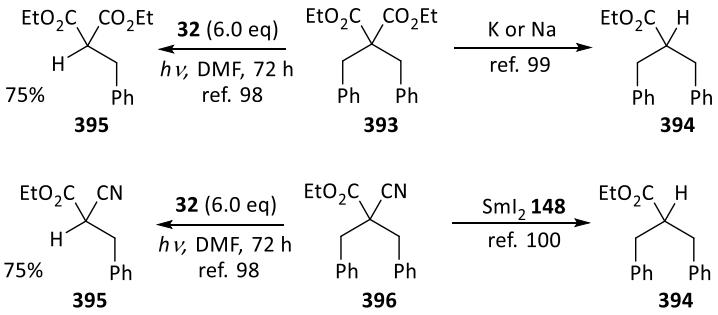
388 which, after fragmentation, would lead to **389**, which could receive another electron from **30**, affording dianion **390**. Cyclisation could occur with **391**, formed after proton transfer from another molecule of **386** (which would then be not be reduced by **30**). This proposed pathway explains why the yield is "only" 30% as only half of the molecules of **386** can undergo reduction.



Scheme 61

The use of DMAP donor under photoactivation went even further, as it led to cleavage of benzyl C-C bonds of C-benzyl malonates and C-benzyl cyanoacetates (see Scheme 62).[98] Interestingly, the reactivity was different than what was already known for the reduction of cyanoacetates by alkali metals[99] and the reduction of malonates by samarium diiodide **148**.[100] The reason for the difference of reactivity can be explained by the absence of metal cations with organic electron donors; therefore, no complexation of a metal species with the substrate is possible under these conditions which should alter reactivity. Also, the extended π-systems of the

donors make them more likely to associate by π-stacking with the arene unit of the substrates, resulting in an initial electron transfer to the arene.



Scheme 62

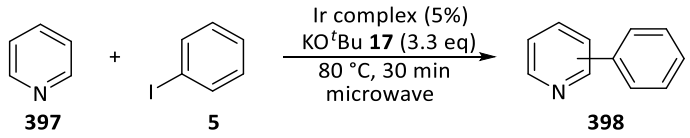
Purely organic species can be used as electron donors and therefore undertake challenging reductions at ground-state and/or under photoactivation usually requiring use of metals. The next part of Chapter 1 will still focus on metal-free conditions but on a particular type of reaction that emerged recently, transition metal-free cross-coupling reactions.

1.3 Transition Metal-Free Cross-Coupling Reactions

Palladium-catalysed cross-coupling reactions have been extensively used in organic chemistry since their discovery by Mizoroki[101] and Heck.[102] A wide variety of chemical species were used as candidate substrates for these reactions: organoborons,[103] organosilicons,[104] organostannanes,[105] organozincs[106] and terminal alkynes.[107] The use of these palladium-catalysed reactions has been of tremendous importance in industry. However, their use requires extensive purification of synthesised drugs to remove any toxic palladium complexes. Very recently, the beginning of a metal-free alternative has emerged for cross-coupling reactions which led to an explosion of interest, as this alternative requires only the use of organic species alongside a strong base.

1.3.1 Early Findings in Transition Metal-Free Cross-Coupling Reactions

The first report of a confirmed transition metal-free cross-coupling reaction was made by Itami *et al.*[108] They initially examined Fujita's iridium-based protocol[109] for the coupling of pyridine **397** with iodobenzene **5**. A variety of iridium complexes were tested but all afforded similar yields of the coupling product **398** (see Scheme 63 and Table 12). The same reaction was carried out in the absence of iridium, and thus only in the presence of base (here potassium *tert*-butoxide **17**) and also afforded the coupling product **398** in similar yield.



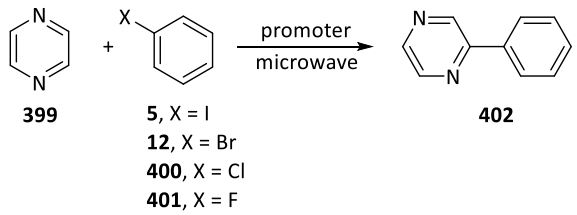
Scheme 63

Entry	Ir complex	Yield (%)
1	$[Cp^*IrCl_2]_2$	32
2	$IrCl(CO)(PPh_3)_2$	41
3	none	39

Table 12: Evidence of a transition metal-free cross-coupling reaction.

When investigating the scope of the reaction, using pyrazine **399** as solvent instead of pyridine **397**, Itami *et al.* found that various aryl iodides were good substrates for this cross-coupling reaction as well as bromobenzene **12**, although it required a higher temperature, but chlorobenzene **400** and fluorobenzene **401** remained unreactive substrates (see Scheme 64 and Table 13). Other organic bases were used such as sodium *tert*-butoxide **403** (NaO^{t}Bu) and lithium *tert*-butoxide **404** (LiO^{t}Bu) but they did not afford the product under these standard conditions used by Itami (50 °C, 5 min). However, NaO^{t}Bu **403** afforded the coupling product when the reaction was run at more than 80 °C. The use of radical scavengers in the reaction stopped the

reaction from happening, leading Itami to suggest that the reaction was going through a radical pathway.



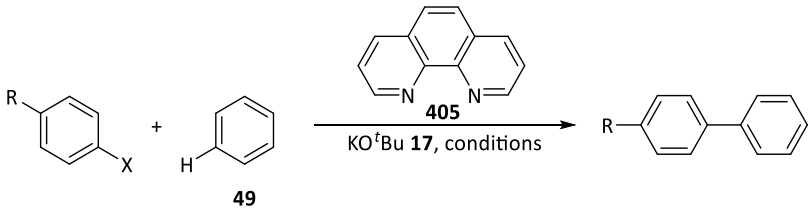
Scheme 64

Entry	X	Promoter	Conditions	Yield (%)
1	I	KO^{t}Bu **17**	50 °C, 5 min	98
2	Br	KO^{t}Bu **17**	80 °C, 30 min	54
3	Cl	KO^{t}Bu **17**	80 °C, 30 min	<1
4	F	KO^{t}Bu **17**	80 °C, 30 min	<1
5	I	NaO^{t}Bu **403**	50 °C, 5 min	<1
6	I	LiO^{t}Bu **404**	50 °C, 5 min	<1
7	I	KO^{t}Bu **17**	TEMPO (1.5 eq), 50 °C, 5 min	<1

Table 13: Scope of transition metal-free cross-coupling of halobenzenes to pyrazine **399**.

In 2010, Shi and co-workers investigated the cross-coupling reaction of aryl halides with benzene **49** using cobalt salts as catalyst and various ligand-type organic compounds.[110] Similarly to Itami's work, they found that the use of the cobalt catalyst was not necessary to form the coupling product. The organic ligands used were based on 1,10-phenanthroline **405** which was chosen as an additive in the substrate scope (see Scheme 65 and Table 14). It is important to clarify the term that should be used when talking about the amount of 1,10-phenanthroline **405** in this reaction as its amount (20% or 40% in Shi's work) was called "catalytic" (a term that has been used

many times, and still is, in the literature when talking about the amount of the organic additive). However, the organic additive is not recovered at the end of the reaction which is why it is more relevant to talk about a "substoichiometric" amount, as the organic additive is not a catalyst.

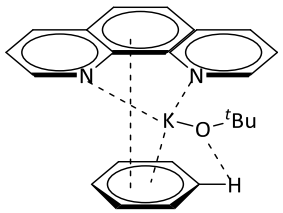


Scheme 65

Entry	Substrate	XX (%)	Conditions	Product (%)
1	R = H, X = I **5**	20	100 °C, 24 h	**18** (83)
2	R = H, X = Br **12**	40	100 °C, 18 h	**18** (74)
3	R = OMe, X = I **8**	20	100 °C, 24 h	**21** (83)
4	R = OMe, X = Br **15**	40	100 °C, 18 h	**21** (86)
5	R = Me, X = I **11**	20	100 °C, 24 h	**24** (69)
6	R = Me, X = Br **16**	40	100 °C, 18 h	**24** (89)

Table 14: Cross-coupling of aryl iodides/bromides with benzene in presence of 1,10-phenanthroline **405**.

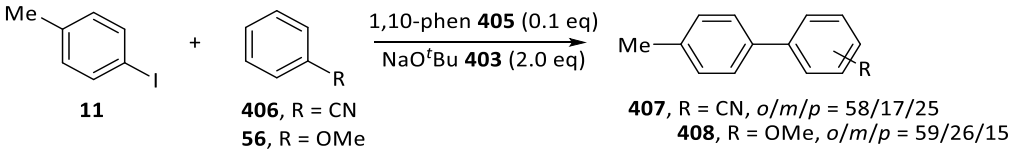
Shi and co-workers proposed an interaction between 1,10-phenanthroline **405**, KO^{t}Bu **17** and benzene **49** (see Scheme 66).



Scheme 66

The interaction was thought to be made by π,π-stacking and ion-π interaction between phenanthroline **405**, benzene **49** and a potassium ion.

Hayashi and co-workers were working at the same time on arylation of benzene with aryl halides promoted by 1,10-phenanthroline and derivatives in the presence of sodium *tert*-butoxide **403**.[111] When using a substituted benzene, they observed formation of a mixture of regioisomers, with a preference for the *ortho* position (see Scheme 67), which suggested that the reaction was going through a homolytic aromatic substitution (HAS) process.[112]



11

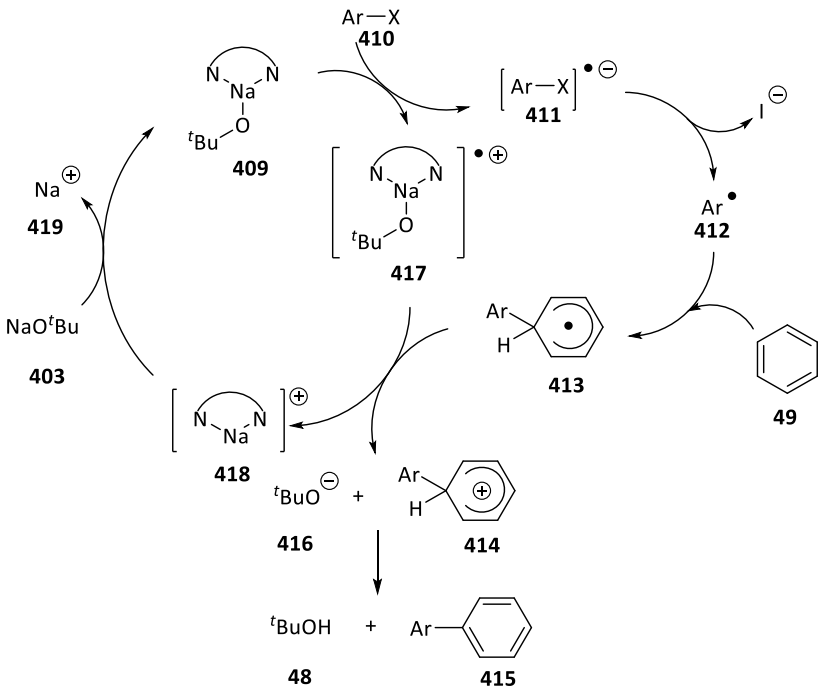
406, R = CN
56, R = OMe

407, R = CN, *o*/*m*/*p* = 58/17/25
408, R = OMe, *o*/*m*/*p* = 59/26/15

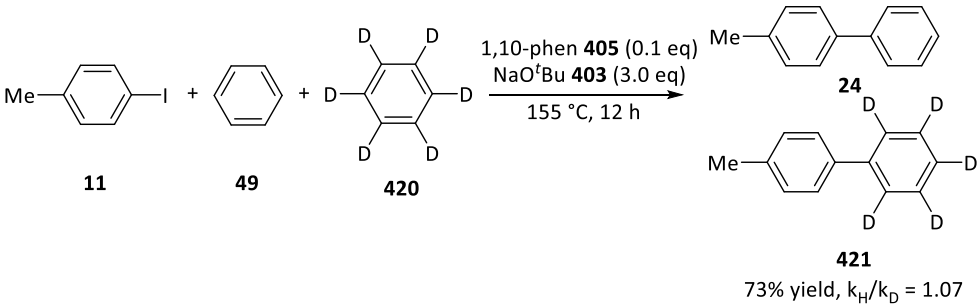
Scheme 67

It was reported that metal *tert*-butoxides could act as single electron donors[113] thus, Hayashi and co-workers proposed a mechanism for the metal-free cross-coupling reaction of aryl halides with arenes (see Scheme 68) in which they proposed that a sodium *tert*-butoxide/1,10-phenanthroline complex **409** would give one electron to an aryl halide **410**. It was already known that aryl halide can receive an electron and the resulting radical anion **411** would release a halide and an aryl radical **412**.[114] This aryl radical could couple with an arene, here benzene **49**, leading to aryl cyclohexadienyl radical **413**. Hayashi proposed that this radical **413** would lose one electron to the radical cation **417** which resulted from the initial electron transfer of **409** to aryl halide **410**. This would result in formation of cation **414** which would afford biaryl product **415** after deprotonation by *tert*-butoxide **416**. The cation complex **418** would then react with another molecule of sodium *tert*-butoxide **403** to regenerate complex **409** and start a new reaction cycle.

To identify the rate-determining step, Hayashi ran the reaction of 4-iodotoluene **11** with 1,10-phenanthroline **405** and NaO^{t}Bu **403** in a mixture of benzene **49** and benzene-d_6 **420** (see Scheme 69) and observed a low "K_H/K_D" value (but presumably this should have been written as k_H/k_D).



Scheme 68

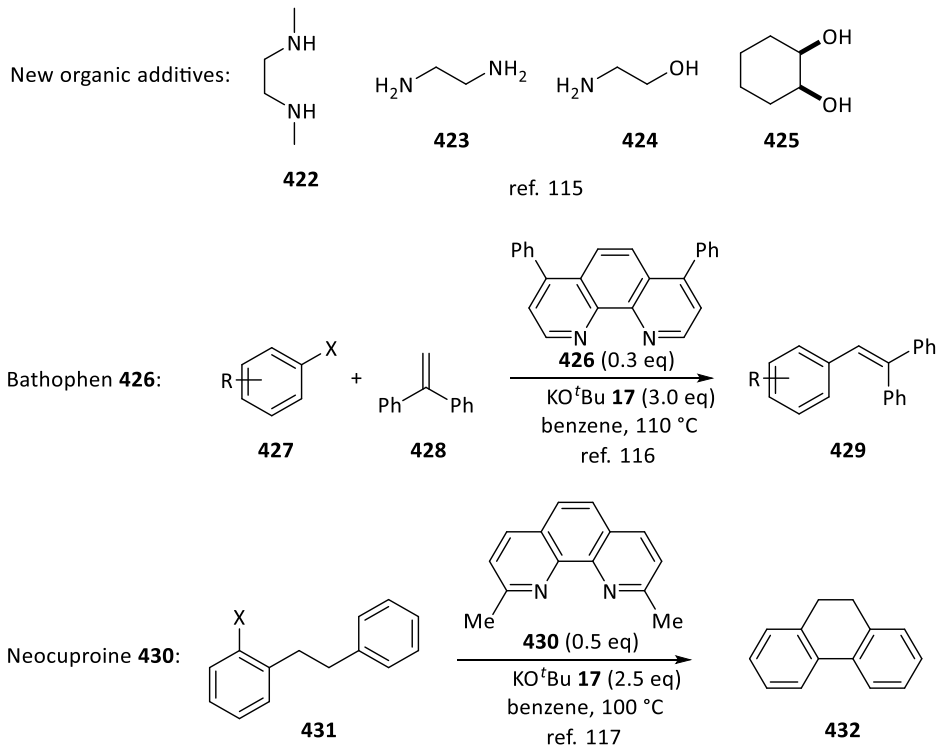


Scheme 69

The small ratio showed that the deprotonation by *tert*-butoxide **416** to form by-product **415** from biaryl cation **414** was not the rate-determining step. Hayashi proposed that the oxidation of biaryl radical **413** to biaryl cation **414** was then the rate-determining step of the process.

In the following years, Lei and co-workers tested several other organic additives that could be used instead of 1,10-phenanthroline **405** in transition metal-free cross-coupling reactions.[115] In particular, they found that *N*,*N*'-dimethylethylenediamine **422** (DMEDA), ethane-1,2-diamine **423**, 2-aminoethan-1-ol **424** and *cis*-cyclohexane-1,2-diol **425** were good organic additives (see Scheme 70). Shi and co-workers found

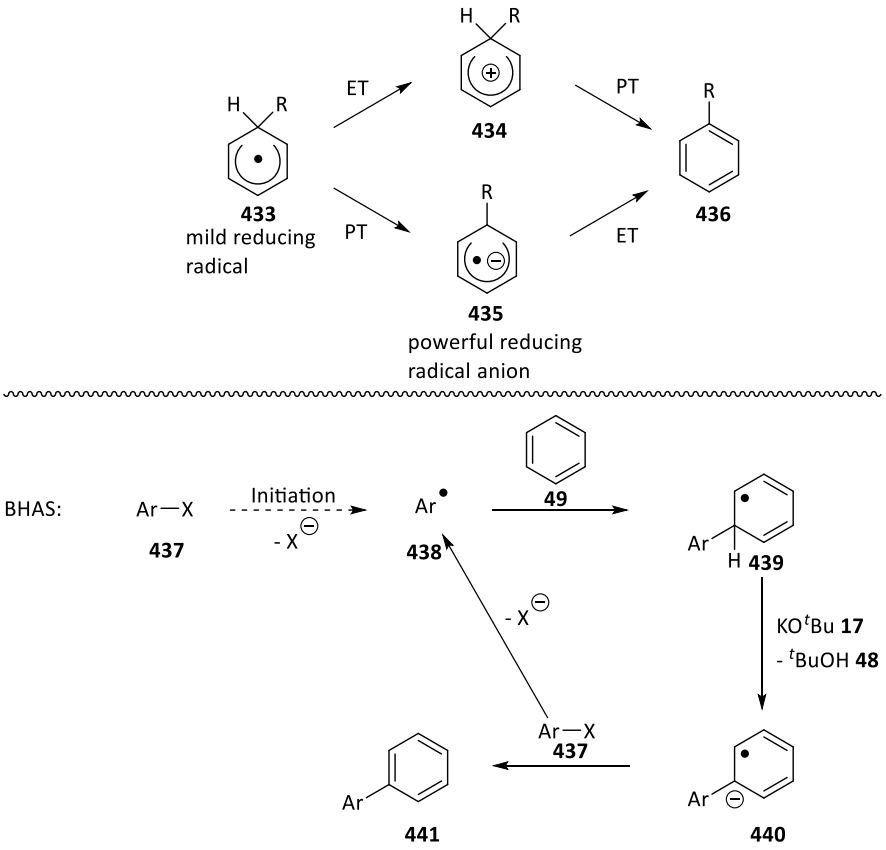
that bathophen **426** was a good additive in the arylation of alkenes with aryl iodides and bromides[116] and that neocuproine **430** could be used to promote intramolecular cross coupling reactions (see Scheme 70).[117]



Scheme 70

In 2011, Studer and Curran published another proposal for the mechanistic pathway involved in these metal-free cross-coupling reactions.[118] The main difference in their proposal, compared with Hayashi's proposal,[111] was about the reactions that happen on the cyclohexadienyl **433** (see Scheme 71). Hayashi's proposal suggested that the cyclohexadienyl radical **433** would undergo an electron transfer followed by a proton transfer while the reverse process would be first a deprotonation, affording radical anion **435**,[119] then an electron transfer. The latter possibility was proposed by Studer and Curran, as the reactions require the use of a strong base (usually KO^{t}Bu **17**) which could deprotonate the cyclohexadienyl radical **433**, form radical anion **435**, which should be a much better reducing agent than the cyclohexadienyl **433** itself. This led Studer and Curran to rewrite the mechanism of transition metal-free cross-coupling

reactions by an established mechanism called "base-promoted homolytic aromatic substitution" or "BHAS" (see Scheme 71).

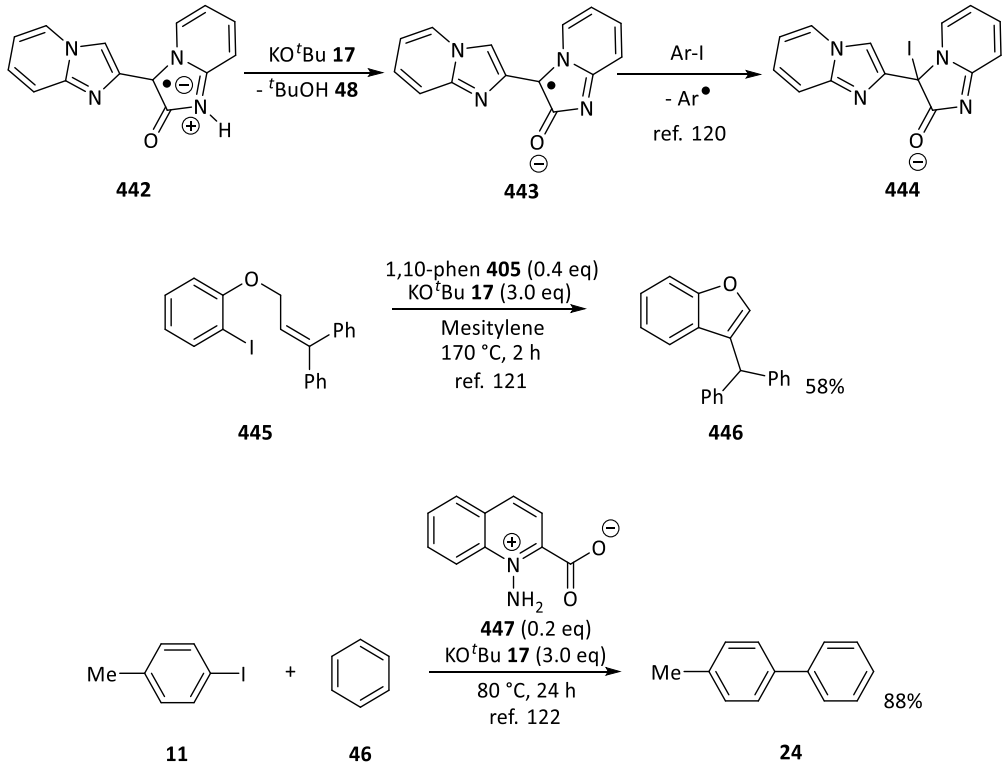


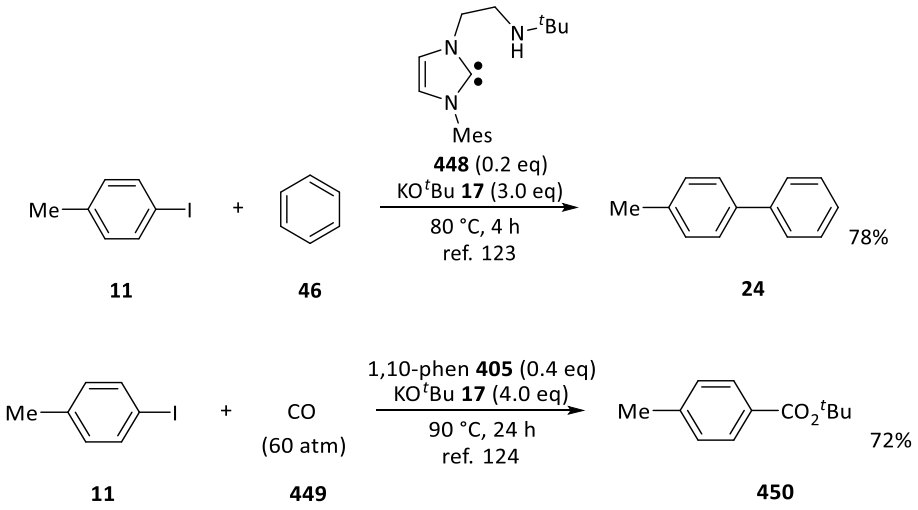
Scheme 71

This mechanism proposed that the aryl radical **438** formed after the initiation step, which is an important matter that will be discussed later, would couple with an arene, here benzene **49**. The resulting radical **439** will be deprotonated by KO^{t}Bu **17** to form biaryl radical anion **440** which will give away one electron to another molecule of aryl halide **437** resulting in formation of both the coupling product **441** and another aryl radical **438** which can then restart a reaction cycle. There are two interesting parts here, firstly, the initiation, for which Studer and Curran agreed that the proposal made by Hayashi of a complex between an organic additive such as 1,10-phenanthroline **405** and the base could be a possibility although it should be an endothermic process; secondly, the propagation of the reaction made by biaryl

radical anion **440**, which means that the reaction can efficiently run by itself once it has been initiated.

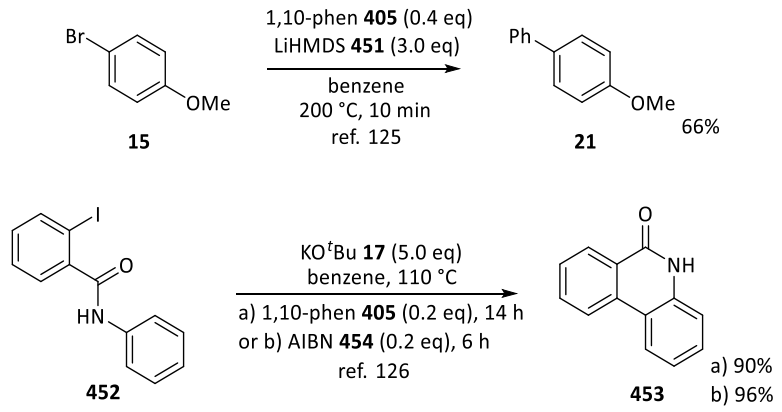
Before focusing on the initiation step of the reaction, and there is a lot to say about it, it is worth mentioning other organic additives and other reactions that have been reported in the literature (see Scheme 72). Li and co-workers used a stable zwitterionic radical **442** to couple aryl halides to benzene (although the structure reported is incompatible with reality), [120] Rueping and co-workers used 1,10-phenanthroline **405** and KO^{t}Bu **17** to perform Heck-type reactions,[121] Jiang *et al.* reported quinoline-1-amino-2-carboxylic acid **447** as an additive that can be used to promote the coupling of aryl halides with arenes,[122] Chen and Ong used amino-linked nitrogen heterocyclic carbenes such as **448**, [123] Lei and co-workers performed alkoxycarbonylation of aryl halides promoted by 1,10-phenanthroline **405** and KO^{t}Bu **17**.[124]

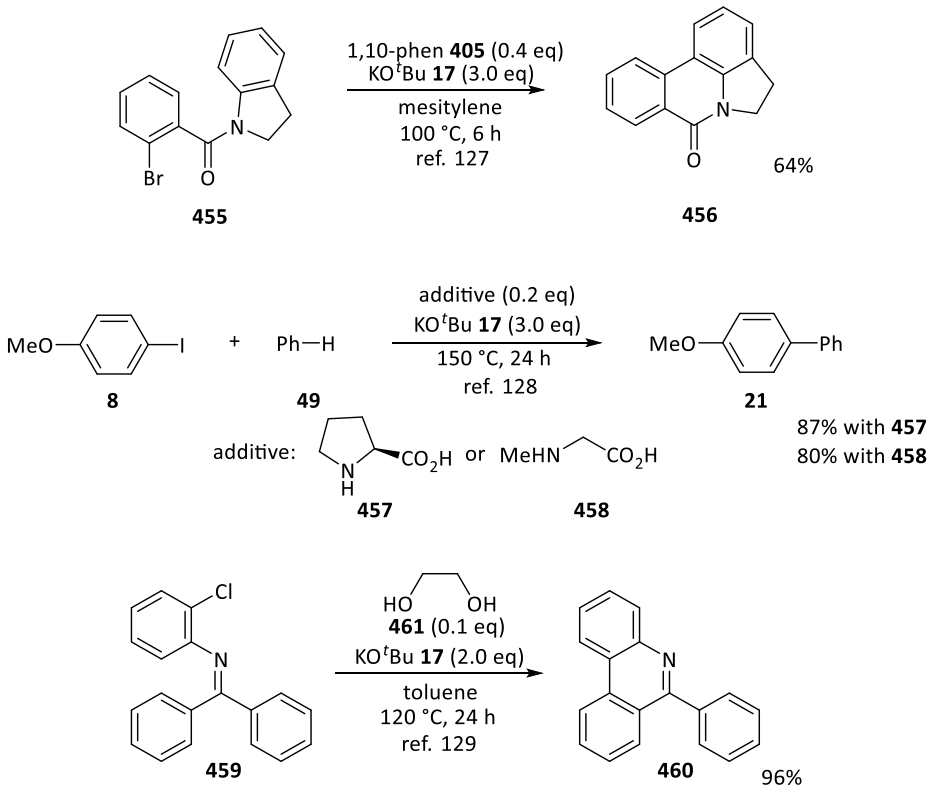




Scheme 72

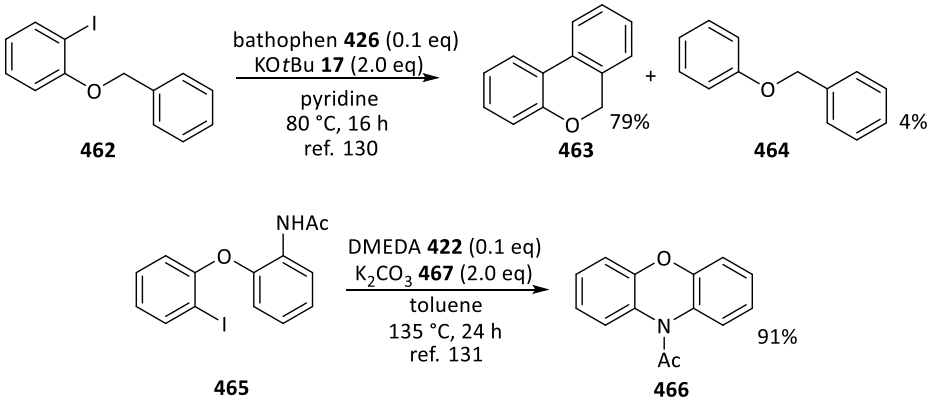
Kappe *et al.* found an efficient coupling reaction of 4-bromoanisole **15** with benzene using 1,10-phenanthroline **405** and lithium bis(trimethylsilyl)amide **451** (LiHMDS), instead of KO^{t}Bu **17**, at high temperature;[125] Kumar and co-workers used 1,10-phenanthroline **405** and azobisisobutyronitrile **454** (AIBN) to synthesise phenanthridinone **453** via cyclisation;[126] Bisai *et al.* used 1,10-phenanthroline **405** and KO^{t}Bu **17** to perform intramolecular dehydrohalide coupling reactions and applied these reactions to the synthesis of natural products,[127] Tanimori and co-workers found that several amino acids, in particular proline **457** and sarcosine **458**, were efficient organic additives in the BHAS of unactivated aryl halides with arenes;[128] Kwong *et al.* used ethane-1,2-diol **461** with KO^{t}Bu **17** for intramolecular C-H bond arylation of aryl chlorides (see Scheme 73).[129]

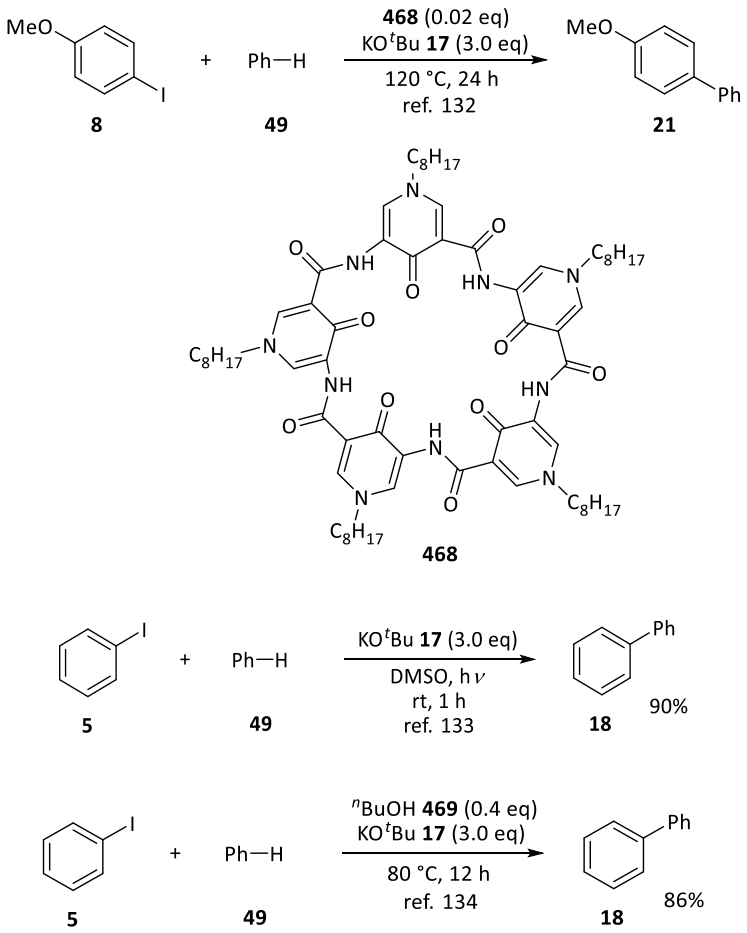




Scheme 73

Charette *et al.* used bathophen **426** and KO^{t}Bu **17** to perform intramolecular arylation,[130] Bolm and Thomé used DMEDA **422** with potassium carbonate **467** in intramolecular *N*-arylations;[131] Zeng and co-workers used a macrocyclic aromatic pyridone pentamer **468** as additive in arylation of unactivated arenes;[132] Rossi *et al.* used KO^{t}Bu **17** in DMSO under photoactivation to promote homolytic aromatic substitutions;[133] Liu *et al.* used simple alcohols alongside KO^{t}Bu **17** to promote the coupling of aryl halides with benzene (see Scheme 74).[134]



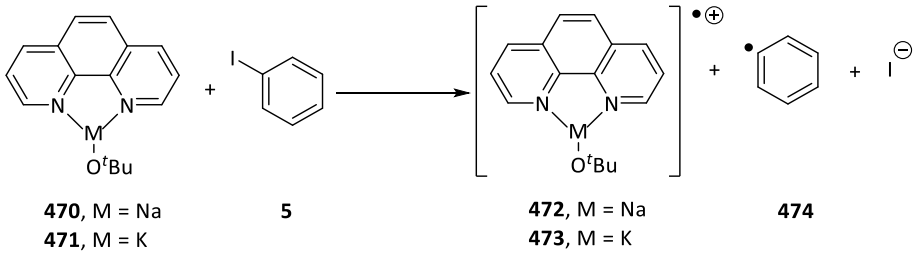


Scheme 74

Many applications were quickly found for the use of the BHAS reaction and with them, many organic additives were reported as we just saw. However, one question remained about the initiation process required to start the mechanistic pathway, proposed by Studer and Curran.[118] Although the proposal, made by Hayashi, of an electron being transferred from a complex formed between the base and the organic additive,[111] was suggested, there was no proper evidence for such an interaction. This initiation process has been of major interest to the Murphy group and is still the topic of debate in transition metal-free cross-coupling reactions.

1.3.2 Investigations of the Initiation Process in Transition Metal-Free Cross Coupling Reactions

The initiation step of the BHAS mechanism became a field of investigation for the Murphy group since the calculation of the thermodynamics of an electron transfer from a complex between 1,10-phenanthroline **405** and NaO^{t}Bu **403** or KO^{t}Bu **17** to iodobenzene **5** were made (see Scheme 75).[135] The free energy difference found for the sodium case was ΔG_{rel} = 63.9 kcal/mol and, for the potassium case, ΔG_{rel} = 59.5 kcal/mol. These values were sufficiently endergonic to suggest that a different process was involved.



470, M = Na
471, M = K

5

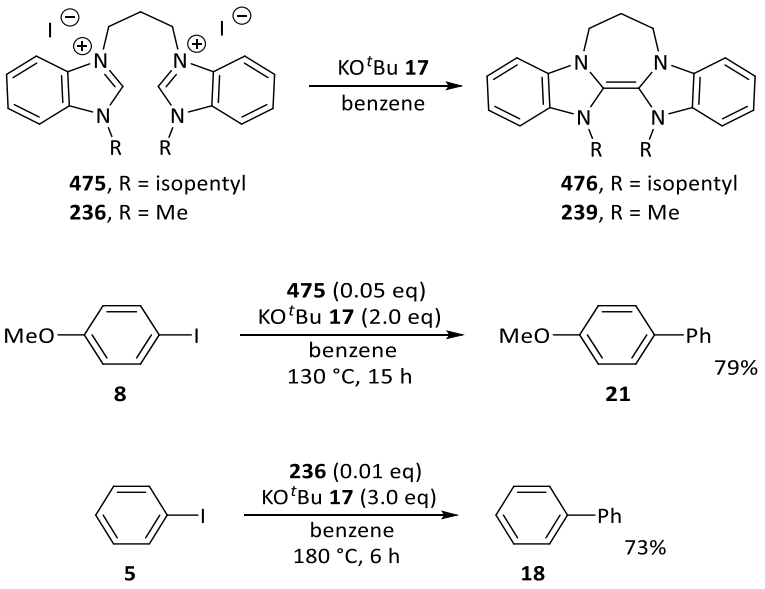
472, M = Na
473, M = K

474

Scheme 75

It was questioned whether organic electron donors, such as **239**, could trigger these BHAS reactions. The reaction of salt **475** (similar to salt **236** but with *N*-isopentyl rather than *N*-methyl substituents as the solubility of the resulting donor **476** in benzene was greater) with KO^{t}Bu **17** afforded a vibrant yellow colour, a sign that the donor **476** was formed by action of potassium *tert*-butoxide **17** (see Scheme 76). The reaction of 4-iodoanisole **8** with salt **475** (5%) and KO^{t}Bu **17** (2.0 eq) in benzene afforded the expected coupling product **21** in good yield.

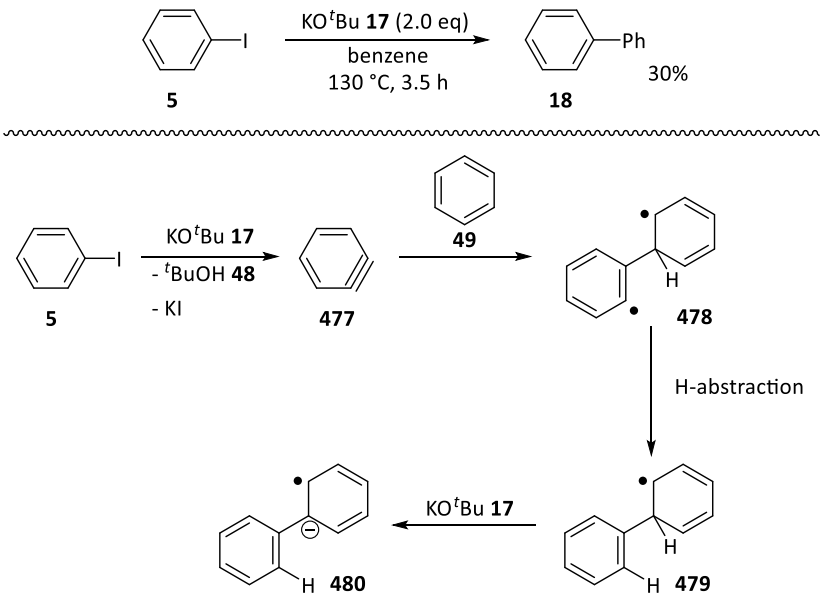
Since salt **475** could be used in a small amount, even the *N*-methyl salt **236** was effectively used alongside KO^{t}Bu **17** in the reaction of iodobenzene **5** in benzene. Interestingly, even 1% of salt **236** was enough to get a good yield of biphenyl **18**, which was in accordance with the mechanism proposed by Studer and Curran. Aryl bromides did not lead to efficient coupling reactions which was as expected, as the *N*-methyl benzimidazole donor **239** did not reduce aryl bromides efficiently.



Scheme 76

Investigations were then turned toward "additives-free" initiation, meaning an initiation in which only the base would be involved. According to the relative energies found through computation, by the Murphy group, for the electron transfer from a complex between 1,10-phenanthroline **405** and metal *tert*-butoxide, *tert*-butoxide **416** cannot be the direct electron donor. However, it was reported that *tert*-butoxide **416** can convert iodobenzene **5** to benzyne **477** (see Scheme 77).[136] Benzynes, known to act as diradical species[137] can react with benzene **49** to form biphenyl **18**,[138] and reaction of benzyne **477** with (*Z*)-alkenes to form benzocyclobutanes proceeds through a diradical intermediate[139-140] and the same was reported for addition of benzyne **477** to thiones.[141-142] It would be possible for benzyne **477**, formed from reaction of KO^{t}Bu **17** with iodobenzene **5**, to couple with benzene **49** and form biradical **478** which could abstract a hydrogen from benzene used as solvent and generate radical **479** which would then form biphenyl radical anion **480** by deprotonation with KO^{t}Bu **17**. According to Studer and Curran's proposal, this biphenyl radical anion would be an excellent electron donor and could undertake the BHAS reaction as soon as it is formed by giving an electron to another iodobenzene **5**, and form biphenyl **18** in the process. In other words, in the absence of an organic additive, a benzyne formation followed by coupling with benzene, H-abstraction and

deprotonation is the overall initiation process. Indeed, blank reaction of iodobenzene **5** with KO^{t}Bu **17** in benzene at 130 °C afforded biphenyl **18** although in a lower yield than when an organic additive is used (see Scheme 77).

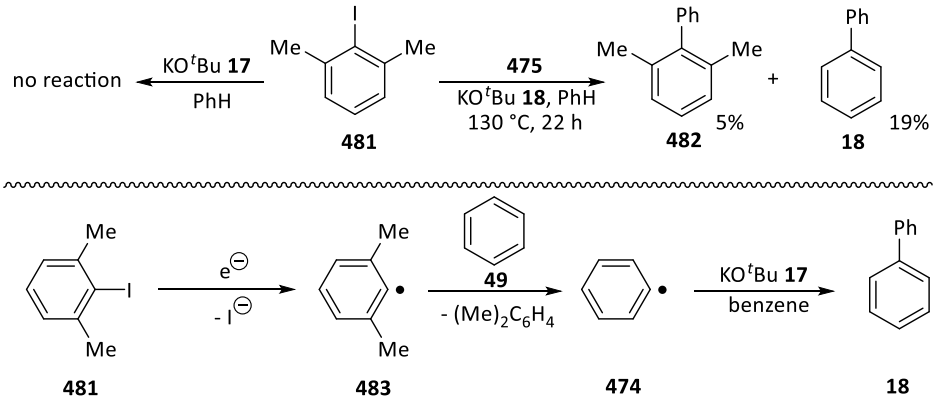


Scheme 77

Interest then turned on substrates incompatible with benzyne formation. 2,6-Dimethyliodobenzene **481** was chosen as a candidate. Both of its *ortho* positions are blocked, and thus no benzyne can be formed by action of KO^{t}Bu **17**. When treating **481** with KO^{t}Bu **17** in benzene, no reaction was observed (see Scheme 78). This ruled out the possibility of KO^{t}Bu **17** alone acting as an electron donor.

2,6-Dimethyliodobenzene **481** was also tested with *N*-isopentyl benzimidazolium salt **475** under the same conditions and this time, an inseparable mixture of biphenyl **18** (19%) and 2,6-dimethylbiphenyl **482** (5%) was formed. While the formation of 2,6-dimethylbiphenyl **482** was expected, the formation of biphenyl **18** was surprising. However, when considering radical **483**, formed after initial electron transfer, and its steric hindrance, it is reasonable to suggest that this radical is a poorly effective coupling agent with benzene **49** due to steric hindrance from its methyl groups. Radical **483** will more easily abstract a hydrogen from a molecule of benzene **49**, thus

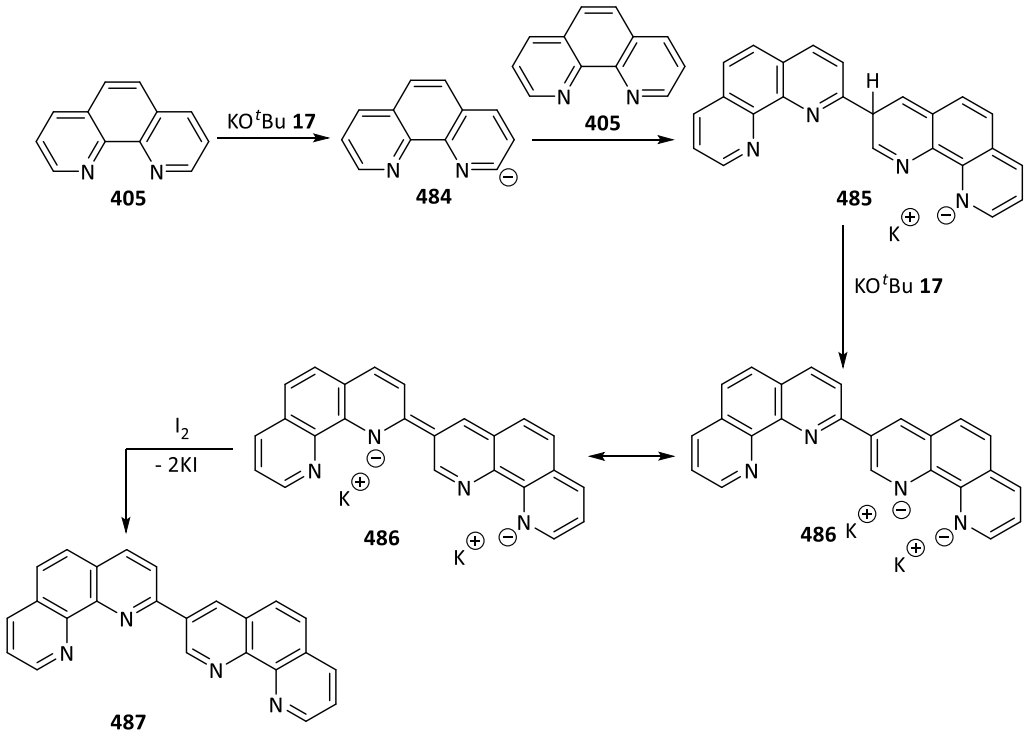
forming phenyl radical **474** which will then couple with benzene **49** to form biphenyl **18**.



Scheme 78

Substrate **481** was also investigated with phenanthroline-derived additives and in each case afforded a mixture of biphenyl **18** and 2,6-dimethylbiphenyl **482**. During the reactions involving phenanthrolines, a deep-green solid material was produced and was investigated. 1,10-Phenanthroline **405** was heated with KO^{t}Bu **17** in benzene and once again, a green solid was observed. When exposed to air, this material was found to be pyrophoric and not suitable for analysis at this stage. The reaction was run again and this time quenched with iodine, as an electron acceptor, before air exposure. Purification and analysis of the resulting red oil showed selective formation (38%) of (2,3'-bis)phenanthroline **487** (see Scheme 79). It was proposed that KO^{t}Bu **17** selectively deprotonates 1,10-phenanthroline **405** on its 2-position affording anion **484** which then selectively adds to the 3-position of another molecule of 1,10-phenanthroline **405** to form anion **485**. Further deprotonation by KO^{t}Bu **17** leads to dianion **486**; in the resonance form shown, this resembles the super-electron donors **30**, **239** and **272**.

Calculations showed that the rate-limiting step for this dimerization of 1,10-phenanthroline **405** is the *ortho* deprotonation to form anion **484** (ΔG_{rel} = 15.8 kcal/mol) meaning that only a small amount of anion **484** is present during the reaction. However, the following steps of the reaction were found to have low energy barriers and the overall formation of disalt **486** is exergonic (-30 kcal/mol).



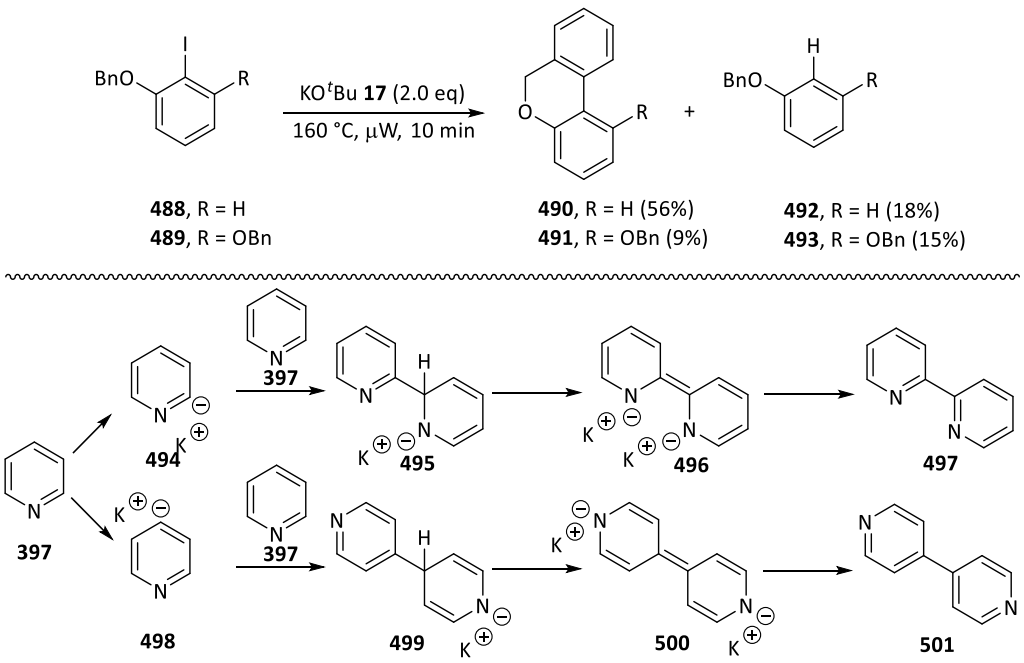
Scheme 79

Knowing that in metal-free cross-coupling reactions, organic additives are of use only in the initiation step and with a substoichiometric amount, it is reasonable to suggest that even a small percentage of formation of dianion **486**, capable of giving away two electrons, would lead to an efficient enough initiation so that enough biaryl radical anion would be formed and then sustain the coupling reaction on its own. This finding was one more piece of evidence that KO^{t}Bu **17** alone or with an organic additive does not act as a single electron donor. However, the use of this strong base is necessary to form electron donor *in situ* by reaction with the additive. Studies turned then to other reported additives or conditions that were thought to be additive-free, and explain how the action of the base would lead to the formation of electron donors.

As seen earlier, pyridine **397** was used as a solvent in several reports of transition metal-free cross-coupling reactions.[108,130] Substrate **481** was tested with pyridine **397** (1.0 eq) and KO^{t}Bu **17** (2.0 eq) but no formation of 2,6-dimethylbiphenyl **482** nor biphenyl **18** were observed. However, the common use of pyridine **397** was as a

solvent and so it was present at a much higher concentration than that of an organic additive.

Charette conditions[130] were tested with two different substrates **488** and **489** which were chosen so that one could form a benzyne (**488**) and the other could not (**489**). Both substrates afforded the respective cyclized products **490** and **491** and the reduced products **492** and **493** resulting from a single electron transfer followed by hydrogen abstraction (see Scheme 80). Since **489** also afforded the two products, investigations were made to find the origin of the electron transfer and, similarly to what had been done with phenanthroline **405**, pyridine **397** was stirred with KO^{t}Bu **17** alone and the reaction was quenched with iodine. The small amount of residue obtained was analysed by GCMS and showed two peaks with the correct *m*/*z* for bipyridine, meaning that two of its isomers were formed. Further purification and analysis confirmed formation of 2,2'-bipyridine **497** as a major product and of 4,4'-bipyridine **501** (see Scheme 80). The formation of these two bipyridine is following the same process for both: deprotonation by KO^{t}Bu **17**, selective addition on another molecule of pyridine **397** and further deprotonation to afford dianions **496** and **500** which contain the structure of super-electron-donors.

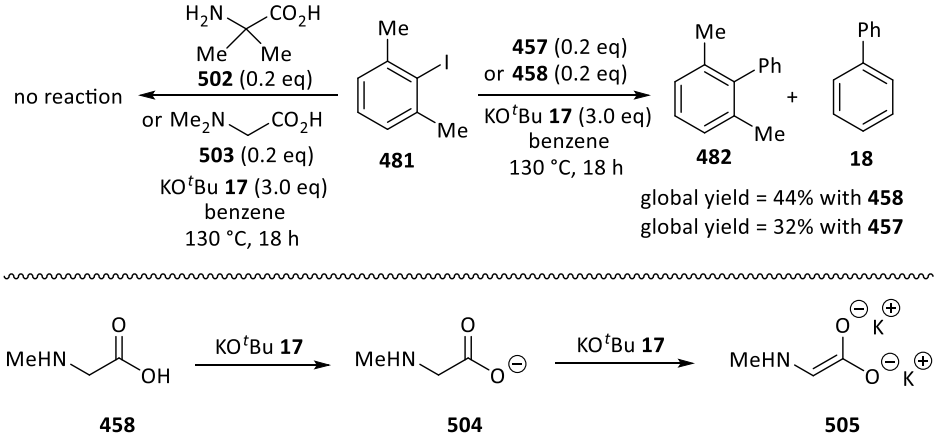


Scheme 80

This finding can relate to the work of Charette[130] and of Itami[108] who used pyridine as a solvent and explains how the electron transfer process is happening by dimerization of pyridine **397** (or pyrazine **399** which can dimerize as well) to generate *in situ* organic electron donors.

Investigations focused then on the role of amino acids, alcohols and 1,2-diamines as organic additives in coupling of aryl halides to arene.[143] Tanimori and co-workers reported sarcosine **458** and proline **457** as being efficient organic additives; both are secondary amino acids.[128] Several tests were made with 2,6-dimethyliodobenzene **481** as substrate and amino acids to assess their ability to promote an electron transfer process and lead to formation of biphenyl **18** and 2,6-dimethylbiphenyl **482** (see Scheme 81, global yield reported for formation of both **18** and **482**). Both sarcosine **458** (global yield = 44%) and proline **457** (global yield = 32%) afforded evidence of an electron transfer process.

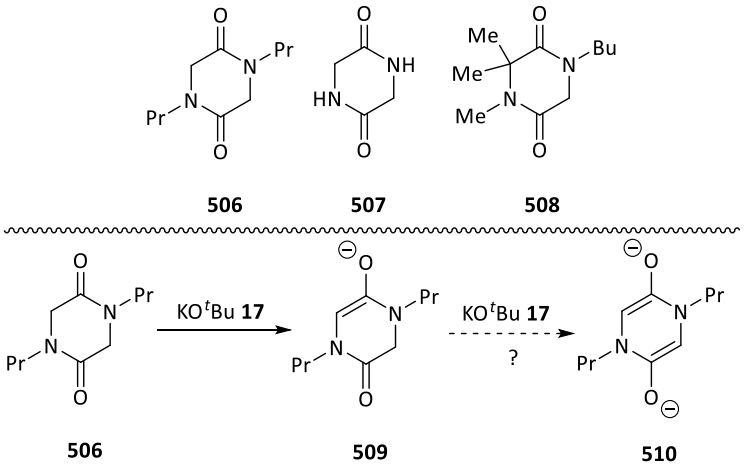
An enolate dianion (such as **505** in Scheme 81) could be the electron donating species used during the initiation. To verify this possibility, the Murphy group tested C,C-dimethyamino acid **502** which afforded no reaction as expected. Interestingly, *N*,*N*-dimethylglycine **503** gave no product as well, suggesting that a double deprotonation of this amino acid was a too unfavourable process for steric reasons. Since this tertiary amino acid was not a good additive, there was a possibility for *N*-monosubstitution of the amino acid to help the initiation of the coupling reaction.



Scheme 81

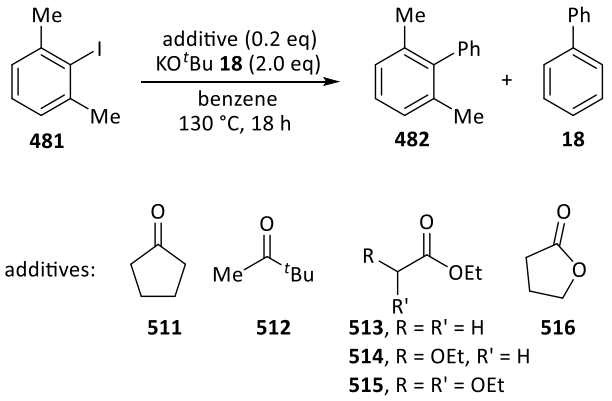
It was already known that secondary amino acids can undergo condensation with carboxylic acids simply on heating to form linear N-alkyl amides or cyclic piperazinedione dimers.[144] Investigations for the formation of such condensation products, by heating several secondary amino acids with KO^{t}Bu **17** in benzene, were unproductive for the Murphy group. However, knowing that only a trace amount of these products would be enough to initiate cross-coupling reactions, the chemistry of piperazinediones (or diketopiperazines, usually called DKP) which are cyclic dimers of amino acids, used as organic additives in transition metal-free cross-coupling reactions, was explored.

Several DKPs (see Scheme 82) were tested, the *N*,*N*'-dipropyl piperazinedione **506** was particularly effective for initiating an electron transfer process using 2,6-dimethyliodobenzene **481** as substrate (global yield = 45%). Under action of KO^{t}Bu **17** this DKP can form the electron-rich enolate **509** and possibly the antiaromatic dianion **510**. Its analogue **507** with free N-H groups did not afford a reaction, which can be attributed to the selective deprotonation of the amide N-H rather than the CH_2. To probe further this proposal of an enolate formation, DKP **508** was tested and was chosen such as it could only form a mono-enolate. This DKP worked as well as **506** did with substrate **481** (global yield = 53%) showing that formation of dianion **510** was not necessary.



Scheme 82

To check if enolates of esters and ketones were indeed acting as electron donors, tests were made with several simple esters and ketones under usual coupling conditions with substrate **481** (see Scheme 83 and Table 15). All of them afforded the coupling products **482** and **18** in various global yields.



Scheme 83

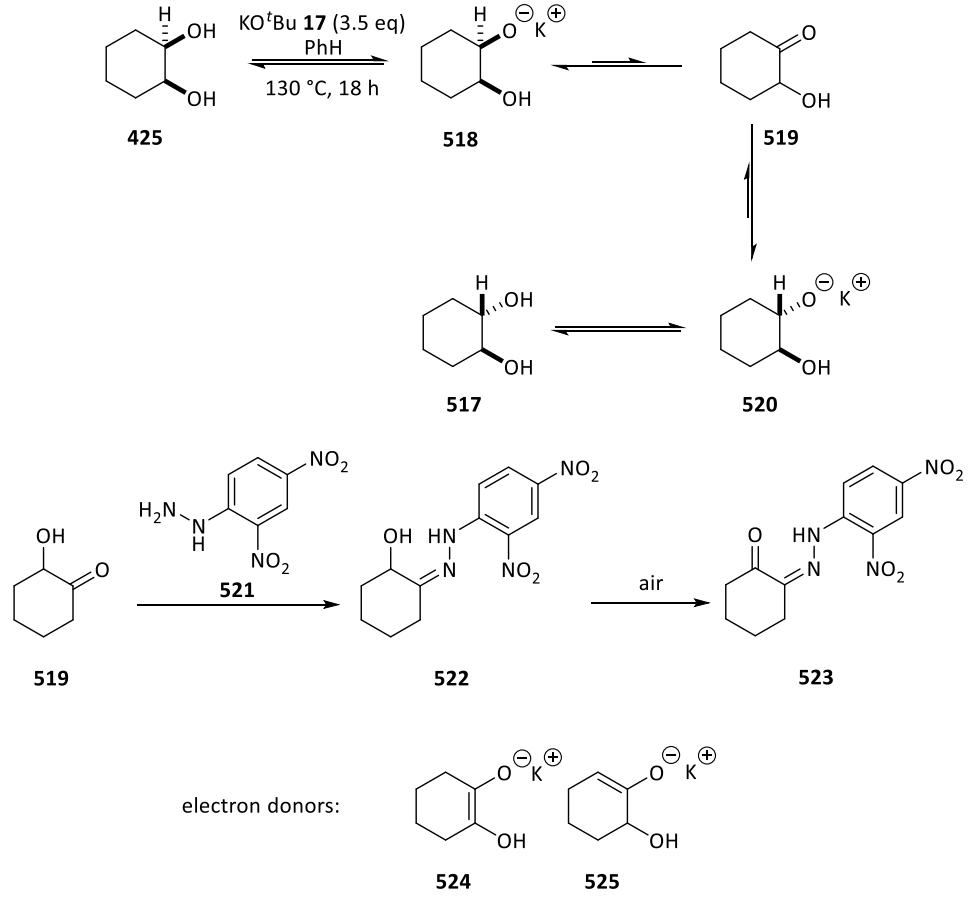
Entry	Additive	Global Yield (%)
1	**511**	42
2	**512**	32
3	**513**	19
4	**514**	44
5	**515**	35
6	**516**	9

Table 15: Enolates as electron donors in transition metal-free cross-coupling reactions.

The ability of alcohols and 1,2-diols to form electron donors, after reaction with potassium *tert*-butoxide **17**, was tested by heating a range of these species with substrate **481** in benzene. *Cis*-1,2-dihydroxycyclohexane **425** (global yield = 32%) and *trans*-1,2-dihydroxycyclohexane **517** (global yield = 64%) both led to efficient electron donors under basic conditions. To understand the process leading to formation of an electron donor from an alcoholate, investigations of the formation of an enolate from

the alcoholate were made. The Oppenauer oxidation is a process leading to conversion of alkoxides to ketones mediated by an aluminium alkoxide and requires a hydride to be delivered to a carbonyl although, it was shown that such a reaction could be triggered by potassium *tert*-butoxide **17** in toluene.[145]

A blank reaction of *cis*-1,2-dihydroxycyclohexane **425** and KO^{t}Bu **17** in benzene at 130 °C (see Scheme 84) resulted in a mixture of both *cis* and *trans* isomers **425** and **517** and of 2-hydroxycyclohexanone **519** which was isolated as 2,4-dinitrophenylhydrazone **522** which oxidized quickly, when exposed to air, into ketone **523**. The electron donating species could be enediolate **524** (which could also be deprotonated again to form a dianion) or possibly its regioisomer **525**, although it would be less electron rich thus less reactive than **524**.

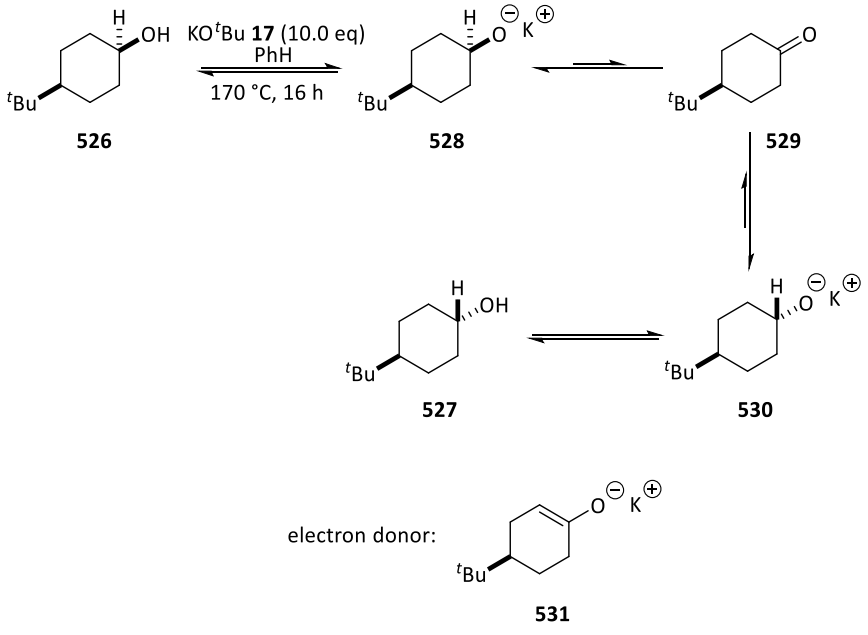


425 518 519 517 520 521 519 522 523 524 525

Scheme 84

Mono-alcohols have also been tested with *cis*-*tert*-butylcyclohexanol **526** (global yield = 10) and *trans*-*tert*-butylcyclohexanol **527** (global yield = 5%) showing that these alcohols are less efficient than 1,2-diols to promote electron transfer reaction. A blank reaction of *cis*-*tert*-butylcyclohexanol **526** with KO^{t}Bu **17** in benzene at 130 °C afforded a mixture of *cis* **526** and *trans* **527** isomers and a small amount of *tert*-butylcyclohexanone **529** (ratio: 1.00:6.54:0.32) (see Scheme 85). Similarly to the reaction of 1,2-diols, the intermediate ketone **529** was converted to its corresponding enolate **531** which can act as an electron donor although its efficiency should be lower than the proposed electron donating species **524** in the case of 1,2-diols as it is less electron-rich, which was in accordance with experimental results.

Investigations were then turned to 1,2-diamines, especially DMEDA **422** (shown on page 59) which was also tested with 2,6-dimethyliodobenzene **481** (global yield = 46%). Blank reactions of diamines with KO^{t}Bu **17** in benzene were unsuccessful as no products were isolated. It was known that magnesium diisopropylamide **532** can form imine **533** by expulsion of a hydride;[146-147] in the present case, diamines could also react that way in the presence of KO^{t}Bu **17**.

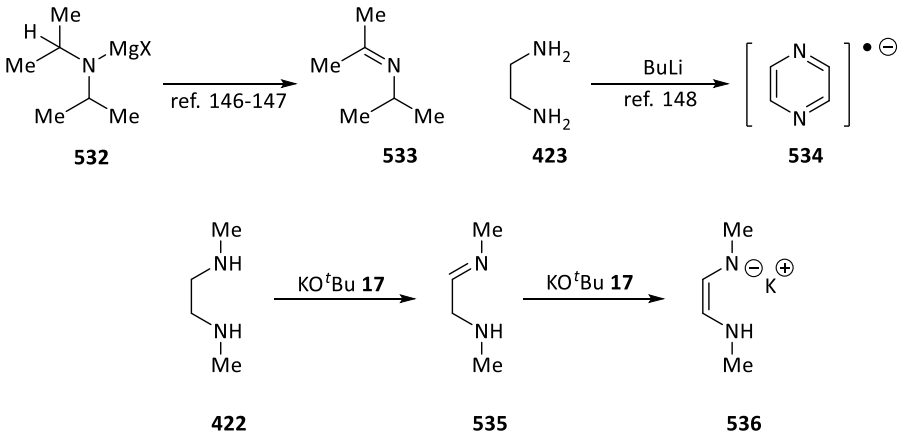


526 **528** **529** **527** **530** **531**

Scheme 85

It had been shown that ethylenediamine **423**, treated with a base, formed pyrazine radical anion **534** (see Scheme 86), likely through condensation of imines.[148]

If vicinal diamines such as DMEDA **422** can undergo an imine formation (**535**) by expulsion of a hydride then it could be further deprotonated to afford an enamine salt **536**, which could act as a single electron donor (see Scheme 86).

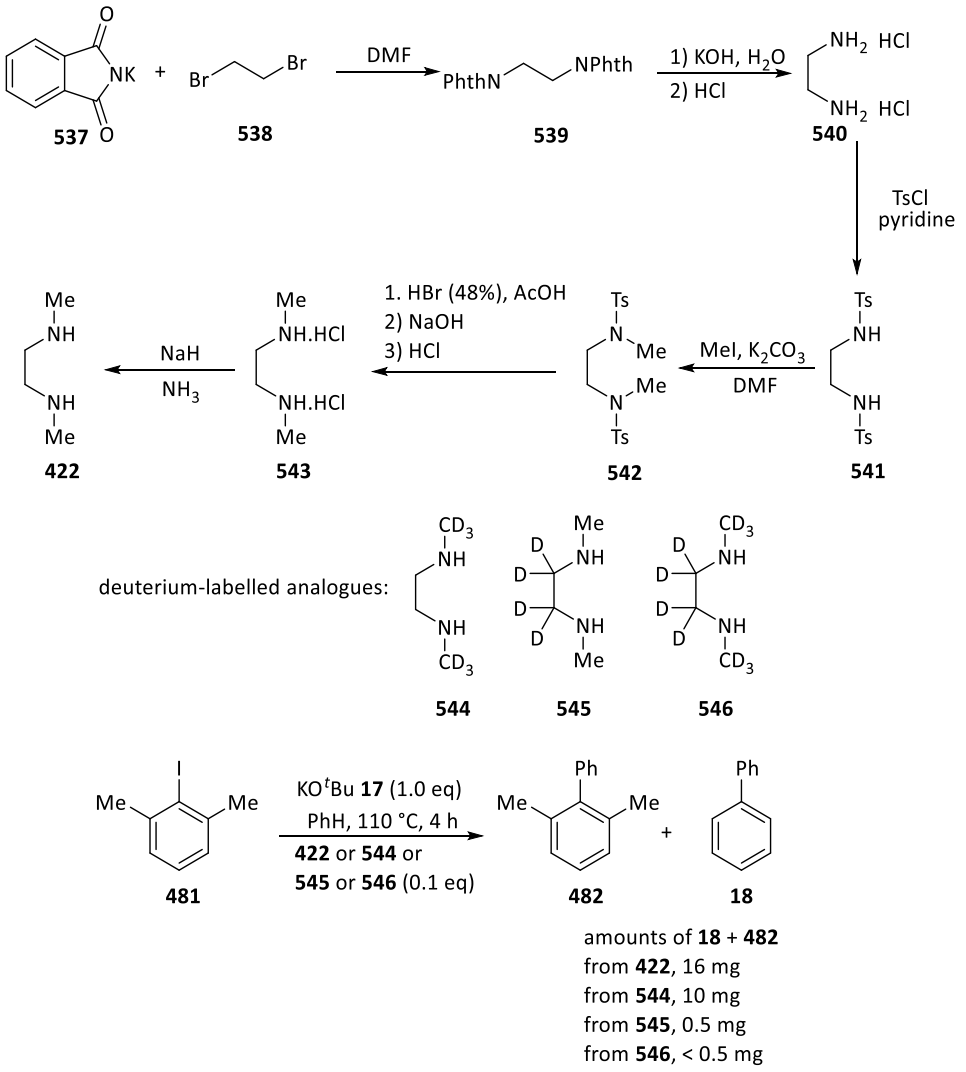


Scheme 86

To probe the formation of electron donor **536** and identify its rate-determining step (likely to be the hydride elimination), several deuterium-labeled analogues **544**-**546** of DMEDA **422** were used (see Scheme 87). These analogues as well as DMEDA **422** itself were all synthesised following the same strategy and using the corresponding deuterated starting materials. These four species were tested in four parallel reactions with substrate **481** and for a reaction time which led to about half conversion of **481** when unlabelled DMEDA **422** was used.

The results clearly showed that the breaking of a C-H bond within a methylene is involved in the rate-determining step for the initiation of the coupling reaction as the non-deuterated species **422** and **544** are efficient in initiating the reaction while the deuterated species **545** and **546** are not. This was good evidence for the formation of an electron donating species such as **536** when DMEDA **422** is used as an additive in the presence of KO^{t}Bu **17**.

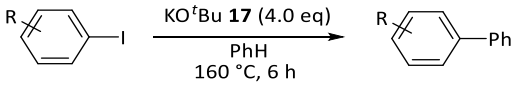
Studies on amino acids, enolates, alcohols and diamines were all leading to same conclusion: there was no evidence for a complex formed between potassium *tert*-butoxide **17** and organic additives to allow butoxide to give away one electron. However, several reports made in the following years were contradictory with this assertion.



Scheme 87

In 2014, Wilden *et al.* reported transition-metal free and organic additive-free cross-coupling reaction of aryl halides with benzene.[149] In their study, they proposed that the degree of dissociation of the potassium cation and *tert*-butoxide **416** was sufficient to allow the base to give one electron to aryl halides without requirement of any additive. Several substrates were reported with reasonable to good yields for

the coupling of aryl halides with benzene (see Scheme 88 and Table 16). However, it turned out that only aryl iodides were candidates for these conditions as the reactions with aryl bromides were not successful (an investigation on the results published by Wilden will be described in the Results and Discussion part of this thesis).

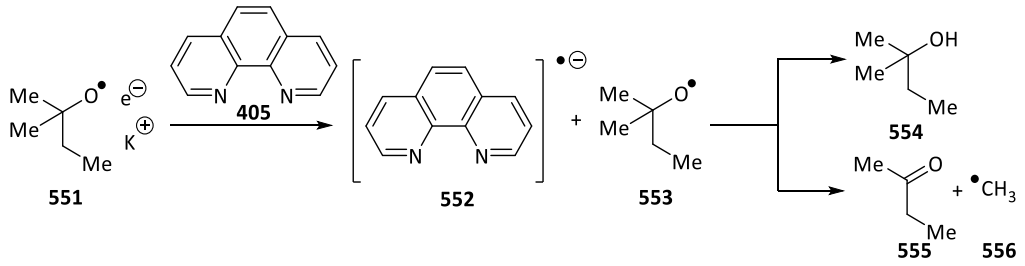


Scheme 88

Entry	Substrate	R	Product	Yield (%)
1	**5**	H	**18**	77
2	**11**	*p*-Me	**24**	66
3	**8**	*p*-OMe	**21**	48
4	**547**	3,5-Me	**549**	48
5	**548**	*p*-^{t}Bu	**550**	30

Table 16: Additive-Free Cross-Coupling of Aryl Iodides with Benzene.

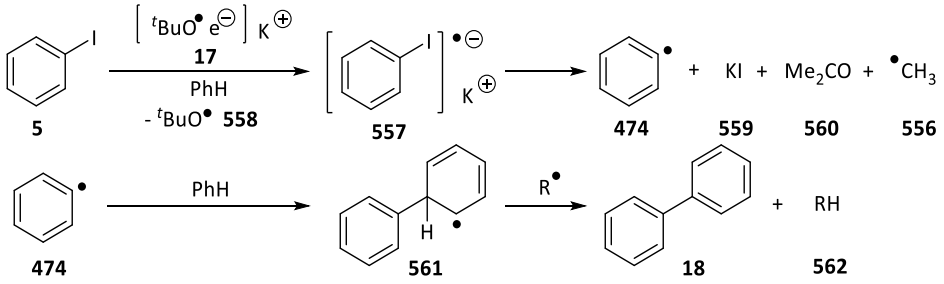
In the case where an additive such as 1,10-phenanthroline **405** is present, Wilden proposed that it would receive an electron from butoxide (similarly to an electron shuttle) and the resulting alkoxyl radical would collapse to form a ketone and release a radical species. Several tests were made by Wilden to probe the collapse of the alkoxide. An equimolar mixture of KO^{t}Bu **17** and 1,10-phenanthroline **405** was observed by ^{1}H NMR in $CDCl_3$ and showed collapse of the ^{t}Bu signal of KO^{t}Bu **17**. Also, potassium pentoxide **551** was reacted with 1,10-phenanthroline **405** at room temperature (see Scheme 89, potassium pentoxide **551** is drawn as Wilden represented it in his report).



Scheme 89

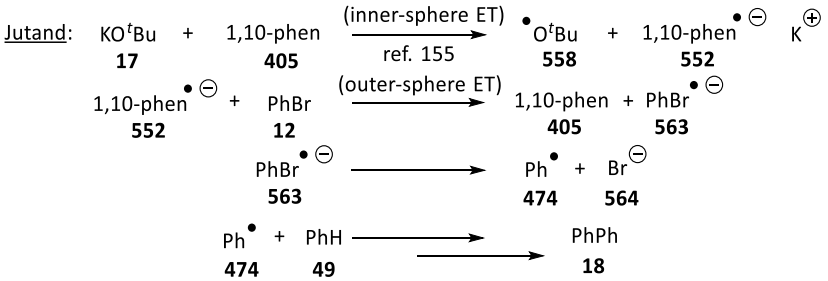
The reaction mixture was submitted to the Janovsky test,[150] which resulted in an intense purple colour indicating that an enolisable ketone **555** was formed during the reaction as a result of the collapse of pentoxyl radical **553**.

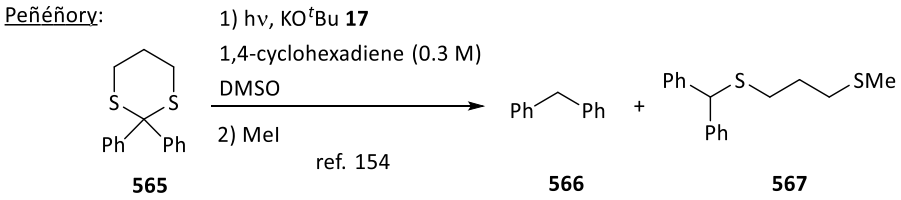
To explain the process involved in the coupling of aryl iodides to benzene under these conditions, Wilden proposed a mechanistic pathway which was clearly different from the proposal made by Studer and Curran[118] but still relying on a base-promoted homolytic substitution (see Scheme 90). Iodobenzene **5** receives one electron from *tert*-butoxide **416** to form iodobenzene radical anion **557** and *tert*-butoxyl radical **558**. Radical anion **557** dissociates into aryl radical **474** and iodide (interacting with potassium cation to form potassium iodide **559**) and radical **558** collapses to form acetone **560** and methyl radical **556**. Coupling between aryl radical **474** and benzene **49** forms aryl cyclohexadienyl radical **561** which will be a source of hydrogen for a radical (derived from reactions of methyl radical **556**) to finally afford biphenyl **18**. This mechanism does not have an initiation step nor a propagation cycle as no biaryl radical anion is formed during this reaction. More intriguingly, the role of potassium *tert*-butoxide **17** in this proposed reaction is limited to giving away an electron which is surprising, considering that it is a strong base and there are several labile protons which should be reacting with KO^{t}Bu **17** (such as the *ortho* protons which would lead to formation of benzyne **477** by elimination).

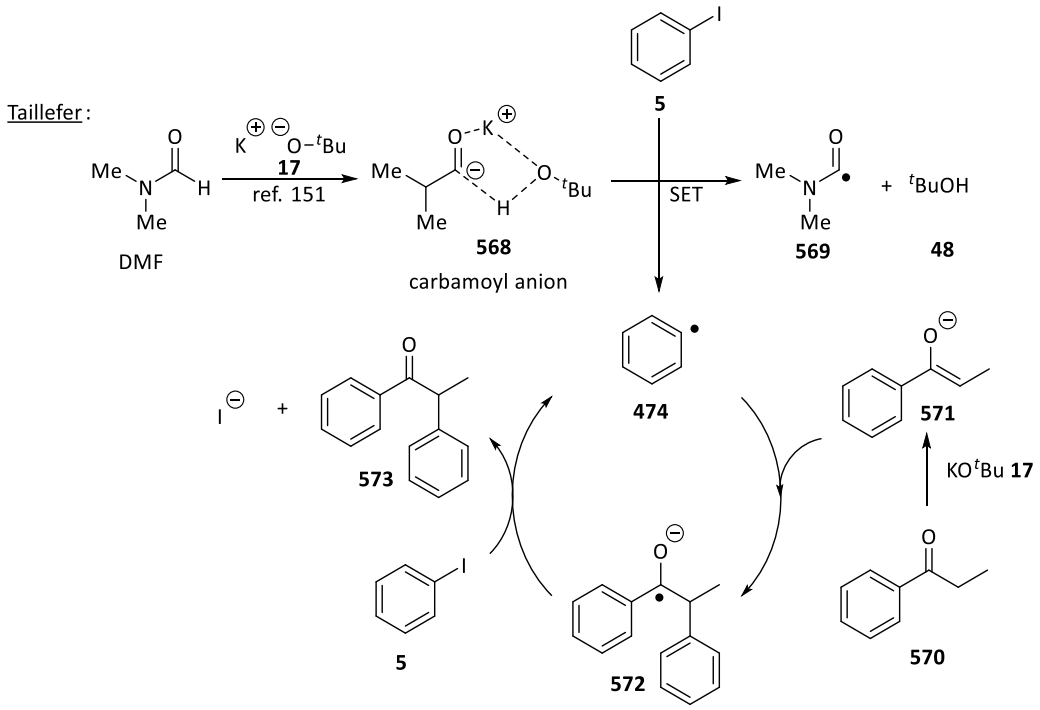


Scheme 90

Other reports have been made on electron transfer reactions involving KO^{t}Bu **17**. Taillefer *et al.* reported α-arylation of enolisable aryl ketones with aryl halides using KO^{t}Bu **17** in DMF,[151] suggesting that a complex between KO^{t}Bu **17** and DMF would be the electron donating species;[152-153] Peñéñory *et al.* cleaved dithianes using KO^{t}Bu **17** in DMSO;[154] Jutand and co-workers used EPR and cyclic voltammetry to probe the formation of 1,10-phenanthroline radical anion **552** and *tert*-butoxyl radical **558** from the interaction between KO^{t}Bu **17** and 1,10-phenanthroline **405** (see Scheme 91).[155]





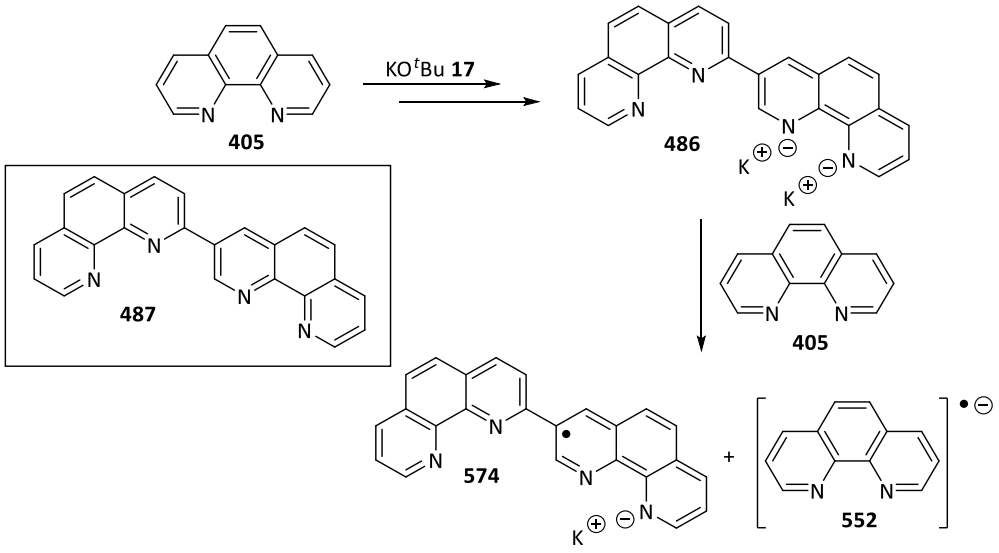


Scheme 91

The Murphy group investigated the cases mentioned above to find out the exact role of KO^{t}Bu **17** in these reactions and to explain the results suggesting that the base itself could be an electron donor.[156] EPR studies of the reaction of KO^{t}Bu **17** with phenanthroline **405** were conducted, as Jutand and co-workers did,[155] and confirmed that radicals were indeed formed during the reaction. However, the EPR spectrum reported by Jutand was not symmetrical, which meant that there were likely more than one phenanthroline-type radical anion formed during the reaction.

As seen earlier, evidence for the formation of a dianionic phenanthroline-dimer **486**, reported as being the electron donating species, were found.[135] In a reaction involving only 1,10-phenanthroline **405** and KO^{t}Bu **17**, the electron donor **486** will have no other choice but to give one electron to 1,10-phenanthroline **405** and form two radical anions **552** and **574** (see Scheme 92) perhaps explaining the asymmetry of the reported EPR spectrum. Also, Jutand reported that the electrochemical reduction of phenanthroline **405** was inhibited when KO^{t}Bu **17** was present meaning that both species should react together, which is in accordance with the dimerisation of **405** under the action of KO^{t}Bu **17**. Cyclic voltammetry studies were made using the

oxidised phenanthroline dimer **487** and three reduction waves were found: -1.70; -1.94; -2.19 V vs. SCE in DMF, while the same study with 1,10-phenanthroline **405** gave only two reduction waves: -2.05; -2.24 V vs. SCE in DMF. The potentials found for dimer **487** clearly show that the first and second electrons that can be transferred from dianion **486** should reduce aryl iodides, as other organic super electron donors could achieve this and were not as strongly reducing as dimer **486**. Since Jutand and co-workers found that KO^{t}Bu **17** has an oxidation potential of +0.10 V vs. SCE in DMF, and that it cannot directly reduce aryl iodides, it is very unlikely that the base alone could reduce phenanthroline **405** even through an inner sphere complex. These results were once again in accordance with the proposal of the formation of dianion **486** from phenanthroline **405**.

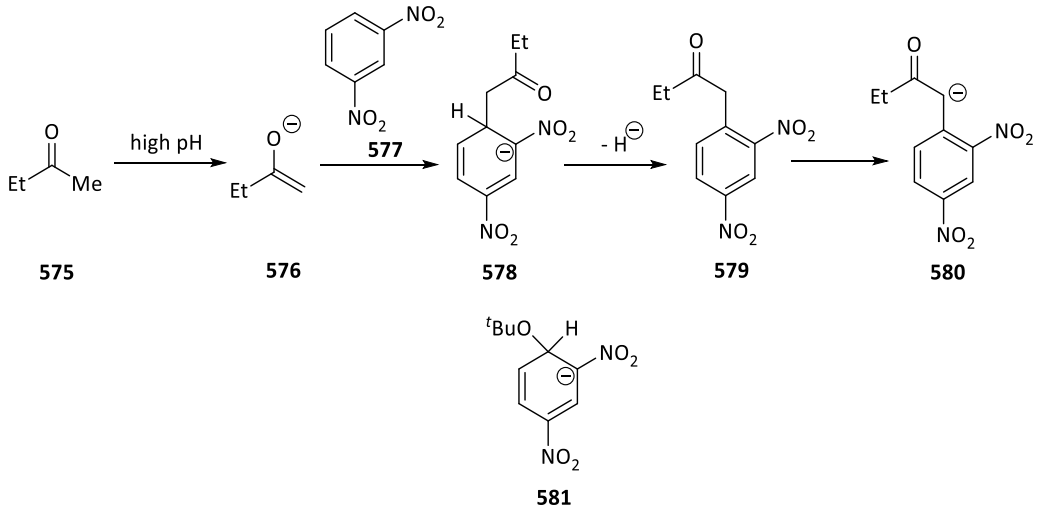


Scheme 92

Investigations were made toward Wilden's report[149] which suggested that KO^{t}Bu **17** alone could promote the coupling reaction of aryl halides with benzene. The proposal made by the Murphy group on the formation of benzynes, from aryl halide under the action of KO^{t}Bu **17**, and how these benzynes could initiate the cross-coupling reaction was seen earlier (Scheme 77). Interestingly, repeating Wilden's conditions gave evidence for the formation of benzynes (the reactions made will be described in the Results and Discussion part of this thesis). It is also important to remember that when 2-iodo-*m*-xylene **481** (which does not allow formation of benzyne) was tested

without any organic additives, no reaction was observed.[143] Wilden reported evidence for his proposal, resulting from the Janovsky test to probe formation of ketones resulting from the collapse of an alkoxyl radical (Scheme 89).

However, formation of the Janovsky adduct had to be reconsidered (see Scheme 93). Wilden proposed that the enolate **576**, of butanone **575**, (proposed to be formed from collapse of pentoxyl radical **533**) would add to 1,3-dinitrobenzene **577** and form a coloured adduct **580**. Since the reaction is made at high pH, the Murphy group suggested that the enolate **576** would react with 1,3-dinitrobenzene **577** and afford adduct **578**, which, upon oxidation and deprotonation, could lead to adduct **580**.



Scheme 93

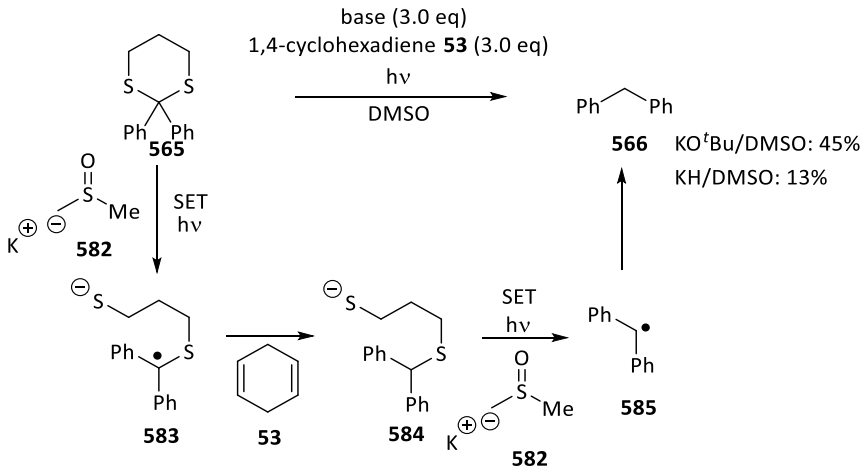
Several tests were made, all of them including KO^{t}Bu **17** and 1,3-dinitrobenzene **577** in THF at least. Both reactions made with 1,10-phenanthroline **405** and acetone afforded a purple colour. Another experiment was made with only KO^{t}Bu **17** and 1,3-dinitrobenzene **577** in THF and once again a purple colour was obtained showing that the presence of a ketone cannot be confirmed by a Janovsky test alone. Another proposal can be that the addition of *tert*-butoxide **416** on 1,3-dinitrobenzene **577** affording **581** is the origin of the purple colour.

Wilden *et al.* also reported the collapse of the ^{t}Bu signal of KO^{t}Bu **17** when analysing the reaction of the base with 1,10-phenanthroline **405** by ^{1}H NMR. Their NMR

spectrum shows a singlet at 7.28 ppm that should be the residual $CHCl_3$ in $CDCl_3$ that was likely the NMR solvent used. It is reasonable to suggest that KO^{t}Bu **17** would react with such a solvent.[157] When the same experiment was run in THF-d_8 in the Murphy lab, no collapse of the ^{t}Bu signal was observed. After two hours, diluting the reaction with $CDCl_3$ led to an almost total collapse of that signal, clearly showing that chloroform was the reason Wilden *et al.* saw such a collapse of that signal.

During the reaction between potassium pentoxide **551** and phenanthroline **405**, Wilden reported formation of butanone **575** resulting from fragmentation of pentoxide. However, this reaction was run in THF as solvent which happens to have the same molecular mass as butanone **575**. The observation of the expected mass would then need reassurance on the actual species it refers to, especially since pentoxyl radical **533** was reported to preferentially fragment into acetone and ethyl radical (more stable than methyl radical),[158] rather than into butanone and a methyl radical.

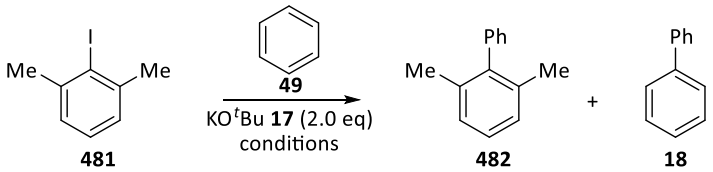
Investigations into the reductive fragmentation of dithianes when they are reacted with KO^{t}Bu **17** in DMSO under photoactivation were made by Peñéñony *et al.* who suggested a charge transfer complex between dithiane **565** and KO^{t}Bu **17**.[154] The Murphy group proposed a charge transfer complex between dithiane **565** and dimsyl salt **582** (see Scheme 94). Indeed, when dithiane **565** and KO^{t}Bu **17** were reacted in DMSO and exposed to UV irradiation, the charge transfer complex between these two species was assigned to a peak at 467 nm in the UV-visible spectrum and, when the same reaction was made with potassium hydride **586** as a base, the same absorption was observed (at 466 nm) while running the reaction with KO^{t}Bu **17** as a base in DMF gave no such absorption. These findings suggested that DMSO is playing a part in the reaction process and both KO^{t}Bu **17** and KH **586** could be used (although potassium hydride leads to a lower yield for the cleavage).



Scheme 94

The report of Taillefer *et al.*[151] was intriguing, as the role that DMF as solvent could have, when KO^{t}Bu **17** is reacted with it, was not clear. Knowing that strong bases (such as LDA) can deprotonate DMF,[159-160] Taillefer *et al.* suggested that salt **568** (as represented in Scheme 91) was the electron-donating species.

The action of DMF, used in a substoichiometric amount in the metal-free cross-coupling reaction of 1,3-dimethyliodobenzene **481** with benzene, was tested. As the previous reactions that were made with this substrate, the interesting output was the amount of biphenyl **18** and 1,3-dimethylbiphenyl **482** that was formed (see Scheme 95 and Table 17). As seen earlier, when no additive was used, there was no reaction with substrate **481**. However, repeating the reaction showed formation of biaryl products **18** and **482** at a very low yield (0.5% as determined by internal standard in ^{1}H NMR of the crude product). When DMF was added (1% relative to benzene (v/v)), the yield of biaryl products was increased (2.6%) showing that DMF was likely reacting with KO^{t}Bu **17** to form an electron donating species.

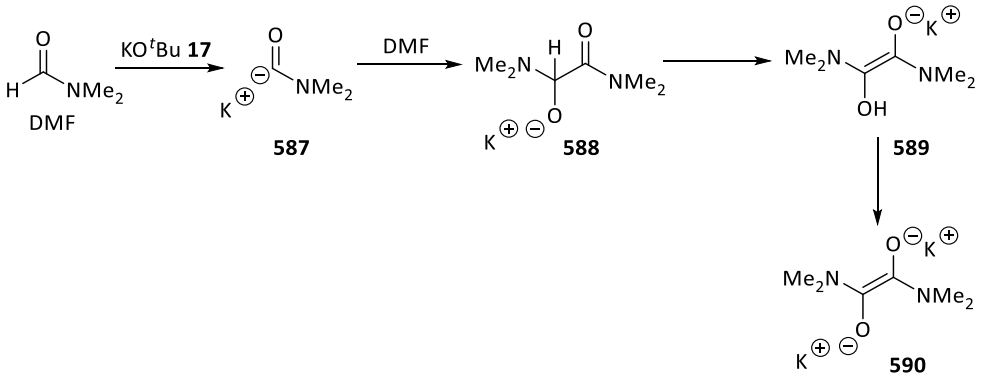


Scheme 95

Entry	Additive	Conditions	482 + 18 (%)
1	none	130 °C, 18 h	0.5
2	DMF (1%)	130 °C, 18 h	2.6
3	DMF (1%)	110 °C, 4 h	0.4

Table 17: Use of DMF as an additive in transition metal-free cross-coupling reaction.

The following pathway for the reaction between DMF and KO^{t}Bu **17** was proposed (see Scheme 96): deprotonation by KO^{t}Bu **17** to form anion **587**, nucleophilic addition to another molecule of DMF to form anion **588**, proton transfer to get enolate **589**, which is a candidate electron donor, although it could be further deprotonated to dianion **590**, which should be an even more powerful electron donating species.



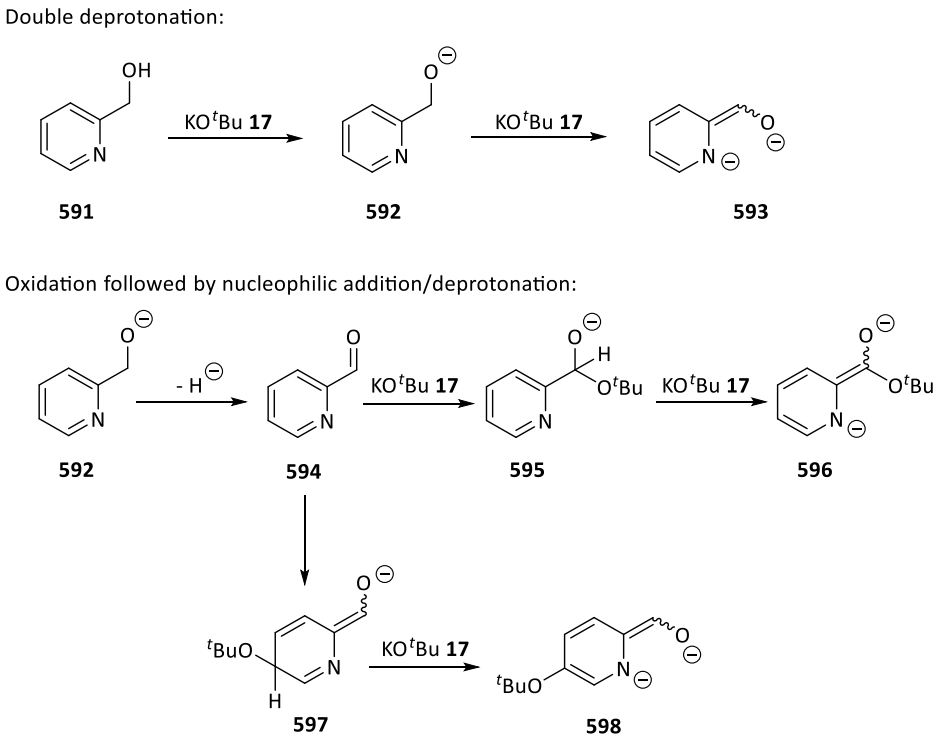
Scheme 96

With this proposal for the dimerisation of formamides, the role of KO^{t}Bu **17** as an electron donor, whether it is complexed with another species or not, was excluded once again.

Barham *et al.* recently published a study on the mechanism of action of pyridinols used as electron donors under basic conditions. The use of pyridinols had already been reported by Kwong *et al.* in 2014.[161] Barham proposed a double deprotonation of these pyridinols to afford the electron donor **593** (see Scheme 97).[162] An alternative pathway was also proposed in which an oxidation (loss of a hydride) and

a nucleophilic addition of *tert*-butoxide would lead to the formation of the electron donor, where candidate structures were **596** and **598**.

Understanding the mechanism involved in the initiation of transition metal-free cross-coupling reactions has clearly been of great importance for the Murphy group, especially since it is still a topic of debate in research as some reports are still suggesting direct electron transfer from potassium *tert*-butoxide **17** or are proposing a different initiation pathway.

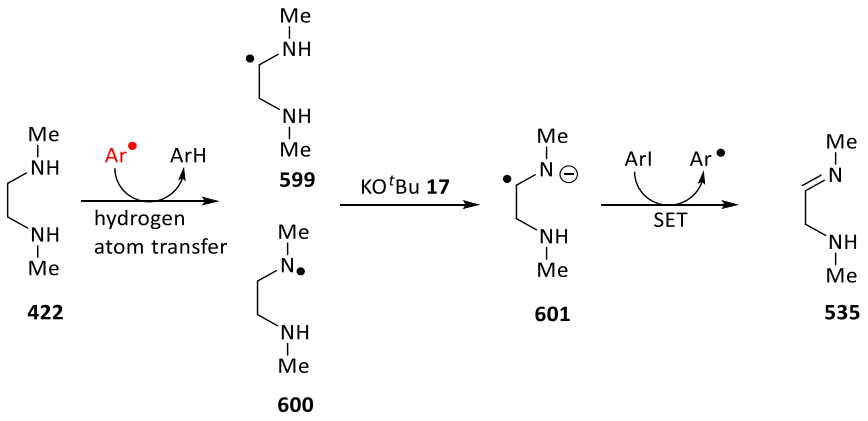


Scheme 97

For example, Jiao and co-workers recently revisited the initiation of the DMEDA **422** promoted cross-coupling reaction.[163] Their proposal was clearly different from the one seen earlier,[143] but surprisingly shows a clear anomaly at the very first step of their proposed initiation (see Scheme 98 for the beginning of the initiation's proposal). We know that the aim of the initiation process is to sufficiently generate aryl radicals from aryl halides so the reaction can be undertaken on its own by the formation of biaryl radical anions. In Jiao's proposal, the first step of the initiation

already involves an aryl radical, which is the species that initiation requires to generate.

It is clear that the debate around the initiation process in transition metal-free cross-coupling reactions is not over yet and will remain a topic of study and research for many years to come, as there are probably many other organic additives yet to be discovered, especially in order to promote the coupling of aryl chlorides and fluorides which mostly remain non-reactive substrates under metal-free cross-coupling reaction conditions.



Scheme 98

1.4 Aims of this study

This thesis aims to explore the use of new organic additives in metal-free cross-coupling reactions as well as investigating the role of these additives in the reaction by comparing the outcome of promoted reactions and non-promoted reactions. This aims to get more evidence of the role of the strong organic base (usually potassium *tert*-butoxide) in these reactions. This study is supported by computation of electron transfer reactions and cross-coupling reactions, affording the Gibbs free energies of these processes and thus their feasibility.

This thesis also aims to explore other electron-transfer chemistry such as the deprotection of alkyl aryl ethers and the reduction of nitrobenzene and azobenzene.

The main idea of studying electron-transfer chemistry is to find new chemical species and processes that would lead to a decrease of the negative impact on the environment of traditional chemistry by replacing heavy metal complexes by organic species capable, under certain conditions, of performing strong reduction reactions.

Chapter 2: Diketopiperazines as Electron-Donor Initiators in Transition Metal-Free Haloarene-Arene Coupling

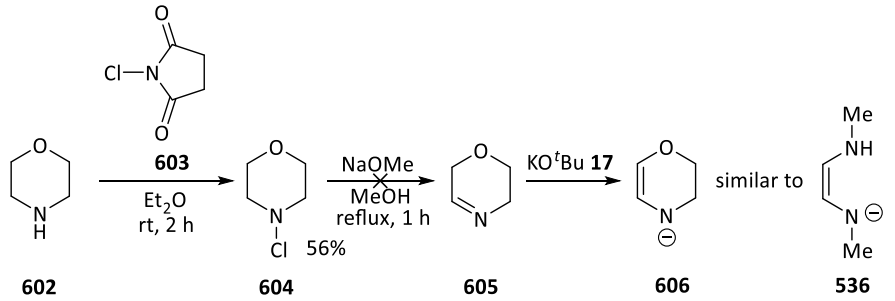
Since metal-free cross-coupling reactions were discovered by Itami in 2008,[108] many more reports have been made and a large variety of organic additives, promoting the reaction under basic conditions, has been found. The Murphy group reported diketopiperazines (DKP) **506** and **508** (as represented in Scheme 82, page 72),[143] which were able to efficiently promote the coupling reaction of aryl iodides with benzene and confirmed that only one deprotonation (thus formation of a mono-enolate) was enough to obtain a strong electron donor. This chapter will focus on four other diketopiperazines with different *N*-substituents, chosen as to improve the solubility of the DKPs in benzene used as solvent and to improve the reducing ability of the electron donor formed by deprotonation of these DKPs by potassium *tert*-butoxide **17**. Before starting with this study of DKPs, the effect of an organic additive on the cross-coupling reaction will be investigated by comparing "additive-free" vs "non-additive-free" conditions focusing especially on the conditions that were reported by Wilden.[149]

2.1 Of Organic Additives and Potassium *tert*-Butoxide

This section will discuss two different pathways: the "additive-free" pathway reported by Wilden,[149] affording good coupling reactions of aryl iodides with benzene, and the "benzyne" pathway reported by the Murphy group.[135]

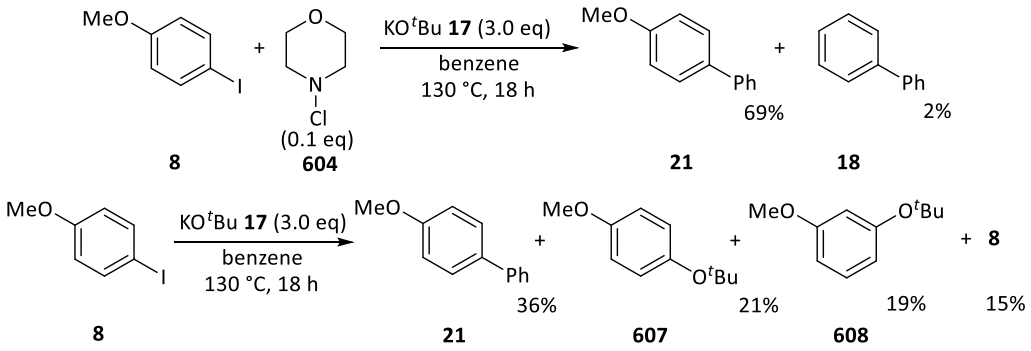
A first concern with Wilden's report arose when a blank reaction (meaning additive-free) was run for the coupling of 4-iodoanisole **8** with benzene, conducted at 130 °C for 18 hours. The reaction was run in parallel with another reaction featuring 4-chloromorpholine **604** as an additive. The reason for the use of morpholine's

structure was to form electron donors similar to those proposed when DMEDA **422** is used (see Scheme 99). However, the formation of 3,6-dihydro-2*H*-1,4-oxazine **605** was unsuccessful. Since its formation requires use of a base, it was decided to use 4-chloromorphiline **604** itself as "precursor of a precursor of an electron donor".



Scheme 99

The results found for the two reactions clearly showed the importance of using 4-chloromorpholine **604** (see Scheme 100).



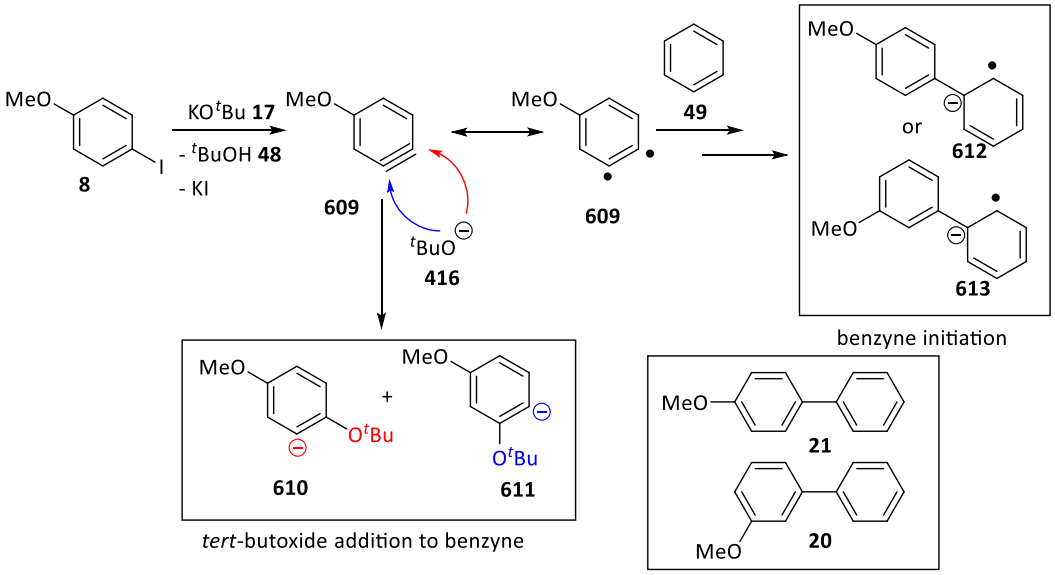
Scheme 100

In the presence of 4-chloromorpholine **604** the expected coupling product **21** is formed in good yield and a small amount of biphenyl **18** was also found (resulting from H-abstraction from benzene forming phenyl radical **474** which then couples with another molecule of benzene (as reported in scheme 78, page 68). However, when no additive was used, the reaction afforded not only the coupling product **21** but also two regioisomers **607** and **608** in an almost 1:1 ratio.

These two regiosomers were good evidence for a benzyne formation from 4-iodoanisole **8** (see Scheme 101). Once benzyne **609** is formed and since KO^{t}Bu **17** is

used in excess, a *tert*-butoxide anion **416** can add to benzyne **609** on its *meta* or *para* position without selectivity and form aryl anions **610** and **611**. Chapter 1 already highlighted how the formation of a benzyne can be part of the initiation process in the cross-coupling reaction (Scheme 77) which can explain why the coupling product **21** is also formed during the reaction without additives.

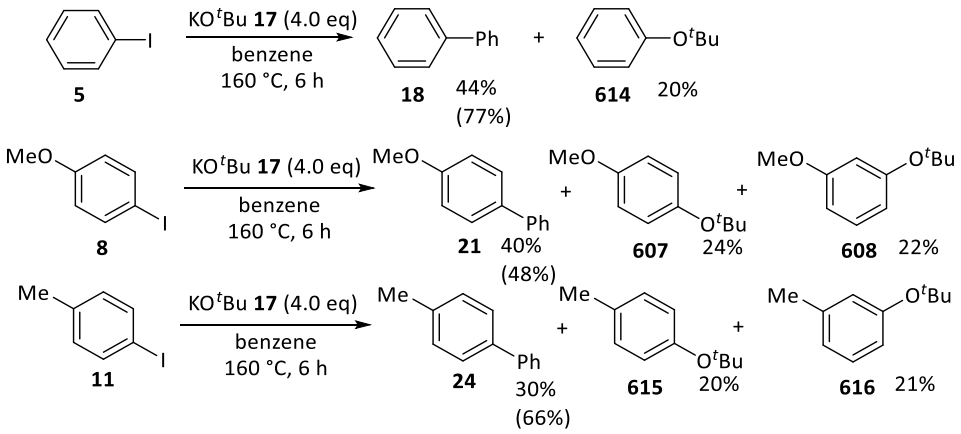
While the formation of two regiosomers for the addition of *tert*-butoxide **17** on benzyne **609** can be easily understood, it might be surprising to find only one coupling product at the end of the reaction since the benzyne initiation should be able to afford both the *para* and the *meta*-biaryl radical anions **612** and **613**. When these radical anions give one electron to another molecule of 4-iodoanisole **8**, both *para* and *meta*-coupling products **21** and **20** are formed. However, the formation of *meta*-isomer **20** is only part of the initiation process. The initiation is far slower than the chain propagation, and thus **613** is formed in a very low amount.



Scheme 101

Since the *meta*-isomer can be formed only during the initiation, a very small number of molecules of 3-methoxybiphenyl **20** will be formed, not enough to be able to see its formation by standard analytical tools (^{1}H NMR or GCMS).

The additive-free reaction afforded a result quite different from what had been reported by Wilden although the reaction conditions were not exactly the same (3.0 eq of base, 130 °C, 18 h vs 4.0 eq of base, 160 °C, 6 h). Repeating Wilden's reaction with iodobenzene **5**, 4-iodoanisole **8** and 4-iodotoluene **11** led to different results than those Wilden reported (see Scheme 102, yields reported by Wilden are in parenthesis).



Scheme 102

Compared to the conditions used for the reactions in Scheme 100, Wilden's conditions led to a complete conversion of the aryl iodide starting material but, in each case, formation of the *tert*-butoxide-addition product(s) was found and none of these species was reported by Wilden, which is surprising as their formation is evident when looking at a ^{1}H NMR of the crude product of these reactions (see Figure 1).

For both addition products **607** and **608**, the singlet signal of their -O^{t}Bu group (1.360 ppm and 1.305 ppm) is good evidence of their formation. The outcome of the repetition of Wilden's reaction were in accordance with the presence of benzyne intermediates.

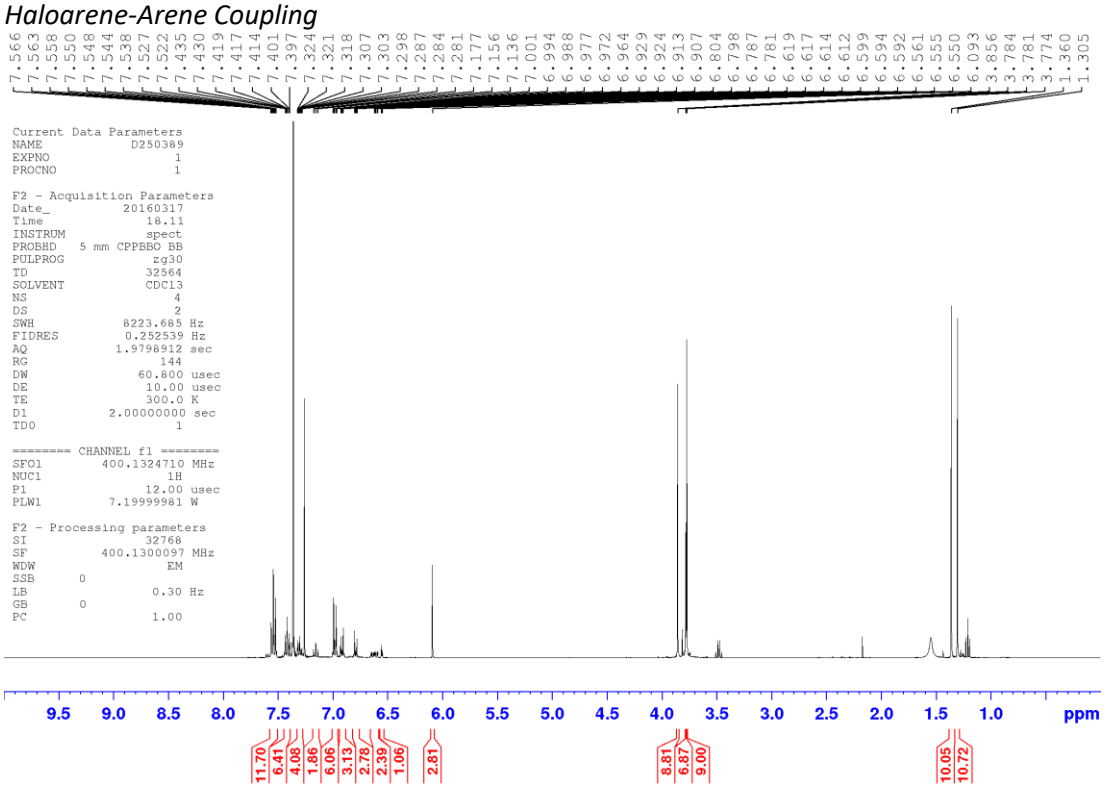
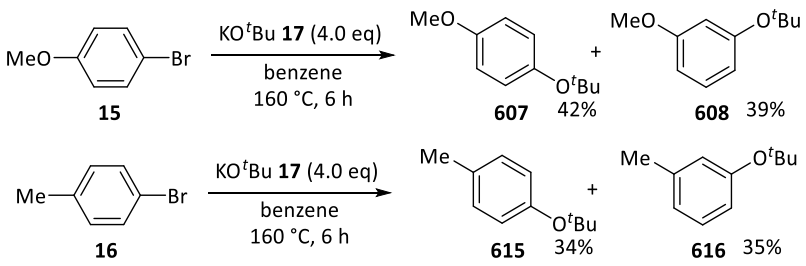


Figure 1: ^{1}H NMR of reaction of 4-iodoanisole **8** with KO^{t}Bu **17** under Wilden's conditions showing formation of benzyne adducts **607** and **608** (singlets at 1.31, 1.36, 3.77, 3.78 ppm).

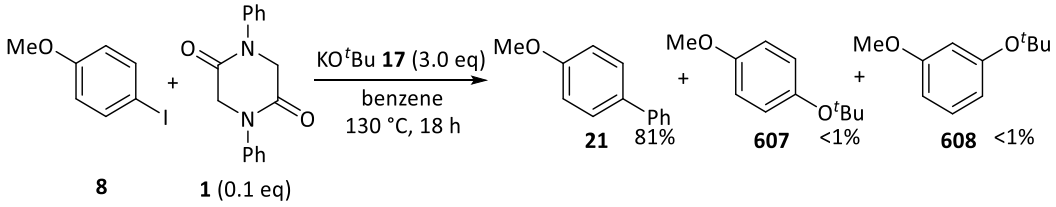
Also, Wilden's report investigated only the coupling of aryl iodides with benzene. Several aryl bromides were tested (4-bromoanisole **15** and 4-bromotoluene **16**) under his conditions (see Scheme 103) and no formation of the coupling products to benzene was observed: only the regioisomers resulting from addition of *tert*-butoxide **416** to a benzyne ring were found.



Scheme 103

This showed that the initiation of the cross-coupling reaction, going through a benzyne formation (as represented in Scheme 101, page 92) is limited to the cross-coupling of aryl iodides with benzene. Aryl bromides are not reactive enough toward metal-free cross-coupling reactions to be able to afford aryl radicals when promoted by a benzyne. They need the presence of an initiator which, under basic conditions, will afford a strong enough electron donor.

As example, Scheme 100 showed that the reaction of 4-iodoanisole **8** with KO^{t}Bu **17** (3.0 eq) in benzene at 130 °C for 18 h and without an organic additive is limited, as all the starting material had not been converted. When the same reaction was run with 10% of DKP **1** the outcome was completely different as the yield of the coupling product **21** drastically increased, all the starting material was converted and the yields of *tert*-butoxide addition products **607** and **608** were very low, meaning that the electron transfer process was very predominant over the benzyne formation (see Scheme 104).

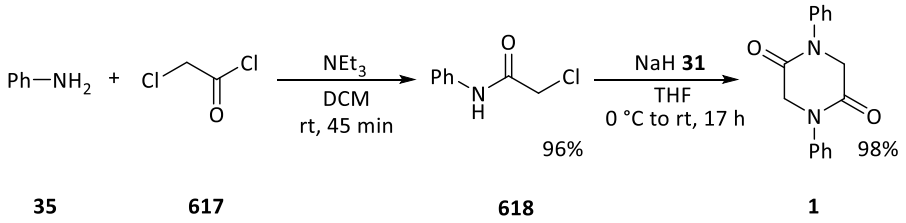


Scheme 104

This provided further evidence of a benzyne pathway that can occur when no organic additive is involved in transition metal-free cross-coupling reactions. The use of an organic additive completely changes the outcome of the reaction, as it leads to a strong selectivity for the cross-coupling product.

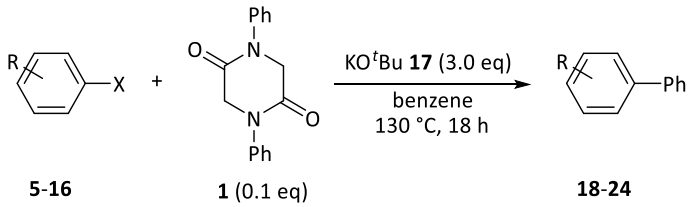
2.2 A Study of Diketopiperazines as Electron Donor Initiators

Investigations were made, in order to improve the use of DKPs as organic additives in transition metal-free cross-coupling reactions, by changing the nature of the *N*-substituents. 1,4-Diphenylpiperazine-2,5-dione **1** was synthesised to see if the phenyl substituents would improve the solubility of the donor in benzene, and thus the electron transfer process. DKP **1** was synthesised by reacting aniline **35** with 2-chloroacetyl chloride **617** to form amide **618** which was reacted with sodium hydride **31** to afford DKP **1** (see Scheme 105).



Scheme 105

DKP **1** was used as initiator with a range of aryl halides (see Scheme 106 and Table 18). While its efficiency was excellent with aryl iodides, the promotion of the coupling reaction of aryl bromides with benzene was limited.



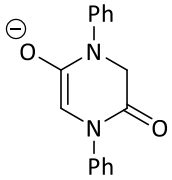
Scheme 106

Computational optimisations (using Gaussian 09,[164] with the MO6-2X functional,[165] the aug-cc-pvdz basis set,[166] and modelling implicit solvation using the Conductor-like Polarizable Continuum Model with the associated parameters of benzene as solvent[167-168]) of the mono-enolate **619** of DKP **620** were made to determine what electronic effects were involved. These calculations found that the phenyl rings of the

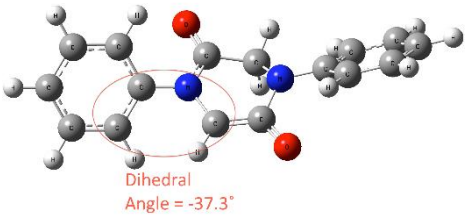
structure of **619** are not co-planar meaning that there is no delocalization of spin density, and thus no stabilization by resonance (see Figure 2).

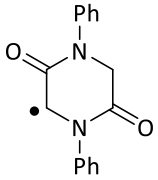
Entry	Substrate	Product	Yield (%)
1	**5**, X = I, R = H	**18**, R = H	80
2	**6**, X = I, R = *o*-OMe	**19**, R = *o*-OMe	64
3	**7**, X = I, R = *m*-OMe	**20**, R = *m*-OMe	61
4	**8**, X = I, R = *p*-OMe	**21**, R = *p*-OMe	61
5	**9**, X = I, R = *o*-Me	**22**, R = *o*-Me	69
6	**10**, X = I, R = *m*-Me	**23**, R = *m*-Me	64
7	**11**, X = I, R = *p*-Me	**24**, R = *p*-Me	60
8	**12**, X = Br, R = H	**18**, R = H	14
9	**13**, X = Br, R = *o*-OMe	**19**, R = *o*-OMe	36
10	**14**, X = Br, R = *m*-OMe	**20**, R = *m*-OMe	2
11	**15**, X = Br, R = *p*-OMe	**21**, R = *p*-OMe	13
12	**16**, X = Br, R = *p*-Me	**24**, R = *p*-Me	12

Table 18: Transition metal-free cross-coupling reaction of aryl iodides and bromides promoted by DKP **1**.



619





620

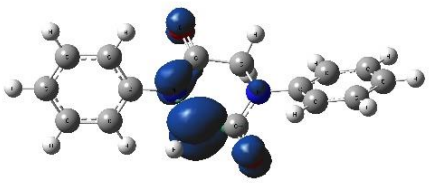
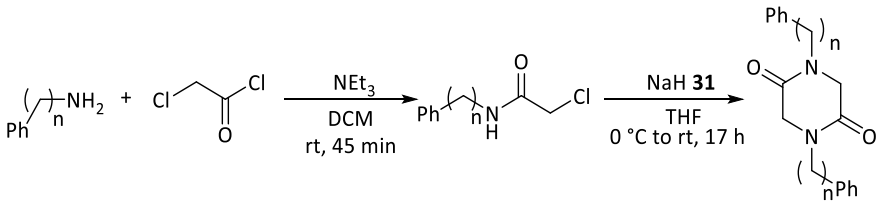


Figure 2: Dihedral angle (C-C-N-C) of electron donor **619** and spin density of radical **620**.

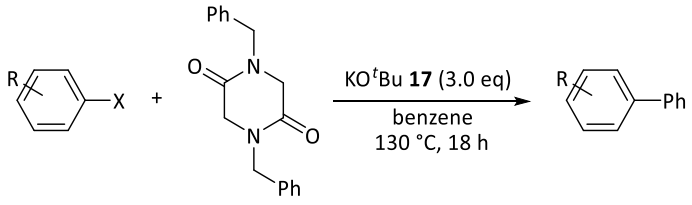
The same observation can be made with radical **620** resulting from **1** after it loses one electron. The spin density of radical **620** shows that the electron is not delocalised over the phenyl rings. Since there is no delocalisation effect involved with DKP anion **619**, the only electrical effect to consider is the inductive effect which is electron-withdrawing with the phenyl substituents.[169] New DKPs **2**, **3** and **4** were synthesised, featuring a carbon chain between the phenyls and the centre ring; all of them were synthesised following the same strategy as DKP **1** (see Scheme 107).



621, n = 1 **617** **624**, n = 1, 80% **2**, n = 1, 43%
622, n = 2 **625**, n = 2, 78% **3**, n = 2, 56%
623, n = 3 **626**, n = 3, 74% **4**, n = 3, 63%

Scheme 107

The addition of a carbon chain between the heterocyclic ring ring of the DKPs and the phenyls should improve their reducing ability as the inductive effect of these alkyl groups would now be donating. *N*-benzyl DKP **2** afforded interesting results as it promoted the cross-coupling reaction of aryl bromides with benzene with a better efficiency than *N*-phenyl DKP **1** (see Scheme 108 and Table 19). Although DKP **2** led to better yields with aryl bromides, it was not as efficient as *N*-phenyl DKP **1** with aryl iodides.



2 (0.1 eq)

Scheme 108

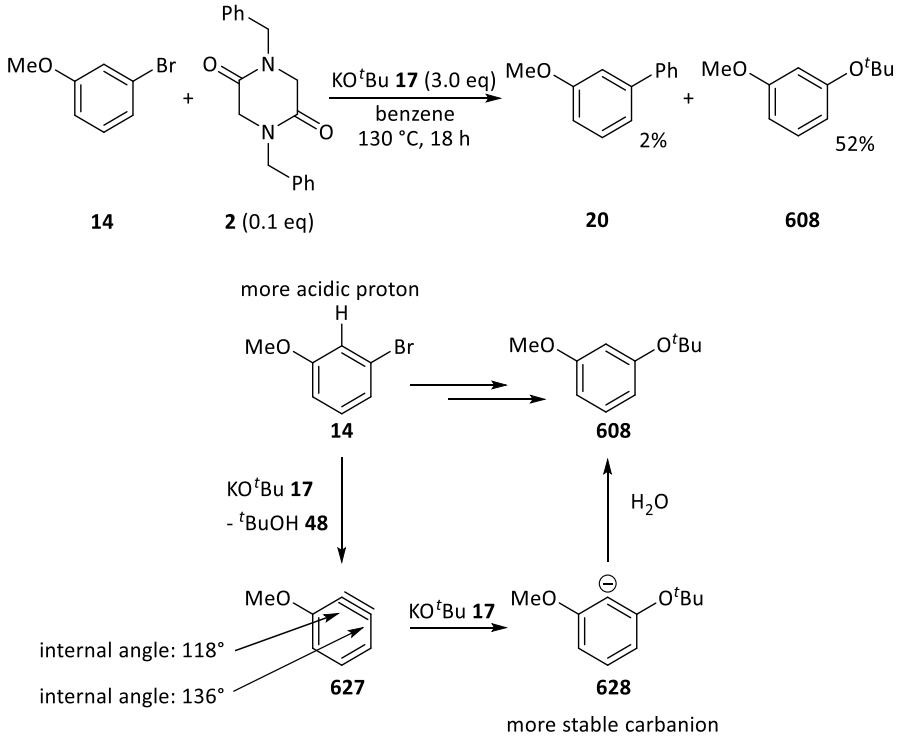
This could be the result of a π,π-stacking complex formed between the DKP and the aryl halide which, in the case of N-phenyl DKP **1**, would bring the aryl halide closer to

the heterocyclic ring, thus allowing an easier electron transfer than in the case of *N*-benzyl DKP **2**, where the aryl halide would be further away from the heterocyclic ring of the DKP.

Entry	Substrate	Product	Yield (%)
1	**5**, X = I, R = H	**18**, R = H	60
2	**6**, X = I, R = *o*-OMe	**19**, R = *o*-OMe	51
3	**7**, X = I, R = *m*-OMe	**20**, R = *m*-OMe	49
4	**8**, X = I, R = *p*-OMe	**21**, R = *p*-OMe	64
5	**9**, X = I, R = *o*-Me	**22**, R = *o*-Me	44
6	**10**, X = I, R = *m*-Me	**23**, R = *m*-Me	57
7	**11**, X = I, R = *p*-Me	**24**, R = *p*-Me	60
8	**12**, X = Br, R = H	**18**, R = H	68
9	**13**, X = Br, R = *o*-OMe	**19**, R = *o*-OMe	50
10	**14**, X = Br, R = *m*-OMe	**20**, R = *m*-OMe	2
11	**15**, X = Br, R = *p*-OMe	**21**, R = *p*-OMe	56
12	**16**, X = Br, R = *p*-Me	**24**, R = *p*-Me	47

Table 19: Metal-free cross-coupling reaction of aryl iodides and bromides promoted by DKP **2**.

There was a particular case with 3-bromoanisole **20** (entry 10 in Tables 18 and 19) for which no DKP seemed to be able to efficiently promote the coupling reaction with benzene. The reaction of this substrate under the cross-coupling conditions led to a selective formation of 1-(*tert*-butoxy)-3-methoxybenzene **608** (42% yield when reaction was made with *N*-benzyl DKP **2**) resulting from a selective benzyne formation followed by a selective nucleophilic addition of *tert*-butoxide **416** (see Scheme 109). Such a process was described in the amination of aryl halides via benzyne formation[170-171] and was recently observed and reported with the same substrate.[172]

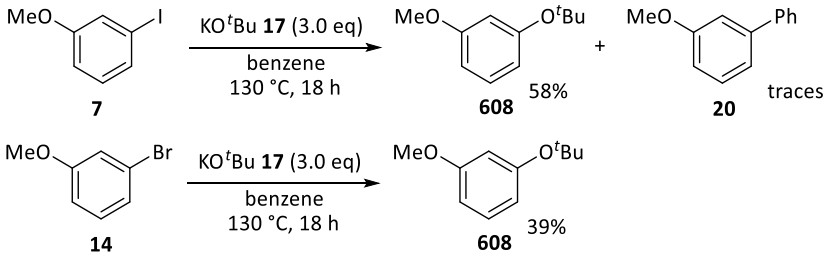


Scheme 109

When considering 3-bromoanisole **14**, there are two labile protons (*ortho* and *para* to the methoxy group) which would lead to two different benzynes by deprotonation. This deprotonation is selective to the proton *ortho* to both the methoxy and the bromide substituents as this proton is the more acidic one. Benzyne **627** could be attacked at both *ortho* and *meta* positions by *tert*-butoxide **416** but the *meta* position is selectively chosen as this leads to carbanion **628**, stabilised by the attractive inductive effect of the methoxy group. Protonation by water then affords 1-(*tert*-butoxy)-3-methoxybenzene **608**.

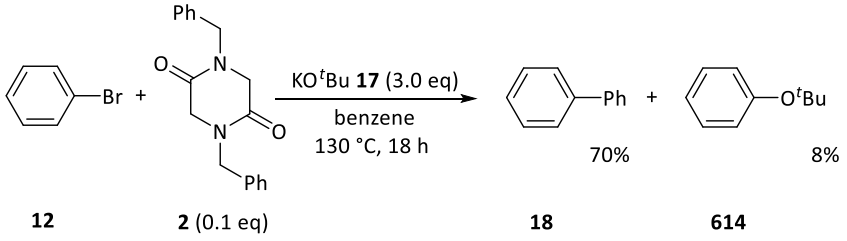
This selectivity of the nucleophilic addition of *tert*-butoxide **416** to benzyne **627** is also in accordance with a computational study published by Houk and Garg[173] who found that the addition should take place on the aryne terminus with the larger internal angle which, in the case of mono-substituted benzyne **627**, is at the *meta* position. Indeed, an optimised structure of benzyne **627** showed that the internal angle at the *meta* position was of 136° and of 118° at the *ortho* position.

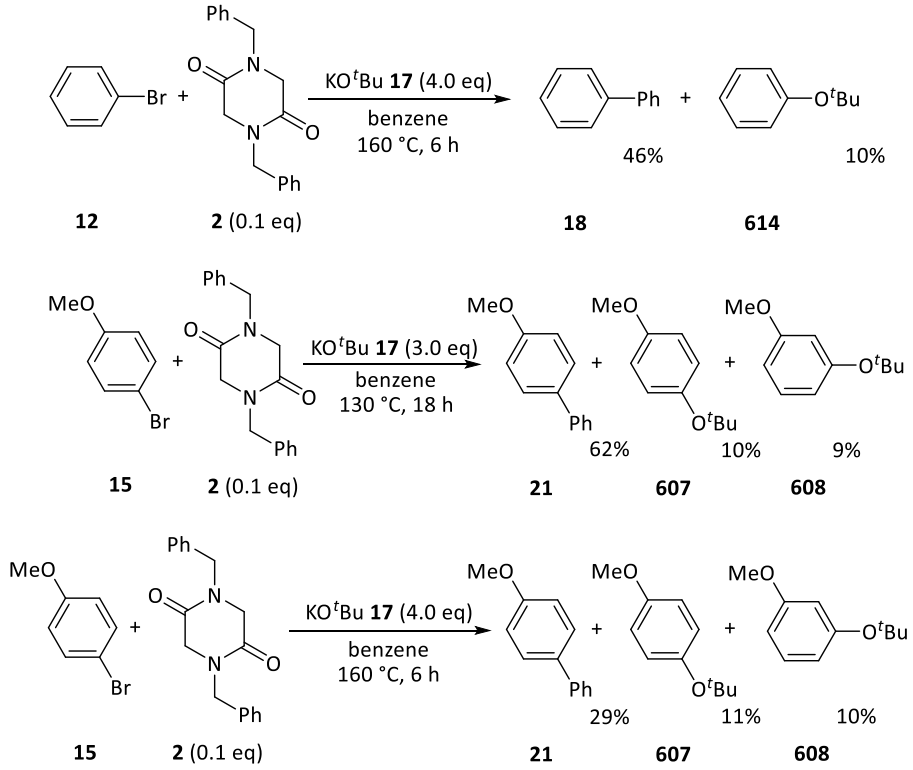
Clearly 3-bromoanisole **14** was not a substrate which could feature in the scope of metal-free cross-coupling reactions. It is interesting to note that the formation of 1-(*tert*-butoxy)-3-methoxybenzene **608** was not observed when the coupling reaction was made with 3-iodoanisole **7**, showing once again that aryl iodides are much better reactive substrates than aryl bromides toward metal-free cross-coupling reactions. However, in the absence of a DKP to promote the coupling reaction, both 3-iodoanisole **7** and 3-bromoanisole **14** afforded selectively 1-(*tert*-butoxy)-3-methoxybenzene **608** (see Scheme 110, a trace amount of coupling product **20** was seen when 3-iodoanisole **7** was used).



Scheme 110

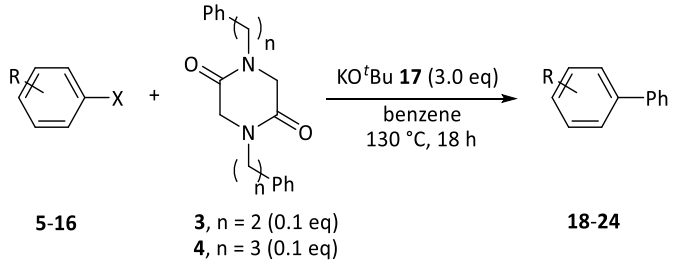
The lack of reactivity of 3-bromoanisole **14** toward metal-free cross-coupling reaction is strong but several other aryl bromides, tested under the standard coupling conditions, showed only a limited formation of species resulting from addition of *tert*-butoxide **416** to benzynes (see Scheme 111). Bromobenzene **12** and 4-bromoanisole **15** also led to formation of *tert*-butoxybenzenes in limited yields. The same reactions were tested under Wilden's temperature and time conditions (160 °C, 6 h) and a smaller amount of the coupling products was found while the amount of the *tert*-butoxybenzenes remained the same.





Scheme 111

The two other DKPs **3** and **4** were also tested with the same scope of substrates (see Scheme 112 and Table 20) to check their efficiency in promoting cross-coupling reactions.



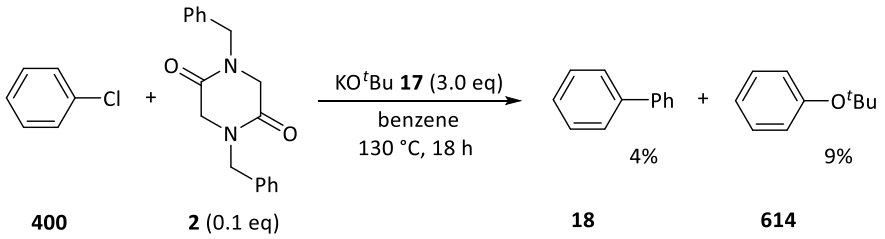
Scheme 112

They were found to be able to promote the cross-coupling reaction of aryl iodides generally more efficiently than *N*-benzyl DKP **2** but not as efficiently for aryl bromides.

Entry	Substrate	DKP	Product	Yield (%)
1	**5**, X = I, R = H	**3**	**18**, R = H	74
2	**5**, X = I, R = H	**4**	**18**, R = H	70
3	**6**, X = I, R = *o*-OMe	**3**	**19**, R = *o*-OMe	59
4	**6**, X = I, R = *o*-OMe	**4**	**19**, R = *o*-OMe	64
5	**7**, X = I, R = *m*-OMe	**3**	**20**, R = *m*-OMe	70
6	**7**, X = I, R = *m*-OMe	**4**	**20**, R = *m*-OMe	69
7	**8**, X = I, R = *p*-OMe	**3**	**21**, R = *p*-OMe	80
8	**8**, X = I, R = *p*-OMe	**4**	**21**, R = *p*-OMe	72
9	**9**, X = I, R = *o*-Me	**3**	**22**, R = *o*-Me	57
10	**9**, X = I, R = *o*-Me	**4**	**22**, R = *o*-Me	56
11	**10**, X = I, R = *m*-Me	**3**	**23**, R = *m*-Me	70
12	**10**, X = I, R = *m*-Me	**4**	**23**, R = *m*-Me	67
13	**11**, X = I, R = *p*-Me	**3**	**24**, R = *p*-Me	78
14	**11**, X = I, R = *p*-Me	**4**	**24**, R = *p*-Me	68
15	**12**, X = Br, R = H	**3**	**18**, R = H	32
16	**12**, X = Br, R = H	**4**	**18**, R = H	32
17	**13**, X = Br, R = *o*-OMe	**3**	**19**, R = *o*-OMe	48
18	**13**, X = Br, R = *o*-OMe	**4**	**19**, R = *o*-OMe	59
19	**14**, X = Br, R = *m*-OMe	**3**	**20**, R = *m*-OMe	2
20	**14**, X = Br, R = *m*-OMe	**4**	**20**, R = *m*-OMe	2
21	**15**, X = Br, R = *p*-OMe	**3**	**21**, R = *p*-OMe	21
22	**15**, X = Br, R = *p*-OMe	**4**	**21**, R = *p*-OMe	29
23	**16**, X = Br, R = *p*-Me	**3**	**24**, R = *p*-Me	29
24	**16**, X = Br, R = *p*-Me	**4**	**24**, R = *p*-Me	37

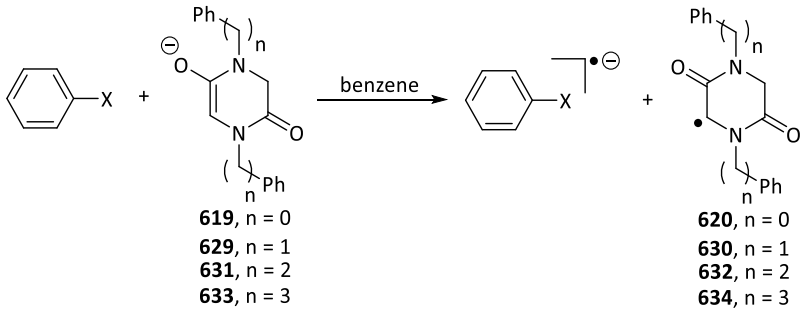
Table 20: Metal-free cross-coupling reaction of aryl iodides and bromides promoted by DKPs **3** and **4**.

Now that aryl iodides and bromides were found to be good substrates for metal-free cross-coupling reaction promoted by DKPs, investigations were made to check if aryl chlorides could also undergo this reaction. Experimentally, no DKP was able to promote the reaction (the best result observed is reported in Scheme 113). Aryl chlorides did not afford the coupling product with benzene in appreciable yields. This raised the question of whether aryl chlorides could receive an electron under the conditions used.



Scheme 113

Optimisations of the electron transfer reactions from the deprotonated DKPs to the aryl halide substrates were now made using Marcus Theory.[174-175] The energies found showed that an electron transfer from a DKP enolate to chlorobenzenes and fluorobenzenes would be a too difficult process to be undertaken (see Scheme 114 and Table 21; only some relevant energies are reported here, the entire set of energies for each donor/substrate system is given in the appendices of this thesis).

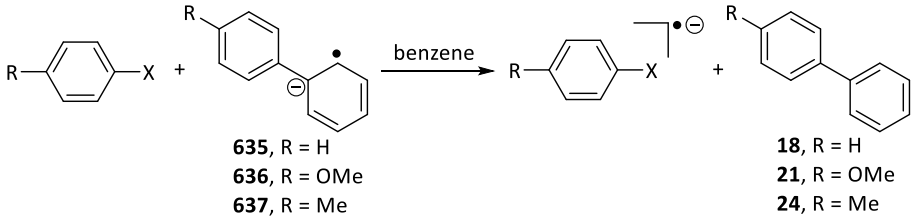


Scheme 114

Entry	Substrate	Initiator	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	**5**, X = I	**619**	31.3	22.9
2	**12**, X = Br	**619**	35.7	27.7
3	**400**, X = Cl	**619**	79.2	54.2
4	**401**, X = F	**619**	92.4	58.4
5	**5**, X = I	**629**	28.6	18.5
6	**12**, X = Br	**629**	32.9	23.4
7	**400**, X = Cl	**629**	68.0	49.9
8	**401**, X = F	**629**	79.5	54.0
9	**5**, X = I	**631**	27.7	17.0
10	**12**, X = Br	**631**	31.9	21.8
11	**400**, X = Cl	**631**	65.0	48.4
12	**401**, X = F	**631**	76.2	52.5
13	**5**, X = I	**633**	27.0	15.1
14	**12**, X = Br	**633**	31.2	20.0
15	**400**, X = Cl	**633**	57.9	46.5
16	**401**, X = F	**633**	56.5	46.5

Table 21: Activation and relative energies of electron transfer reactions from DKP enolates to halobenzenes.

Knowing the mechanistic pathway involved in transition metal-free cross-coupling reactions and the fact that additives such as DKPs are of use only in the initiation process,[143] it is also important to consider the activation and relative energies involved in the electron transfer from biaryl radical anions to aryl halides, as this process is the propagation of the reaction and should, in theory, be an easier process than the initiation. Such energies were calculated and found to be indeed much lower than the energies of the initiation. Interestingly, these energies are low even for aryl chlorides and aryl fluorides (see Scheme 115 and Table 22, more energies are reported in the appendices).



635, R = H
636, R = OMe
637, R = Me

18, R = H
21, R = OMe
24, R = Me

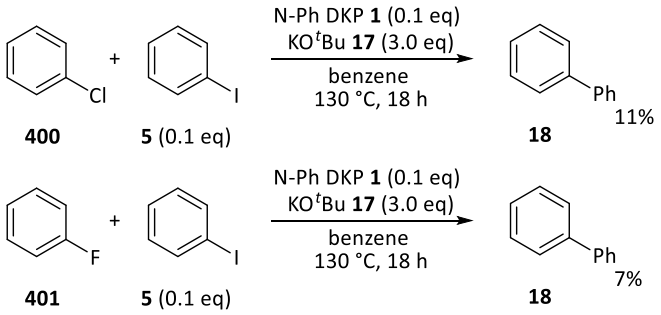
Scheme 115

Entry	Substrate	Donor	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	**5**, R = H, X = I	**635**	8.2	-20.9
2	**12**, R = H, X = Br	**635**	11.2	-16.1
3	**400**, R = H, X = Cl	**635**	10.5	10.4
4	**401**, R = H, X = F	**635**	15.0	14.6
5	**8**, R = OMe, X = I	**636**	6.8	-25.5
6	**15**, R = OMe, X = Br	**636**	9.3	-23.5
7	**638**, R = OMe, X = Cl	**636**	6.7	6.4
8	**639**, R = OMe, X = F	**636**	9.2	8.7
9	**11**, R = Me, X = I	**637**	6.2	-23.7
10	**16**, R = Me, X = Br	**637**	9.8	-19.9
11	**640**, R = Me, X = Cl	**637**	8.2	8.1
12	**641**, R = Me, X = F	**637**	10.5	10.5

Table 22: Activation and relative energies of electron transfer reactions from biaryl radical anions to aryl halides.

Although the energies of the electron transfer involved in the propagation are lower than the electron transfer involved in the initiation, they show that, in the case of aryl chlorides and aryl fluorides, the process is endergonic and the transition state is very late. These results once again suggested that aryl chlorides and aryl fluorides are not good substrates for metal-free cross-coupling reactions. To try to improve their reactivity, reactions were carried out with these substrates in which 10% of the corresponding aryl iodide was also added. The idea was to use this small amount of

aryl iodide to initiate the reaction and see if the generated biaryl radical anions would be sufficient to allow aryl chlorides and fluorides to undergo the coupling reaction with benzene (see Scheme 116).



Scheme 116

Both reactions with chlorobenzene **400** and fluorobenzene **401** as substrates were unsuccessful as the yields of biphenyl **18** suggested that only the substoichiometric amount of iodobenzene **5** reacted efficiently.

There are several concerns that might arise from this kind of reaction. The biphenyl radical anion **635** generated might be at a too low concentration to allow chlorobenzene **400** and fluorobenzene **401** to receive an electron efficiently, although iodobenzene **5** still reacts well at a low concentration. The electron transfer to chlorobenzene **400** and to fluorobenzene **401** might not be happening even if the calculated energies for the electron transfer from biphenyl radical anion **635** suggest that it could be made under the reaction conditions. Another possibility might be the departure of the chloride/fluoride after the corresponding halobenzene has received one electron. The carbon-chlorine/carbon-fluorine bonds are stronger than carbon-iodine, which is likely to make the formation of phenyl radical **474** more difficult with chlorobenzene **400** and fluorobenzene **401**.

Other computational calculations were made to check that the propagation of the cross-coupling reaction was indeed an easy process allowing the reaction to be undergone by itself. Relative energies and energy barriers were calculated for the C-C bond formation between the aryl radical and benzene and for the deprotonation

by KO^{t}Bu **17** to form the biaryl radical anion (see Figure 3 for the case of halobenzenes and Table 22 for the energies of a range of aryl halides).

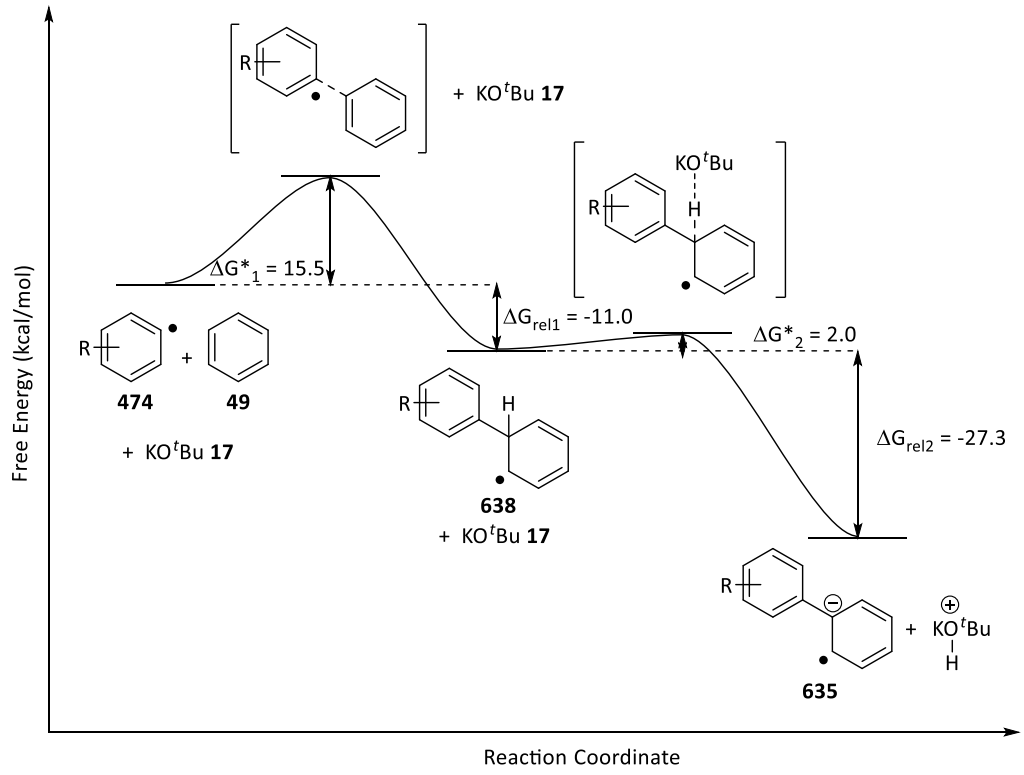


Figure 3: Energy profile of BHAS mechanism with halobenzenes and benzene (energies reported for R = H).

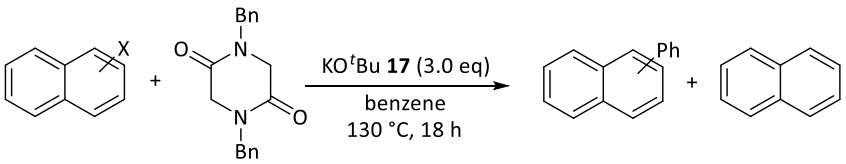
Entry	Substrate	ΔG*$_1$	ΔG$_{rel1}$	ΔG*$_2$	ΔG$_{rel2}$
1	R = *o*-OMe	16.1	-9.8	0.0	-26.1
2	R = *m*-OMe	15.1	-10.7	-0.1	-25.2
3	R = *p*-OMe	13.4	-13.8	0.2	-23.9
4	R = *o*-Me	15.5	-8.7	2.0	-8.7
5	R = *m*-Me	16.0	-10.4	1.8	-27.7
6	R = *p*-Me	10.2	-18.2	2.9	-26.4

Table 22: Energies of BHAS mechanism with substituted aryl halides and benzene.

As expected, the limiting step is the C-C bond formation between the aryl radical and benzene with energy barriers of about 15 kcal/mol which is easily achievable at 130

°C. The deprotonation step is quite straightforward as the barrier is very small (or non-existent) and both steps are exergonic. These results are in accordance with the role of propagation given to this process meaning that, as long as the initiation step is successful, the overall coupling reaction should be successful as well.

Considering the formation of an aryl halide radical anion, the free electron is more likely to be given into a π* orbital of the aromatic ring and will then be delocalised over the entire ring. Correlation between π* orbitals and the σ* orbital of the carbon-halide bond allows the free electron to be then given to the σ* orbital. The resulting destabilisation should lead to the departure of the halide.[176] However, in the case of chloro and fluorobenzenes, the departure of the halide might take too much time, which will stop the formation of the aryl radical. Increasing the delocalisation of the free electron of the aryl halide radical anion should improve the SET process and give enough time for the departure of the halide. A range of halonaphthalenes were tested with *N*-benzyl DKP **2** under the standard coupling conditions (see Scheme 117 and Table 23). As expected, the coupling with benzene was successful with 1-iodonaphthalene **639**, 1- and 2-bromonaphthalene **280** and **640** and surprisingly a notable amount of the coupling product **642** was seen when 1-chloronaphthalene **641** was used which can be explained by the LUMO of **641** being much lower in energy than the LUMO of chlorobenzene **400**. Also, reduction into naphthalene **110** was observed when 1-halonaphthalenes were used.



639, 1-I
280, 1-Br
640, 1-Cl
641, 2-Br

2

642, 1-Ph
643, 2-Ph

110

Scheme 117

Entry	Substrate	Coupling Product (%)	Naphthalene 110 (%)
1	**639**	**642** (46)	(16)
2	**280**	**642** (42)	(8)
3	**640**	**642** (15)	(3)
4	**641**	**643** (49)	(0)

Table 23: Metal-free cross-coupling reactions of halonaphthalenes with benzene promoted by N-benzyl DKP **2**.

Although the reaction happened with 1-chloronaphthalene **641**, the yield was still limited compared with the corresponding iodide and bromide substrates. This substrate was not exclusive to the promotion of the coupling reaction by N-benzyl DKP **2** as the commonly used promoter, 1,10-phenanthroline **405**, also afforded 1-phenylnaphthalene **642** (29%) and naphthalene **110** (9%).

Some electron-poor aryl halides have also been tested under transition metal-free cross-coupling reaction with benzene conditions. The outcome of these experiments has been reported in the literature (reference added in the author's publications list on the last page of this thesis).

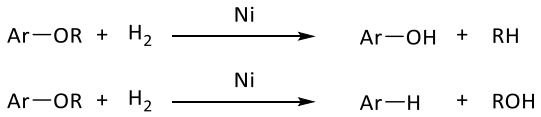
2.3 Conclusion and future work

A range of diketopiperazines have been found to be able to promote the metal-free cross-coupling reaction of various aryl iodides and bromides with benzene. Both *N*-phenyl DKP **1** and N-benzyl DKP **2** offer interesting organic additives as they are easy to synthesise and the first is a good promoter for the coupling of aryl iodides with benzene while the second is a good one for the coupling of aryl bromides with benzene. The remaining challenge of this transition metal-free cross-coupling reaction is to extend its scope to aryl chlorides and fluorides which would likely require even stronger electron donors and a way to overcome their poor reactivity.

Another process limiting their reactivity toward a cross-coupling reaction is benzyne formation which is an easier process for these substrates to undertake under the conditions usually used (use of KO^{t}Bu **17** and a high temperature). Due to the poor reactivity of aryl chlorides and fluorides toward transition metal-free cross-coupling reactions with benzene, it may be more promising to focus toward the expansion of the scope of species the aryl halides could be coupled with. The challenge would be even bigger as some arenes, such as toluene, have been reported to lead to the formation of three regioisomers when coupled with an aryl radical,[111] which would lead to difficult purifications.

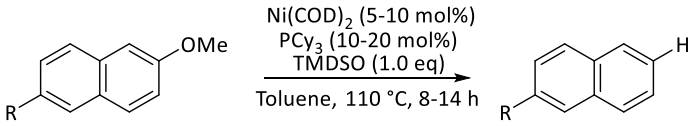
Chapter 3: Unexpected reactivity of *tert*-butyllithium with benzene and alkyl aryl ethers

The reduction of alkyl aryl ethers is highly desirable in organic chemistry as it can be used to deprotect sensitive phenolic compounds, featured in many natural products. In 1912, Mailhe and Murat used nickel and hydrogen to reduce, without selectivity, alkyl aryl ethers to the corresponding phenols, alkanes, alcohols and benzenes (see Scheme 118).[177]



Scheme 118

The use of alkali metals[178] and transition metal complexes combined with reducing agents ($NaBH_4$,[179] $PhSiH_3$[180] or Bu_3SnH[181]) was also reported. The use of nickel catalysts has led to extensive advances in the reduction of inert C-O bonds. Martin used tetramethyldisiloxane (TMDSO) as a hydride source and tricyclohexylphosphine (PCy_3) as a ligand in the presence of a nickel catalyst to reduce alkyl aryl ethers into the corresponding arenes and alcohols in excellent yields (see Scheme 119).



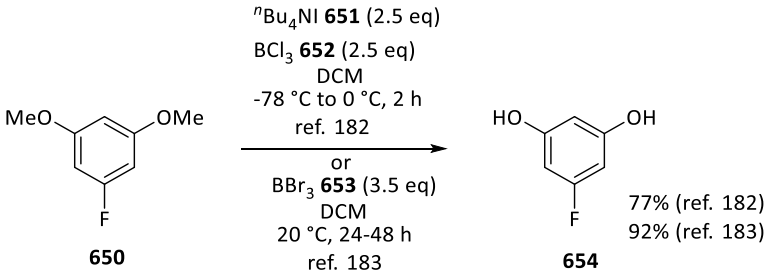
644, R = H
645, R = TMS
646, R = Ph
647, R = CO_2Me

110, R = H, 99%
648, R = TMS, 86%
643, R = Ph, 89%
649, R = CO_2Me, 88%

Scheme 119

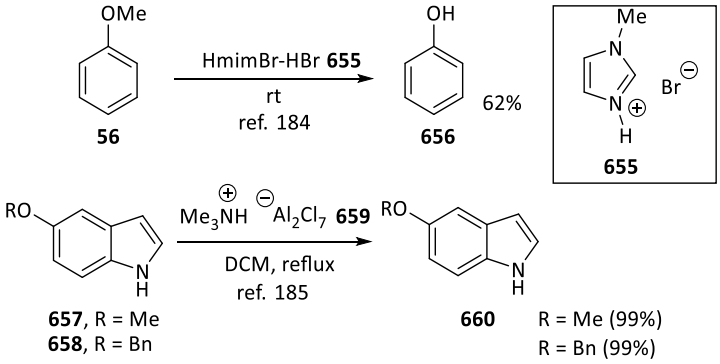
Lewis acids were also used for the deprotection of alkyl aryl ethers. Coe and co-workers used boron trichloride **652** and enhanced its reactivity toward primary alkyl aryl ethers by adding tetra-*n*-butylammonium iodide **651**.[182] The efficiency of this

procedure was greater than the use of the more common boron tribromide **653**,[183] as Coe showed with the cleavage of 3,5-dimethoxyfluorobenzene **650** (see Scheme 120).



Scheme 120

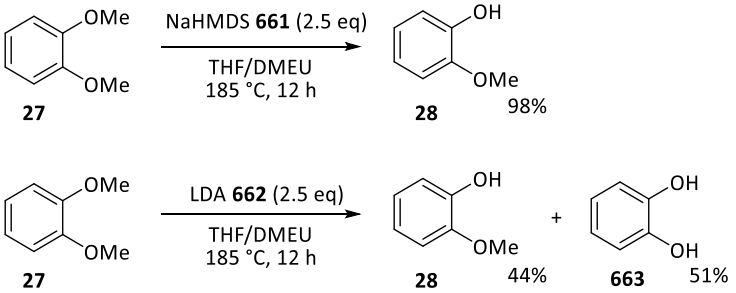
Ionic liquids were also found to be able to dealkylate alkyl aryl ethers. Driver and Johnson used 3-methylimidazoliumbromohydrogenate **655** to cleave anisole **56** in good yield,[184] while Kemperman extended the use of ionic liquids to the cleavage of methyl, allyl and benzyl ethers (see Scheme 121).[185]



Scheme 121

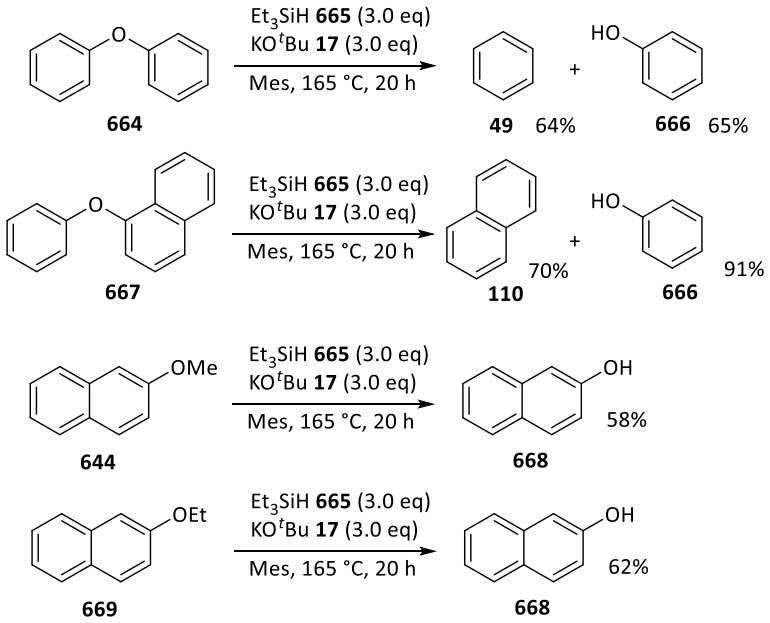
Several bases were used to deprotect alkyl aryl ethers including NaHMDS **661** and LDA **662**.[186] They were reported as efficient nucleophiles for the cleavage of alkyl aryl ethers and the α-stabilizing effect of the silyl groups of NaHMDS **661** made it less reactive and thus more selective than LDA **662** (see Scheme 122).

This difference of reactivity allowed selective formation of 2-methoxyphenol **28** from 1,2-dimethoxybenzene **27** when NaHMDS **661** was used while the reaction with LDA **662** afforded both 2-methoxyphenol **28** and catechol **663** in similar yields.



Scheme 122

Recently, Grubbs and co-workers used triethylsilane **665** and KO^{t}Bu **17** to regioselectively cleave diaryl ethers and alkyl aryl ethers without requirement for any transition metal (see Scheme 123).[187]

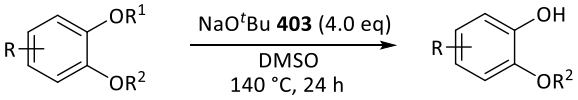


Scheme 123

Even more recently, Loh reported a selective dealkylation of alkyl aryl ethers using sodium *tert*-butoxide **403** in DMSO.[188] These conditions were applied to a range of ethers, including mono and polymethylated aryl ether systems (see Scheme 124 and Table 24).

Several radical scavengers (benzoquinone, 2,6-di-*tert*-butylphenol…) shut down the reaction which was interpreted as meaning that radicals were involved in the process.

Using TEMPO as a radical scavenger did not stop the reaction from happening, which can be explained by the ability of TEMPO to abstract a hydrogen from phenols.[189] Loh proposed an electron transfer from dimsyl anion **582** (formed by deprotonation of DMSO by NaO^{t}Bu **403**) to the alkyl aryl ether **674** to form radical anion **675** which undergoes homolysis to release methyl radical **556** and phenolate **677** which affords phenol **678** upon protonation (see Scheme 125).



Scheme 124

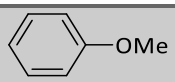
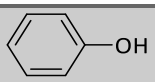
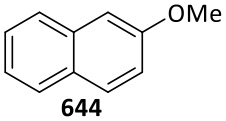
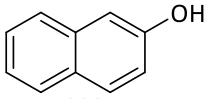
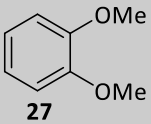
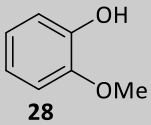
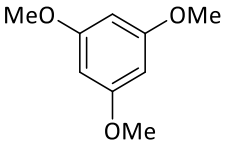
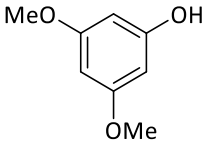
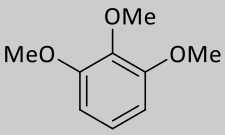
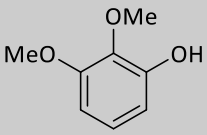
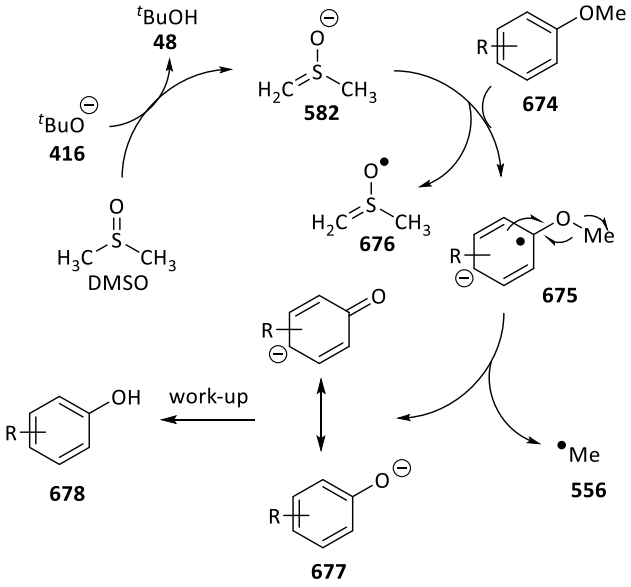
Entry	Substrate	Product	Yield (%)
1	 **56**	 **666**	62
2	 **644**	 **668**	93
3	 **27**	 **28**	73
4	 **670**	 **671**	86
5	 **672**	 **673**	63

Table 24: Selective deprotection of alkyl aryl ethers.



Scheme 125

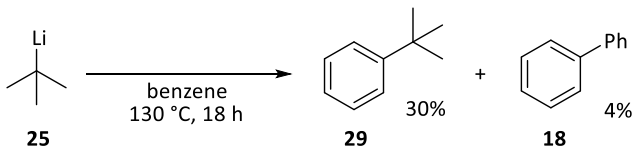
This section will focus on the investigations of the ability of the strong base *tert*-butyllithium **25** to perform the deprotection of alkyl aryl ethers and on evidence showing the addition of phenyl anion and *tert*-butyl anion to a benzene ring.

3.1 Action of *tert*-butyllithium on benzene

The idea to use such a reactive and strong base as *tert*-butyllithium came up while experimenting a possible double deprotonation of diketopiperazines. Evidence that only a single deprotonation was necessary for initiating cross-coupling reactions has already been reported in this thesis but achieving a double deprotonation to generate an antiaromatic dienolate such as **510** (Scheme 82, page 72) would afford powerful electron donors. However, no single evidence of any formation of a dienolate such as **510** has ever been observed. More importantly, the presence or the absence of DKP had no impact on the chemistry that will be described here.

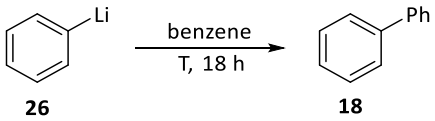
Before focusing on the deprotection of alkyl aryl ethers, it is worth mentioning the formation of *tert*-butylbenzene **29** as a side-product in these reactions.

Investigations were conducted on the reactivity of ^{t}BuLi **25** with benzene (see Scheme 126). Reacting the base in benzene for 18 h at 130 °C did not only afford *tert*-butylbenzene **29** (30%) but also biphenyl **18** (4%).



Scheme 126

Considering the reaction between ^{t}BuLi **25** and benzene **49**, it is reasonable to suggest that the base might be strong enough to deprotonate benzene and afford phenyllithium **26**. The question remained on how phenyllithium **26** could react with benzene **49** to form biphenyl **18**. Phenyllithium **26** (1.0 mmol) was reacted in benzene at various temperatures and showed formation of biphenyl for temperatures higher than, or equal to, 130 °C (see Scheme 127 and Table 25, a fresh bottle of phenyllithium **26** was used for these experiments). It is commonly known that phenyllithium **26** can oxidise to phenyl radical **474**, with traces of air,[190] which leads to formation of biphenyl **18** by combination of two phenyl radicals **474**. For this reason, phenyllithium **26** (1.0 mmol) was quenched with water at 0 °C and a small amount of biphenyl **18** was found (4%).



Scheme 127

These experiments showed the influence of the temperature on the reaction between PhLi **26** and benzene **49**. There were two hypotheses on how this reaction would occur (see Scheme 128):

Entry	T (°C)	18 (%)
1	rt	4
2	70	4
3	100	4
4	130	30
5	160	42

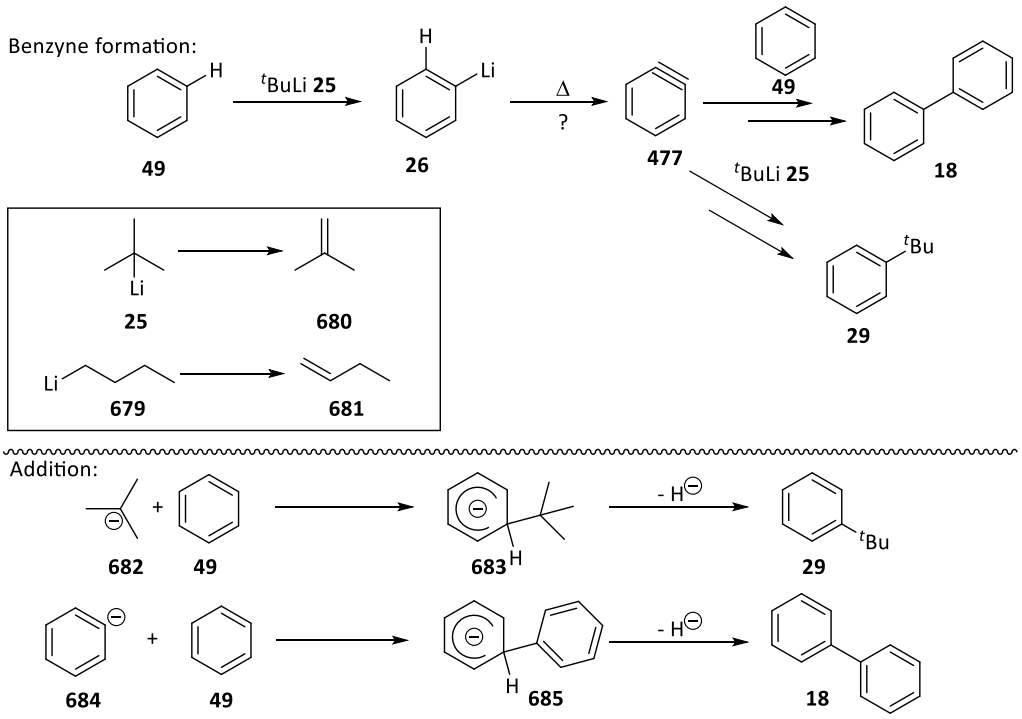
Table 25: Biphenyl **18** formation from reaction of phenyllithium **26** with benzene at various temperatures.

-Benzyne formation: It is known that ^{t}BuLi **25** and ^{n}BuLi **679** undergo a thermal decomposition into 2-methylprop-1-ene **680** and but-1-ene **681** respectively when exposed at room temperature.[191] If PhLi **26** could undergo a similar decomposition into benzyne **477** then it would be able to couple with benzene. Benzyne **477** could also be attacked by *tert*-butyl anion **682** leading to formation of *tert*-butylbenzene **29**.

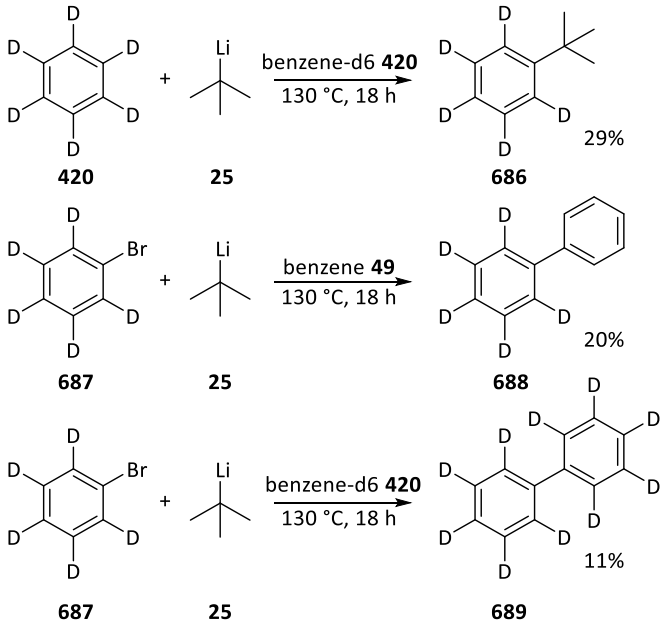
-Nucleophilic addition to benzene: The other possibility would be a direct addition of phenyl anion **684** to a benzene ring **49** followed by a hydride elimination. Similarly, *tert*-butyl anion **682** would add to benzene **49**.

To get evidence on the nature of the mechanistic pathway involved here, several deuterium-labelling experiments were conducted (see Scheme 129). Reacting ^{t}BuLi **25** in benzene-d6 **420** led to formation of *tert*-butylbenzene-d5 **686** (29%), and no biphenyl-type species was observed in the crude product.

Two experiments were run with bromobenzene-d5 **687** which was reacted with ^{t}BuLi **25** (1.0 eq), to perform a lithium/bromide exchange, in both benzene **49** and benzene-d6 **420**. In benzene **49**, the reaction afforded biphenyl-d5 **688** (20%) while in benzene-d6 **420**, it afforded biphenyl-d10 **689** (11%). Since all three reactions were quenched with water and no deuterium was replaced by a hydrogen, the benzyne mechanism can be ruled out.



Scheme 128



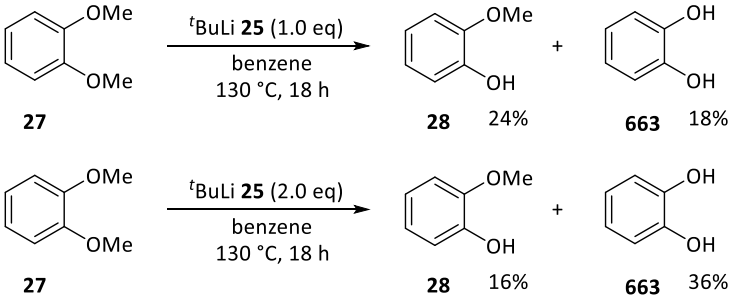
Scheme 129

This study highlighted the possibility for *tert*-butyl anion **682** and phenyl anion **684** to add to benzene at high temperature which leads to a hydride elimination. The process is fundamentally different than normal nucleophilic aromatic substitutions

which require a good leaving group (I, Br, Cl or F) and preferentially an electron-withdrawing group on the *ortho*- and/or *para*-positions (usually NO_2). In the case represented here, no such good leaving group nor electron-withdrawing groups are present, which explains the requirement for high temperatures (as seen in Table 25) as no particular stabilisation is involved.

3.2 Alkyl aryl ether deprotection by *tert*-butyllithium

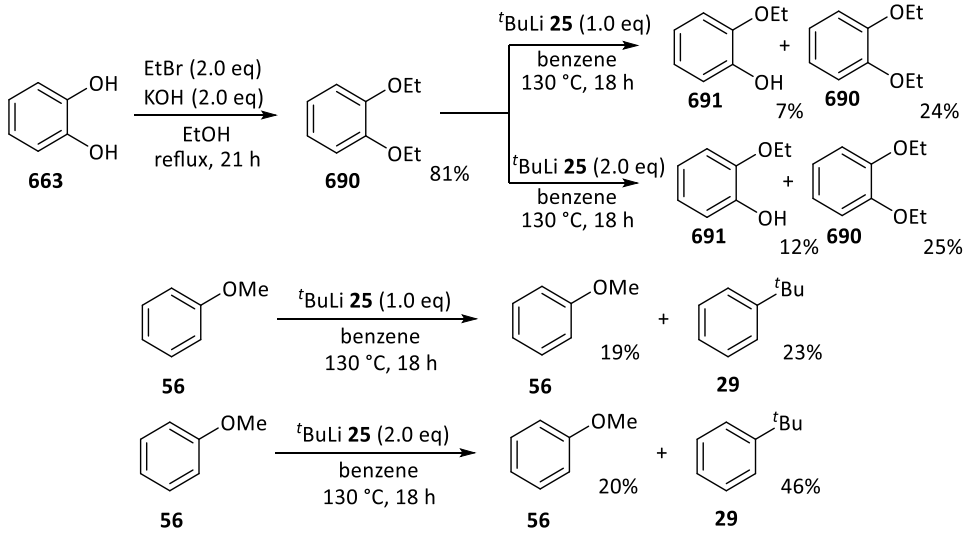
As mentioned earlier, ^{t}BuLi **25** was found to be able to deprotect alkyl aryl ethers. Reaction of 1,2-dimethoxybenzene **27** with ^{t}BuLi **25** in benzene at 130 °C for 18 h afforded both mono-deprotected product, 2-methoxyphenol **28**, and doubly-deprotected product, catechol **663** (see Scheme 130). Increasing the amount of ^{t}BuLi **25**, from one equivalent to two, also increased the amount of catechol **663** being formed. The yields were not found to be particularly high, which is not surprising when knowing that ^{t}BuLi **25** also reacts with benzene (as seen in 3.1) and, the conversion of the starting material was not complete. When some substrates, especially 1,2-dimethoxybenzene **27**, were tested, an inseparable mixture of the starting material and other unidentified anisole species were formed. This mixture could be separated from the deprotection products but only as a mixture.



Scheme 130

The same reaction was tested on 1,2-diethoxybenzene **690** (synthesised by alkylation of catechol **663** with ethyl bromide) and a clearly decreased reactivity was observed

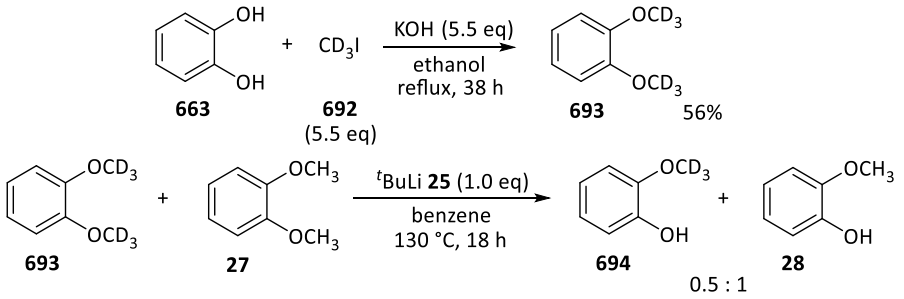
(see Scheme 131). No formation of catechol **663** was observed and the yields of the mono-deprotection, to afford 2-ethoxyphenol **691**, were low. This highlighted the limit of the scope of the alkyl group of the alkyl aryl ethers, that could undergo deprotection by action of ^{t}BuLi **25**. Also, reaction of anisole **56** under these conditions did not afford any phenol **666** and anisole **56** (19%) was recovered from the reactions, along with *tert*-butylbenzene **29**. This showed another limitation of the scope as mono alkyl aryl ethers were not affording the corresponding phenol.



Scheme 131

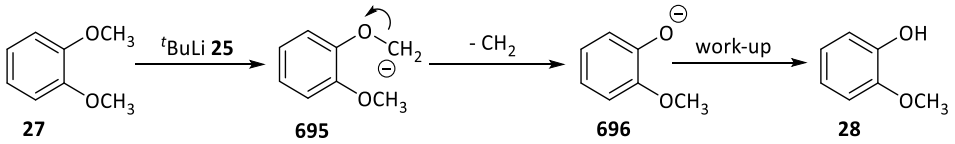
To understand what role the base had in this reaction, 1,2-bis(methoxy-d_3)benzene **693** was synthesised and tested in a one-pot competition experiment alongside 1,2-dimethoxybenzene **27** under the same conditions with one equivalent of ^{t}BuLi **25** (see Scheme 132). The reaction afforded both deuterated **694** and non-deuterated **28** 2-methoxyphenols with a ratio of 0.5: 1 respectively showing that the reaction is more easily achieved with non-deuterated substrate.

This would suggest a deprotonation on the methyl of the methoxy group to afford anion **695** (see Scheme 133 for a representation with 1,2-dimethoxybenzene **27** as substrate) which could undergo a carbene elimination to form phenolate **696** which would afford phenol **28** upon protonation.



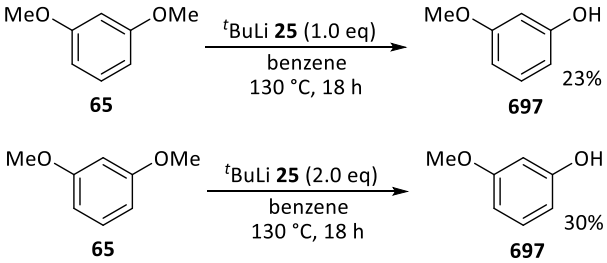
Scheme 132

This carbene elimination has not been put into evidence as the substrate scope of this alkyl aryl ether deprotection does not include ethers with large alkyl groups therefore, no isolation of any species resulting from further reaction of the carbene would occur.



Scheme 133

Other ethers were tested with ^{t}BuLi **25**. 1,3-Dimethoxybenzene **65** was found to be able to undergo a mono-deprotection to form 3-methoxyphenol **697**. The reaction showed a similar efficiency with one and two equivalents of ^{t}BuLi **25** and overall, was less efficient than with 1,2-dimethoxybenzene **27 (**see scheme 134).

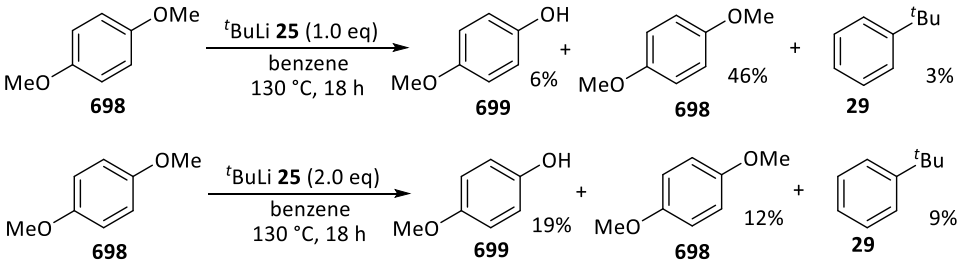


Scheme 134

Similarly to the same reactions made with 1,2-dimethoxybenzene **27**, an inseparable mixture of anisoles and remaining starting material was found in the crude product of the possible phenolic products and only the mono-deprotected product was

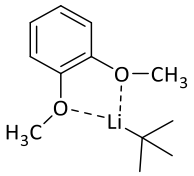
formed (in 23% yield when one equivalent of ^{t}BuLi **25** was used and 30% when two equivalents were used).

The reaction with 1,4-dimethoxybenzene **698** also afforded only the mono deprotection product, 4-methoxyphenol **699** (see Scheme 135). The reaction was much less efficient than with 1,2-dimethoxybenzene **27** and 1,3-dimethoxybenzene **65** and no unidentified products were formed this time; only the remaining starting material **698**, the deprotected product **699** (6% when one equivalent of ^{t}BuLi **25** was used and 19% when two equivalents were used) and *tert*-butylbenzene **29** were found.



Scheme 135

The difference of reactivity between *o*-, *m*- and *p*-dimethoxybenzenes under these conditions might come from a chelation between the lithium of ^{t}BuLi **25** and the oxygens of 1,2-dimethoxybenzene **27** which would facilitate the deprotonation of one of the methoxy groups (see Scheme 136). The chelation would be much less efficient with 1,3-dimethoxybenzene **65** (or could not occur) and would not occur with 1,4-dimethoxybenzene **698**.

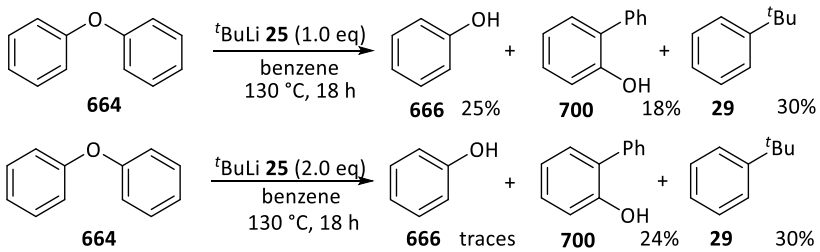


Scheme 136

A biaryl ether case was tested using diphenyl ether **664** which led to a particular reaction (see Scheme 137). When one equivalent of base was used, formation of phenol **666** was observed alongside another species which primary data analysis

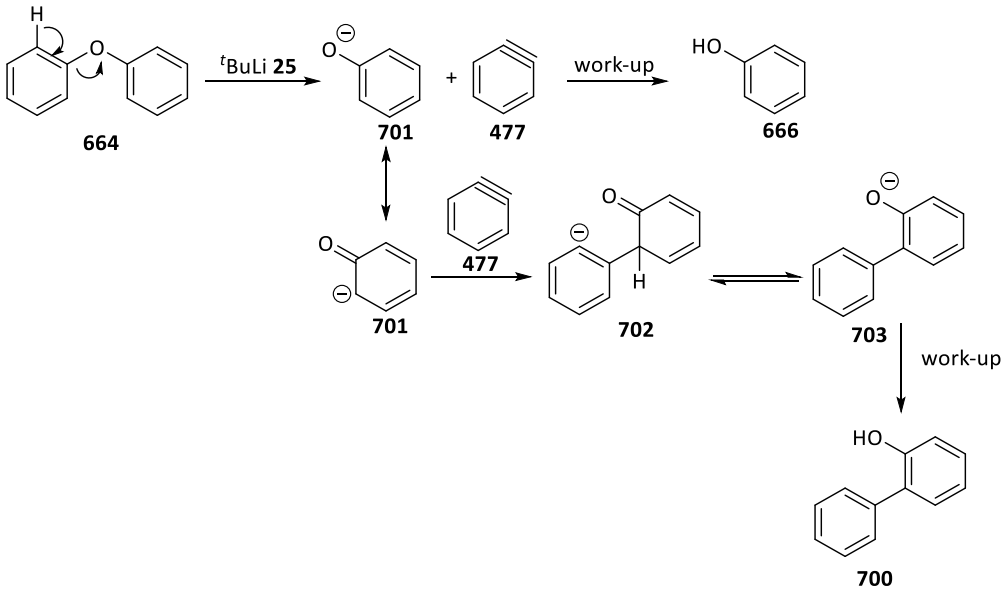
showed to contain a phenol and had the same mass as the starting material. Further analysis and comparison with literature confirmed formation of biphenyl-2-ol **700**. When two equivalents of base were used, only a trace amount of phenol **666** was found alongside an increased amount of biphenyl-2-ol **700**.

The reaction pathway proposed here is a benzyne formation by elimination of one *ortho* proton of diphenyl ether **664**. The resulting phenolate **701** can either not react any further and will be protonated upon work-up to afford phenol **666** or, react through its *ortho* carbon to add to benzyne **477** to form aryl anion **702** in equilibrium with biphenyl-2-olate **703** (see Scheme 138).



Scheme 137

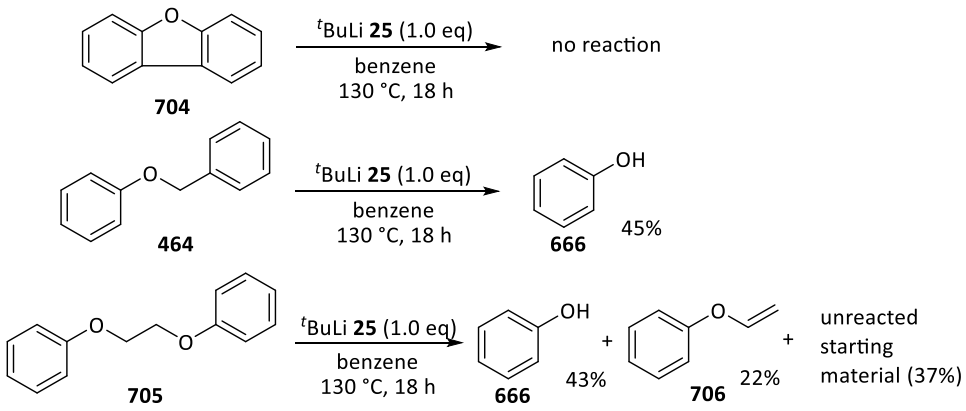
Reaction of diphenyl ether **664** with Grignard reagents at high temperature was reported to afford both phenol **666** and biphenyl-2-ol **700**.[192]



Scheme 138

Since no incorporation of the alkyl part of the Grignard reagent was observed in this case, it is likely that the use of the Grignard reagent led to the same elimination process and formation of both phenolate **701** and benzyne **477**.

Dibenzofuran **704** was also tested under the same conditions but it showed no reactivity and thus no formation of biphenyl-2-ol **700** (see Scheme 139). Benzyloxybenzene **464** afforded phenol **666** while diphenoxyethane **705** afforded phenol **666** and vinyloxybenzene **706**.



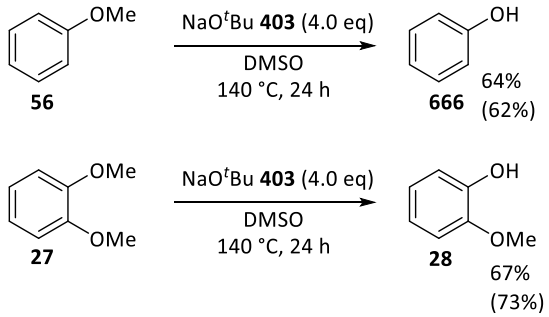
Scheme 139

tert-Butyllithium **25** has been shown to be able to deprotect several ethers using its strong basicity. The process leads to elimination of carbenes or phenolates to afford the deprotected products. Although the deprotection is happening, the process is difficult and requires harsh conditions and, in some cases, delicate purification.

3.3 Alkyl aryl ether deprotection by electron transfer, evidence for the mechanism?

The report made by Teck Peng Loh of the deprotection of alkyl aryl ethers by reaction with sodium *tert*-butoxide **403** in DMSO[188] has already been described (Scheme 124). The reaction was reported only with sodium *tert*-butoxide **403** as a base, which could open once again the debate on a possible electron transfer from *tert*-butoxide **416**.

Two reactions reported by Loh were reproduced and afforded similar results (see Scheme 140). Interestingly, anisole **56** was deprotected into phenol **666** under these conditions while it could not be by action of ^{t}BuLi **25**. Other bases were tested (potassium *tert*-butoxide **17** and sodium hydride **31**) under the same conditions and afforded the expected deprotected products (see Table 25) suggesting that the reaction between the base used and the DMSO solvent was the source of the electron transfer.

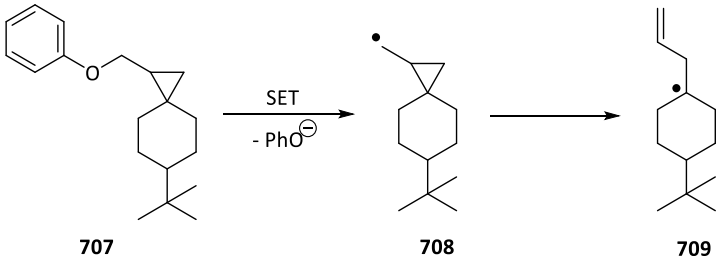


Scheme 140

Entry	Substrate	Base	Product	Yield (%)
1	**56**	KO^{t}Bu **17**	**666**	47
2	**56**	NaH **31**	**666**	53
3	**27**	NaH **31**	**28**	44

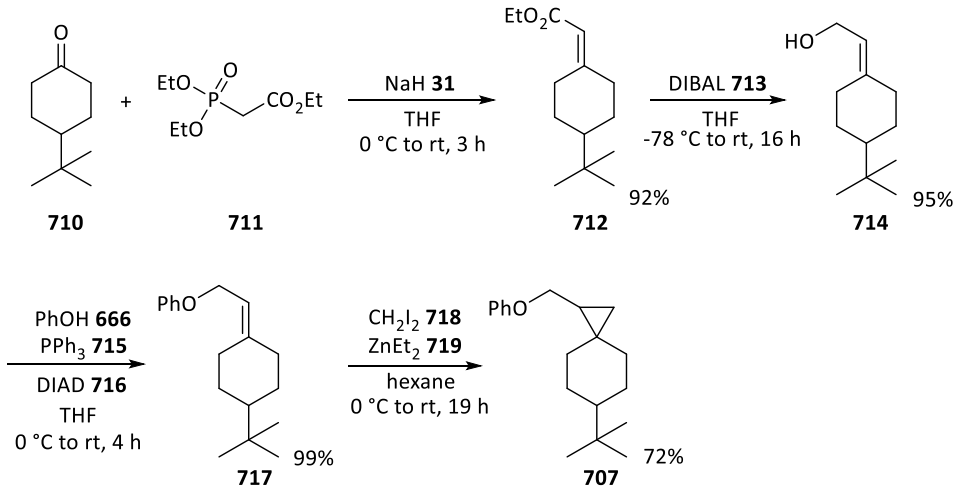
Table 25: Teck Peng Loh reaction with other bases under the same conditions.

To look for evidence of an electron transfer and thus a radical process, a specific substrate, 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane **707**, was synthesised to be tested under Loh's conditions. If the reaction was going via an electron transfer, the radical species **708** resulting from the C-O bond cleavage would open the cyclopropane ring and should lead to a species that could be isolated and characterized (see Scheme 141).



Scheme 141

Substrate **707** was synthesised by a Horner-Wadsworth-Emmons reaction of 4-*tert*-butylcyclohexanone **710** with triethyl phosphonoacetate **711** followed by a DIBAL reduction of ester **712** into alcohol **714** which was then etherified into alkyl aryl ether **717** by a Mitsunobu reaction and finally converted into **707** by a Simmons-Smith cyclopropanation (see Scheme 142).

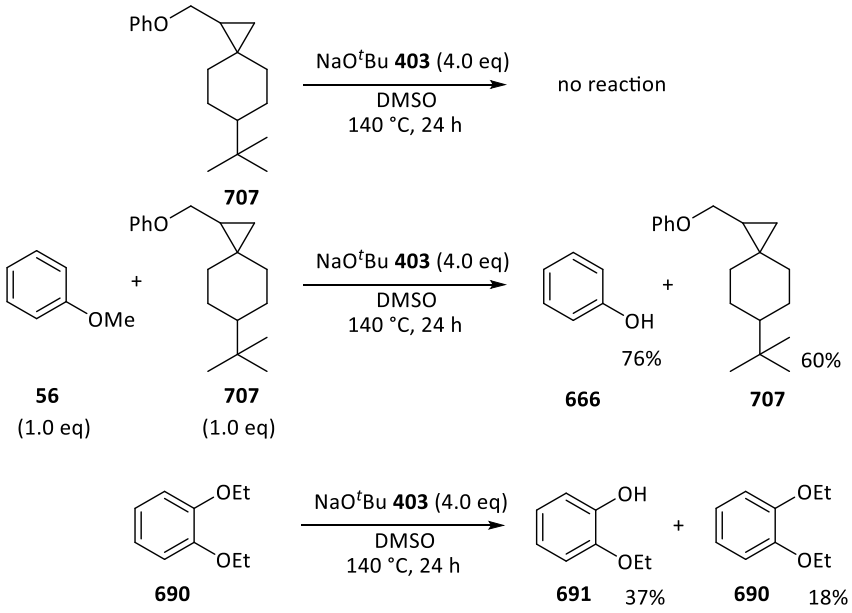


Scheme 142

Reaction of substrate **707** under Loh's conditions led to no reaction; phenol was not formed and only **707** was recovered (88%). The same reaction was run again but with both substrate **707** and anisole **56** present and phenol **666** (76%) was found alongside the remaining substrate **707** (60%). However, no other species that might arise from further reaction of the cleaved alkyl part of **707** was seen.

This led to more evidence of the limited substrate scope for alkyl aryl ether deprotection under these conditions, increasing the size of the alkyl group drastically decreases reactivity. Indeed, while no starting material was seen when anisole **56** and

1,2-dimethoxybenzene **27** were reacted under Loh's conditions, the same reaction made with 1,2-diethoxybenzene **690** showed a mixture of both the starting material (18%) and 2-ethoxyphenol **691** (37%) (see Scheme 143).



Scheme 143

This limited scope for the alkyl group of alkyl aryl ethers will make it difficult to assess the mechanistic pathway involved in their deprotection. Also, substrate **707** was tested with ^{t}BuLi **25** in benzene but, in this case too, no reaction was observed.

3.4 Conclusion and future work

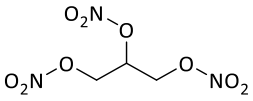
The strong reactivity of *tert*-butyllithium has led to unexpected chemistry by affording evidence of nucleophilic additions to benzene and deprotection of alkyl aryl ethers. Although the reactivity of this base is undeniable, its danger restricts its use. While it could be possible to improve the deprotection of alkyl aryl ethers by increasing the reaction temperature (meaning higher than 130 °C) this would make this chemistry even more experimentally hazardous as it also uses benzene as solvent. Although the chemistry that has been described here is dangerous, the

ability of nucleophiles to add to a benzene ring when exposed at high temperature should be explored further with other aromatic species as similar reactivity could be observed and would eventually lead to new avenues for organic chemistry.

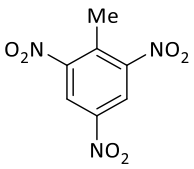
Regarding the electron transfer process likely involved in the deprotection of alkyl aryl ethers reported by Loh,[188] it would require another radical clock substrate to confirm the nature of this process. This would be challenging as the substrate would need to be large enough, so that the product resulting from the radical clock rearrangement could be isolated, without stopping the alkyl aryl ether deprotection from happening.

Chapter 4: Reduction of Nitro and Azobenzenes with DMAP Donor

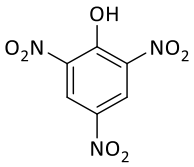
The reduction of nitrobenzenes is of major importance in organic chemistry as it can lead to several nitrogen-containing compounds used as building blocks such as azoxybenzenes, azobenzenes, hydrazines and anilines, depending on the conditions used for the reduction. Then nitro group is also present in many explosive species (see Scheme 145): nitroglycerine **720**, a well-known explosive, firstly synthesised in 1847,[193] particularly used for the fabrication of dynamite in which it is stabilized by celite. 2,4,6-Trinitrotoluene **721** (TNT) firstly synthesised by Wilbrand in 1863,[194] is an explosive still widely used by the US military and for demolition charges, 2,4,6-trinitrophenol **722** (also known as picric acid), firstly synthesised in 1742 and characterized in 1841,[195] is a more powerful explosive than TNT **721** but is less sensitive to shock which makes it an interesting secondary explosive (requiring a detonator).



720



721

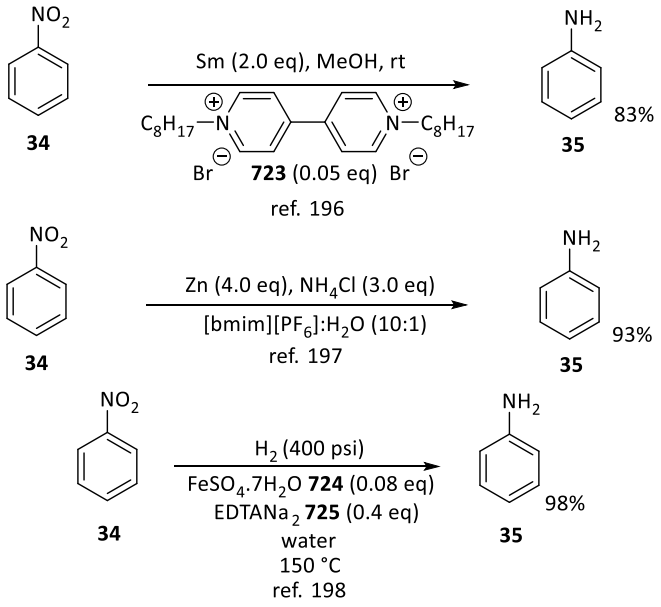


722

Scheme 145

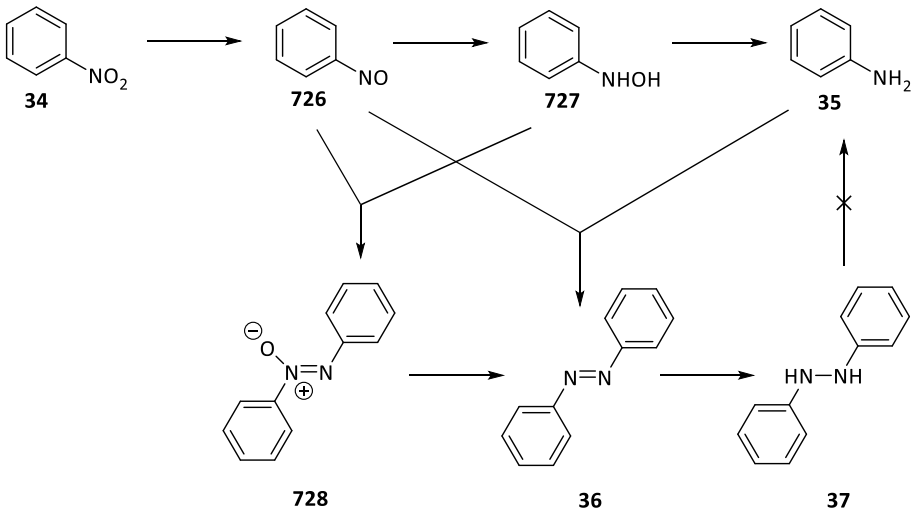
An effective and easy-to-use reducing agent of the nitro groups in these species would provide an interesting way to neutralize explosives.

Nitrobenzenes have been selectively reduced to aniline by electron transfer, using samarium and 1,1'-dioctyl-4,4'-bipyridinium dibromide **723**,[196] by zinc and ammonium salts used in ionic liquids,[197] and by use of iron catalysts for the hydrogenation of nitrobenzene (see Scheme 146).[198]



Scheme 146

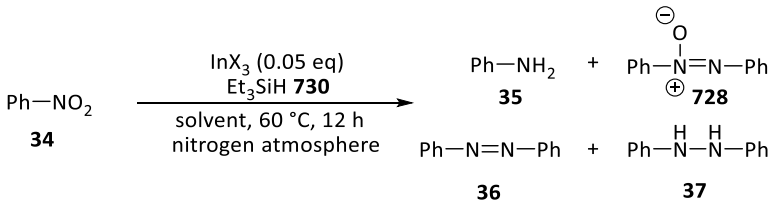
A common way to efficiently reduce nitrobenzenes to anilines involves the use of palladium on charcoal under hydrogen or with hydrazines.[199] These reductions of nitrobenzenes often led to formation of side-products such as hydroxylamines and azo derivatives, also observed with samarium diiodide **148** as a reducing agent.[200,201] The formation of azo derivatives was proposed to be the result of condensation between the intermediates formed during the reduction of nitrobenzenes (see Scheme 147 for the case of nitrobenzene **34**).[196]



Scheme 147

The reduction of nitrobenzene **34** leads to formation of nitrosobenzene **726** and hydroxylamine **727** as intermediates which could condense to form azoxybenzene **728**. Further reduction of azoxybenzene **728** would form azobenzene **36** (which could also be the result of condensation between nitrosobenzene **726** and aniline **35**). Azobenzene **36** was then further reduced to 1,2-diphenylhydrazine **37** which was found not to be reduced to aniline **35**.

Sakai and co-workers found interesting selective reductions of nitrobenzenes depending on the trivalent indium salts, hydrosilanes and solvent used in the reaction.[202] The reduction run with indium tribromide **729** and triethylsilane **730** in chloroform was not effective and not selective (see Scheme 148 and Table 26). Changing the solvent to THF led to an excellent yield of azoxybenzene **728**, while DMF as solvent led to an excellent yield of 1,2-diphenylhydrazine **37**. Using indium(III) trifluoromethanesulfonate **731** for the reduction of nitrobenzene **34** in 1,2-diphenylhydrazine **37** and stirring the reaction under air atmosphere after reduction allowed formation of azobenzene **36**; this particular reduction/oxidation procedure was studied further in 2014.[203]



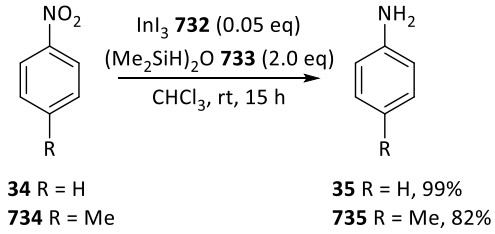
Scheme 148

Entry	InX_3	Solvent	35 (%)	728 (%)	36 (%)	37 (%)
1	$InBr_3$ **729**	$CHCl_3$	9	15	2	10
2	$InBr_3$ **729**	THF	-	96	Trace	Trace
3	$InBr_3$ **729**	DMF	-	-	-	94
4[a]	$In(OTf)_3$ **731**	DMF	-	-	99	-

[a] Reaction run for an additional 15 h under atmosphere.

Table 26: Selective reductions of nitrobenzene **34**.

Sakai and co-workers were also able to selectively form anilines from nitrobenzenes using indium triiodide **732** and tetramethyldisiloxane **733** in chloroform (see Scheme 149).

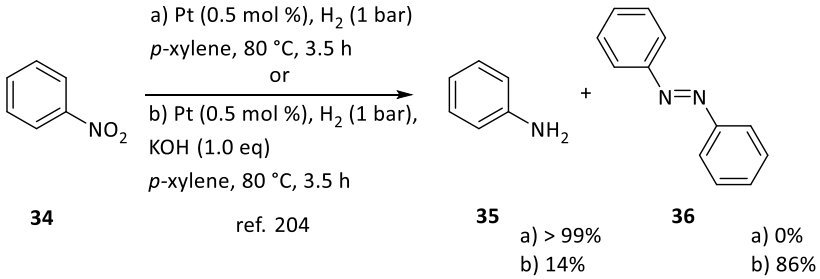


34 R = H
734 R = Me

35 R = H, 99%
735 R = Me, 82%

Scheme 149

Several other conditions were used for the reduction of nitrobenzenes. Gu and co-workers used unsupported ultra-thin platinum nanowires as catalysts to reduce nitrobenzene **34** into aniline **35** exclusively or alongside azobenzene **36** when a strong enough organic base was used in the reaction:[204] Liguori and co-workers used lithium aluminium hydride with titanium tetrachloride for the selective reduction of electron-poor nitrobenzenes into the corresponding anilines,[205] and Benaglia and co-workers performed a continuous-flow synthesis of primary amines from nitrobenzenes using trichlorosilane (see Scheme 150).[206]

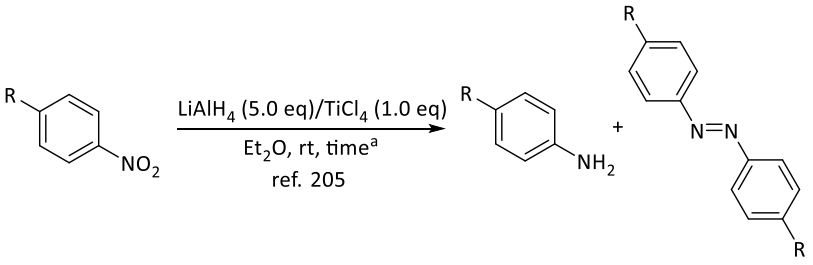


34

ref. 204

35
a) > 99%
b) 14%

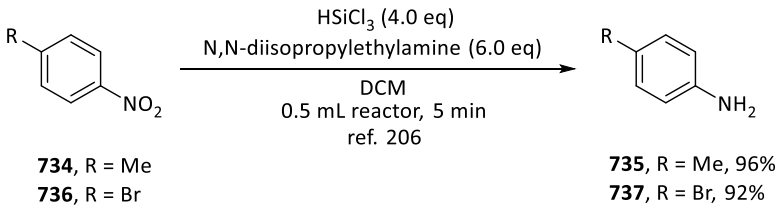
36
a) 0%
b) 86%



34, R = H
736, R = Br

35, R = H, 48%
737, R = Br, 94%

36, R = H, 25%
738, R = Br, 0%



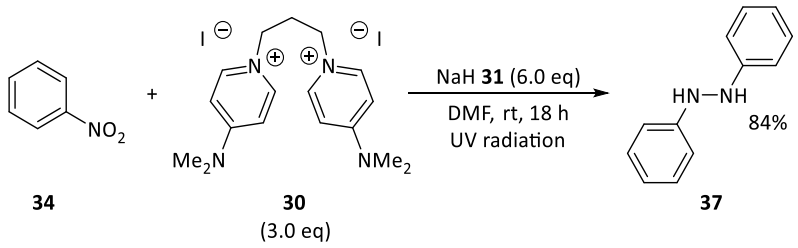
[a] t = 15 h for **734**, t = 45 min for **736**

Scheme 150

Several organic electron donors were reported and shown to be able, in the case of the DMAP donor **32**, to give away two electrons. The reduction of nitrobenzenes with such electron donors was a field of research that required investigation. This will be the topic of this section.

4.1 Reduction of nitrobenzene, azobenzene and hydrazine by photoactivated DMAP donor

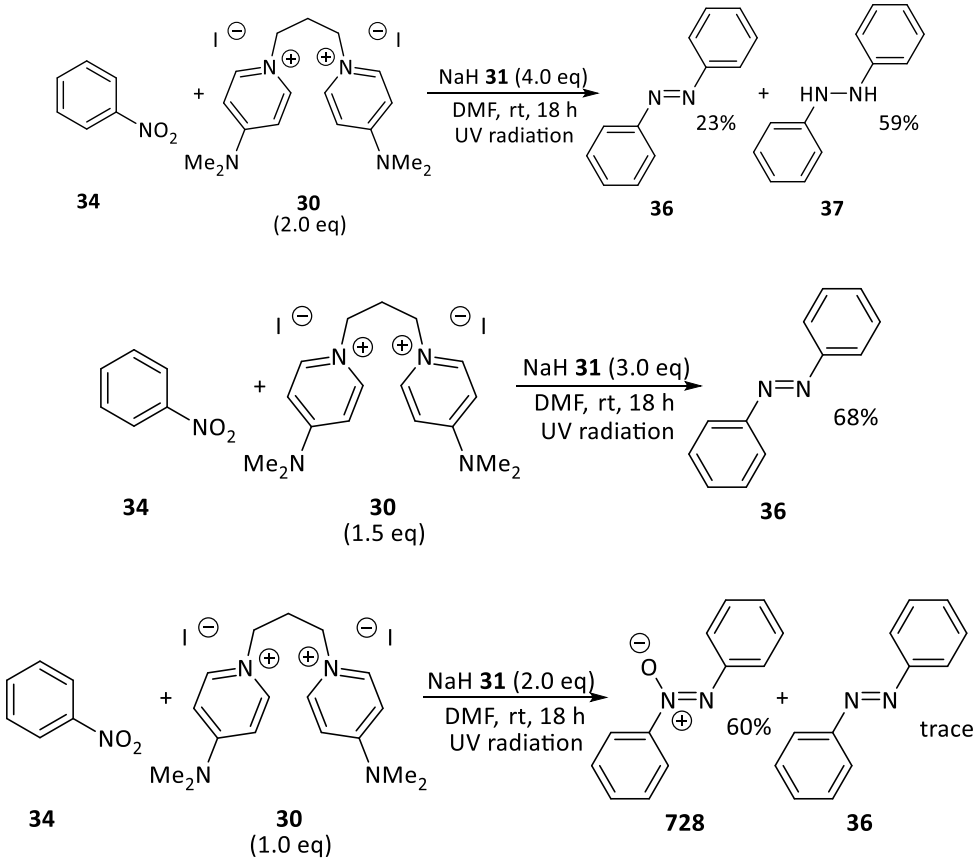
The reduction of nitrobenzene **34** being able to follow two main different pathways (Scheme 147), the initial investigation was to find out which pathway would be followed during the potential reduction using DMAP donor **32**. Since **32** can give away two electrons, it would require three equivalents to form aniline **35** from nitrobenzene **34**. This reduction was undertaken using three equivalents of DMAP salt **30** with 6 equivalents of sodium hydride **31** in DMF at room temperature under UV radiation for 18 h (see Scheme 151).[207]

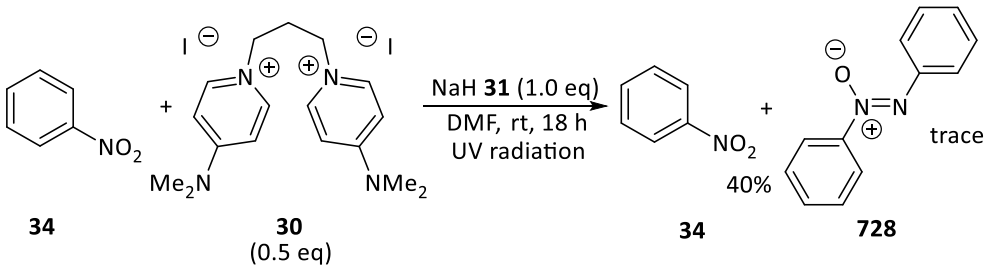


Scheme 151

The result of the reaction was unquestionable as 1,2-diphenylhydrazine **37** was recovered in 84% yield.

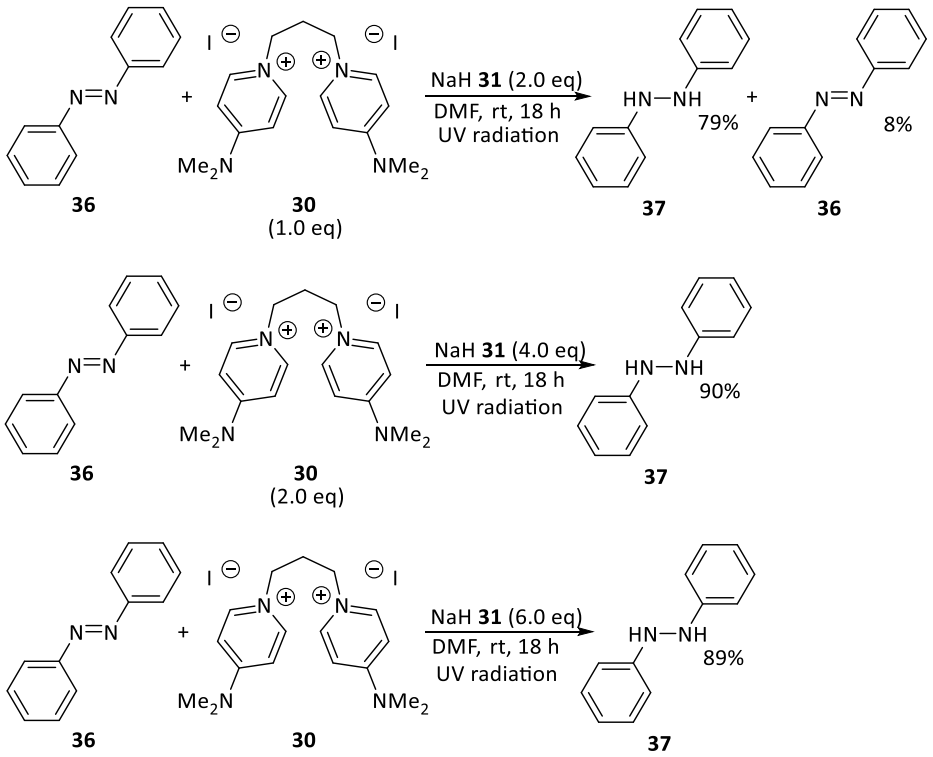
The presence of the DMAP salt **30** was essential as the same reaction run without the salt led to no reaction. Other reductions of nitrobenzene **34** were made using different amounts of salt **30** and sodium hydride **31** to decrease the number of electrons involved in the reduction (see Scheme 152). Using two equivalents of salt **30** (with four equivalents of sodium hydride **31**) led to a mixture of azobenzene **36** (23%) and 1,2-diphenylhydrazine **37** (59%); 1.5 equivalents of salt **30** (with three equivalents of **31**) led to a selective formation of azobenzene **36** (68%); one equivalent of salt **30** (with two equivalents of **31**) afforded mainly azoxybenzene **728** (60%) alongside a trace amount of azobenzene **36**, 0.5 equivalents of salt **30** (with one equivalent of **31**) did not fully convert nitrobenzene **34** and a trace amount of azoxybenzene **728** was seen.





Scheme 152

It was clear that the species that could be isolated during the reduction of nitrobenzene **34** by DMAP donor **32** were, by order of formation, azoxybenzene **728**, azobenzene **36** and 1,2-diphenylhydrazine **37**. The formation of nitrosobenzene **726**, hydroxylamine **727** and aniline **35** were not observed under these conditions. Azobenzene **36** was also tested with DMAP donor **32**. It was not surprising to observe formation of 1,2-diphenylhydrazine **37** in good yields (see Scheme 153).

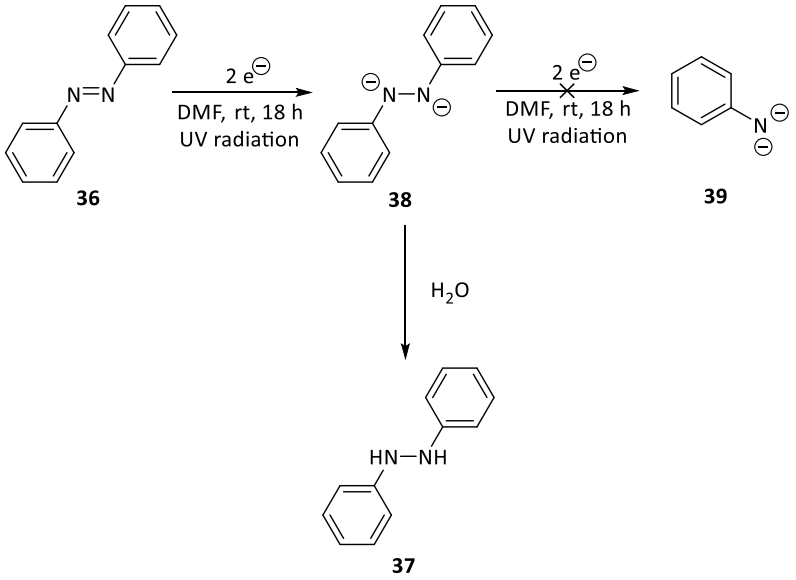


Scheme 153

Only one equivalent of the DMAP salt **30** (thus two electrons available for the reduction) was enough to form 1,2-diphenylhydrazine **37** in excellent yield (79%)

although azobenzene **36** was not fully converted. When the reduction was made with two and three equivalents of the DMAP salt **30**, full conversion of azobenzene **36** was observed and both reactions afforded the same yield of hydrazine **37**. In these last two reactions, formation of aniline **35** was not observed even if there was an excess of electrons, which suggested that hydrazine **37** could not undergo reduction under these conditions. This was confirmed when 1,2-diphenylhydrazine **37** was reacted with DMAP salt **30** and sodium hydride **31** in DMF under UV radiation as no reaction was observed even when three equivalents of the salt **30** were used.

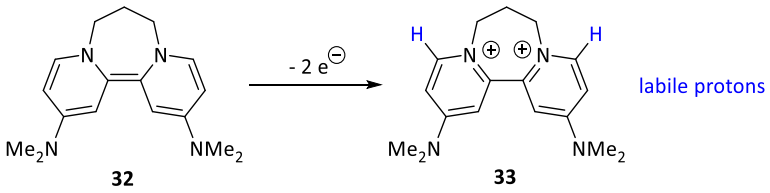
The non-formation of aniline **35** during the reduction of nitrobenzene **34** and azobenzene **36** suggested that dianion **38** formed after azobenzene **36** has received two electrons was not able to undergo further reduction and would remain untouched until being quenched with water to afforded 1,2-diphenylhydrazine **37** (see Scheme 154).



Scheme 154

The mechanistic pathway involved in the reduction of nitrobenzene **34** by DMAP donor **32** requires a dimerisation at some stage. Also, the nature of the intermediates (azoxybenzene **728** and azobenzene **36**) show that oxygen atoms must be eliminated in the process. A possibility to lose these oxygens would be a protonation of their anion followed by a hydroxide elimination. According to the strongly basic conditions

(sodium hydride **31**) used for the reduction of nitrobenzene **34**, it might be unlikely to find any proton source in the reaction. However, when considering dication **33**, resulting from loss of two electrons by DMAP donor **32**, the two symmetrical protons *ortho* to the nitrogen of the pyridinium moiety could be labile enough to be deprotonated by intermediate species of the reduction of nitrobenzene **34** (see Scheme 155).

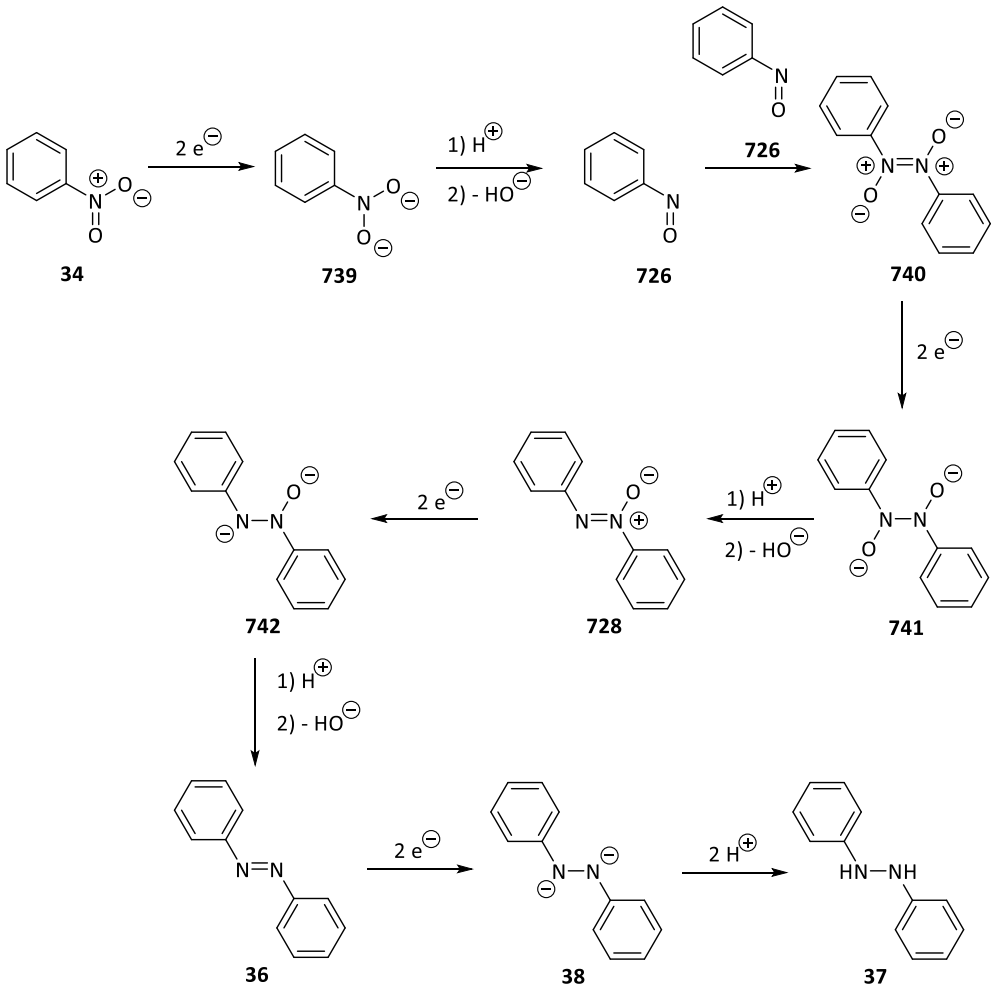


Scheme 155

The proposed mechanistic pathway (see Scheme 156) goes through conversion of nitrobenzene **34** into nitrosobenzene **726** via double electron transfer, protonation and hydroxide elimination. Nitrosobenzene **726** can dimerise[208] into **740**.

Further electron transfer to **740** affords dianion **741** which, upon protonation and hydroxide elimination forms azoxybenzene **728**. Electron transfer to azoxybenzene **728** forms dianion **742** leading to azobenzene **36** via protonation and hydroxide elimination.

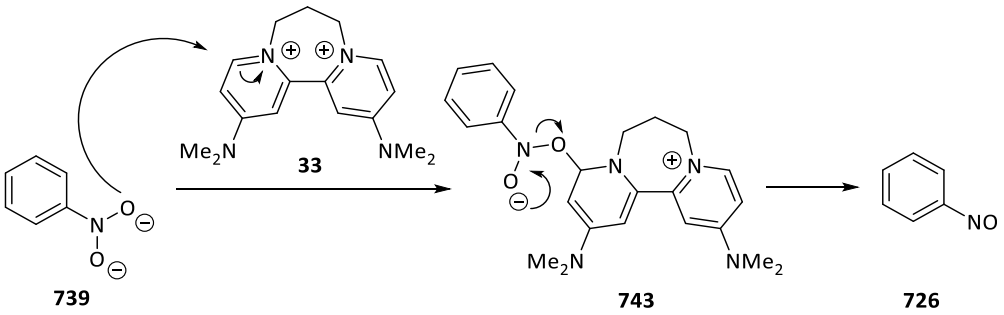
Although this mechanistic pathway can account for the formation of all the observed intermediates, there are two concerns about it. Firstly, the number of electrons involved to form azoxybenzene **728** from nitrobenzene **34** seems too high as three electrons are necessary according to the mechanism but only two already afforded a good formation of azoxybenzene **728** (Scheme 152). However, the yields were never found to be 100% meaning that not necessarily all the nitrobenzene **34** reacted to afford nitrosobenzene **726**. In other words, the all process might be able to undergo several steps without the need for all the nitrobenzene to have been engaged in the reduction. Secondly, the proposed mechanistic pathway goes through formation of nitrosobenzene **729** but this species has never been observed in any reduction of nitrobenzene **34** by the DMAP donor **32**.



Scheme 156

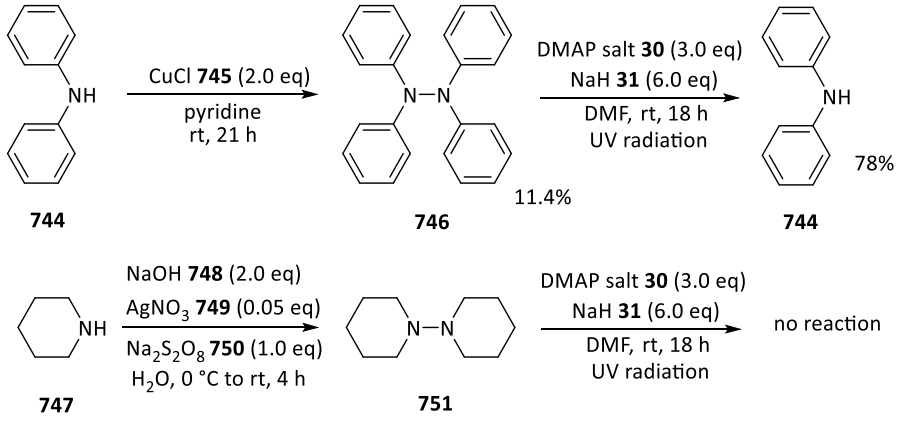
Knowing that nitrosobenzene **726** exists in equilibrium with its dimer **740**,[209-210] the conversion of **740** into dianion **741** could be pushing the equilibrium toward the dimer **740** and then toward formation of azoxybenzene **728** and too few molecules of nitrosobenzene **726** would be left to be observed.

It should also be noted that another process could account for the loss of the oxygens during the reaction. Rather than being deprotonated, dication **33** could be attacked by, for example, dianion **739** leading to intermediate **743** (see Scheme 157) which would contain a good leaving group and allow formation of nitrosobenzene **726**.



Scheme 157

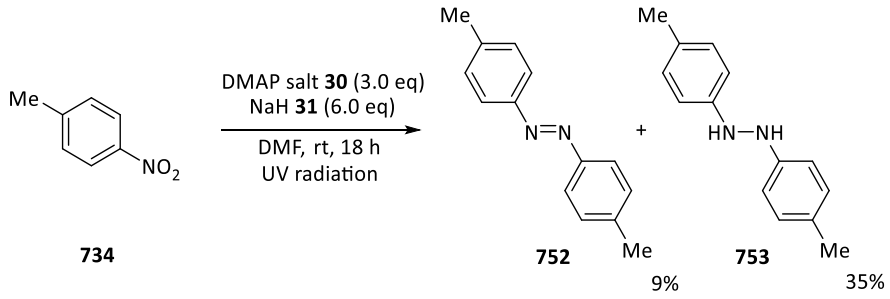
As the reduction of 1,2-diphenylhydrazine **37** could not be made by the DMAP donor **32**, investigations were made to see if N-N single bonds could be reduced. Two substrates were synthesised and tested under the reduction conditions (see Scheme 158). Tetraphenylhydrazine **746** was synthesised by dimerisation[211] of diphenylamine **744** and was successfully reduced back to diphenylamine **744** (78%), and bipiperidine **751** was synthesised by dimerisation[212] of piperidine **747** and was not reduced by the DMAP donor. The difference in yields suggests that the nature of the hybridisation of the orbitals of the carbons next to the nitrogens has a part to play in the reaction. Also, the presence of several phenyl rings might facilitate the electron transfer as their π* orbitals could receive the electron before transferring it to the σ* orbital of the N-N bond.



Scheme 158

While the reduction of nitrobenzene **34** and azobenzene **36** was easily made by the DMAP donor **32**, the reduction of a more electron-rich substrate, 4-nitrotoluene **734**

was more difficult (see Scheme 159). Even with three equivalents of DMAP salt **30**, the azo-product **752** was still present after 18 h (9%) along with the hydrazine-product **753** (35%) although, no starting material was left after the reaction.

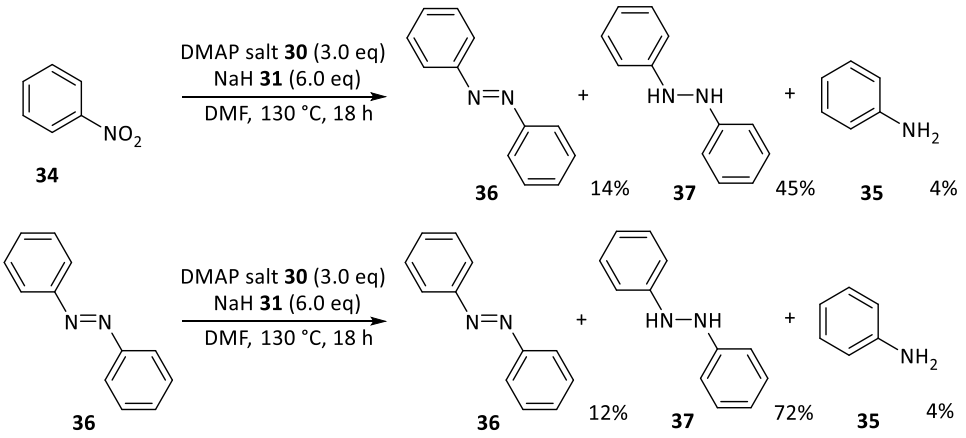


Scheme 159

The reduction of nitrobenzene **34** and azobenzene **36** has been found to be effectively performed by the DMAP donor **32** under UV radiation. The amount of electron donor being used and thus, the number of electrons that can be given to the substrate, allows good selectivity of the reduction product (azoxy, azo and hydrazine products). The next section will focus on thermal conditions, rather than UV-activated conditions, showing that the reduction can be brought one more step forward toward the formation of aniline from nitrobenzene **34** and azobenzene **36**.

4.2 Reduction of nitrobenzene and azobenzene by DMAP donor under thermal conditions

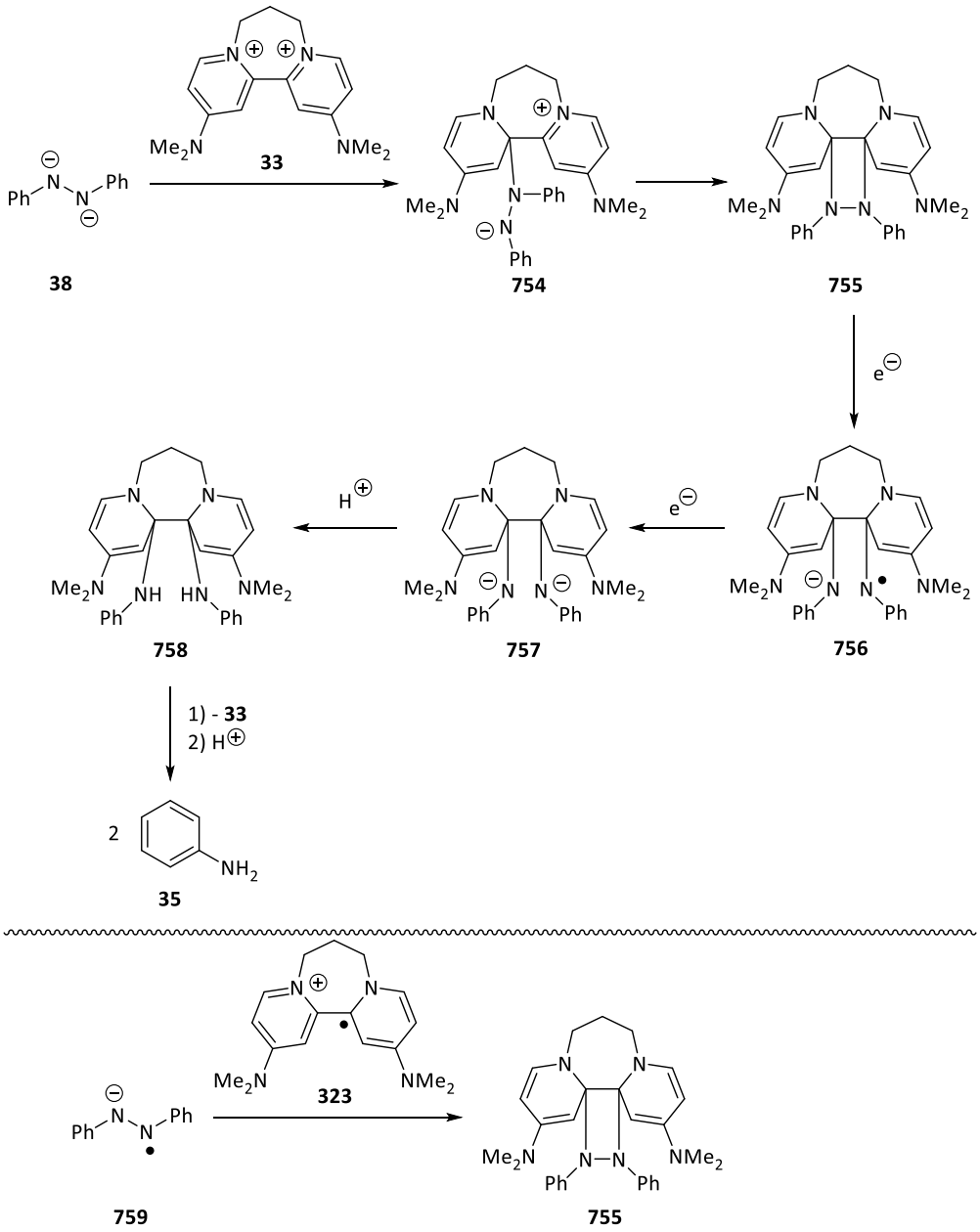
In this section, the conditions used for the reduction of nitrobenzene **34** and azobenzene **36** are almost the same as the ones used in section 4.1 except for the use of UV radiation which was replaced by heating of the reactions at 130 °C. Interestingly, thermal conditions are not as effective as UV-activation conditions in terms of yields but, for the reduction of both nitrobenzene **34** and azobenzene **36**, a small amount of aniline **35** was observed (see Scheme 160).



Scheme 160

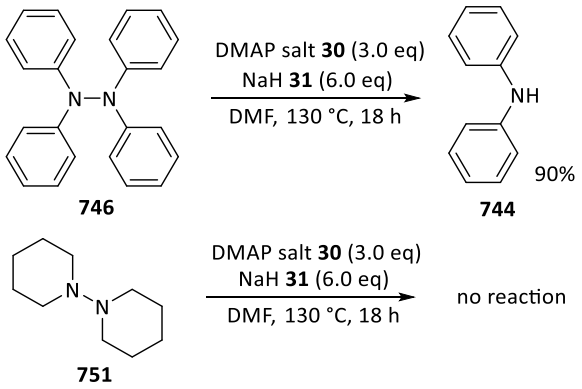
The formation of aniline from both substrates suggests that, under these conditions, dianion **38** could be formed and further reduced to form phenylnitride **39** which would be one more evidence of the strong reducing ability of DMAP donor **32**. It can also be proposed that a stabilising interaction between dianion **38** and dication **33** would lead to the neutral species **755** (see Scheme 161). Further reduction of **755** would afford dianion **757** which, upon protonation, would form **758**. Release of the aromatic dication **33** would afford two molecules of aniline **35**. The formation of the neutral species **755** could also be the result of the reaction between 1,2-diphenylhydrazine radical anion **759** and radical cation **323**.

Still, it is not surprising to see that the yields of aniline **35** are very low as the reduction required to form it (by either electron transfer to a dianion species and thus, a very electron rich species, or a series of reactions involving the reduced diphenylhydrazine and the oxidised DMAP donor) cannot be a process as simple as giving electrons to nitrobenzene **34** or azobenzene **36**. It was also surprising to find that, under these conditions, the conversion of azobenzene **36**, whether it was an intermediate or the starting material, was not complete, unlike when the reaction was conducted under UV radiation.



Scheme 161

Reduction of tetraphenylhydrazine **746** and bipiperidine **751** under these conditions were also tested and afforded similar results to those obtained under UV radiation (see Scheme 162).



Scheme 162

While the evidence for the formation of aniline **35** from both nitrobenzene **34** and azobenzene **36** is an interesting outcome for evidence of how strong DMAP donor **32** is, the use of UV radiation at room temperature is the best choice for the reduction of **34** and **36** as it can lead to a selective formation of their reduced species in good yields.

4.3 Conclusion and future work

A new use for DMAP donor **32** was found with its excellent ability to reduce nitro and azobenzenes as well as some tetrasubstituted hydrazines. Using different amounts of the electron donor **32** led to selective formation of azoxybenzene **728**, azobenzene **36** and 1,2-diphenylhydrazine **37** when nitrobenzene **34** was used. Working under thermal conditions showed evidence for the reduction of a dianion by DMAP donor bringing more evidence of its strong reducing ability. Future work would include a scope of substrates (especially nitro and azobenzenes) to be tested under these conditions. Reduction of nitrosobenzene by DMAP donor **32** should also be investigated to check if the reaction leads to formation of azoxybenzene **728**, azobenzene **36** and 1,2-diphenyhydrazine **37** or to formation of hydroxylamine **727** and eventually aniline **35**. More evidence of the mechanism involved in the reduction of nitro and azobenzenes could be found by performing a crossover experiment when

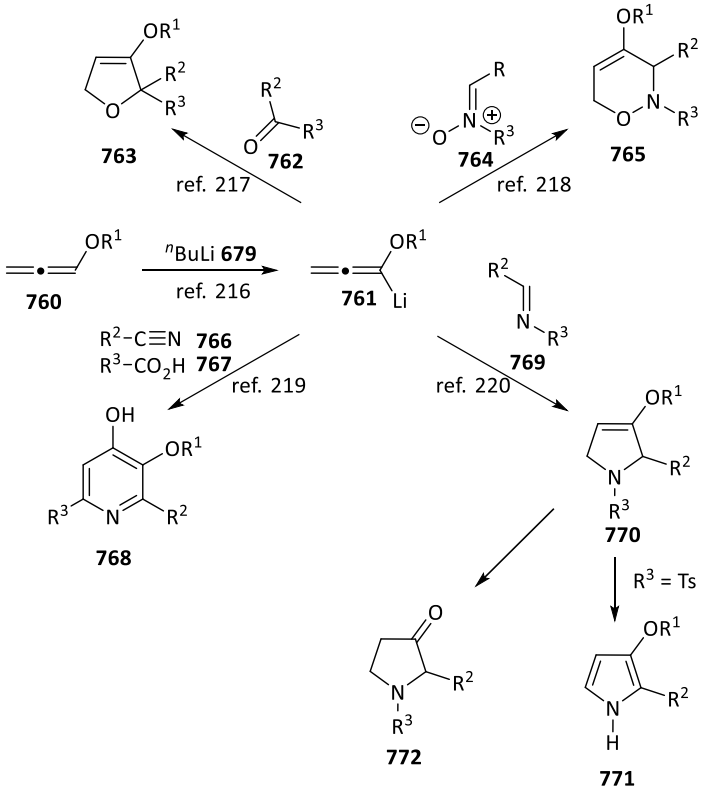
reacting, for example, nitrobenzene **34** together with 4-nitrotoluene **734** and check if a product of the reaction would include components of both reactants.

Strong organic electron donors, such as DMAP donor **32**, could be the first step toward a metal-free reduction of molecular nitrogen into ammonia. Knowing the importance of ammonia in industry (fertilizers and thus global food production, pharmaceutical products) and that the amount of ammonia naturally produced would not be enough to sustain half the world population, it is essential to mankind to produce it on its own.

With time, organic electron donors could afford an alternative to the Haber-Bosch process[213] which is used to industrially produce ammonia from molecular nitrogen and requires a high pressure (200 atm) and a high temperature (400 to 450 °C) as well as an iron catalyst. Finding an alternative route for this reduction with a photo-activated organic electron donor, using sunlight as a source, would be a tremendous change for our industry. Moreover, if the electron donor could be regenerated and thus used in a catalytic amount, the process would become even more environmental friendly and less costly as it would require a small amount of the electron donor and use natural energy to be performed.

Chapter 5: A computational study of intramolecular alkoxide-allene and amide-allene anionic cyclisation

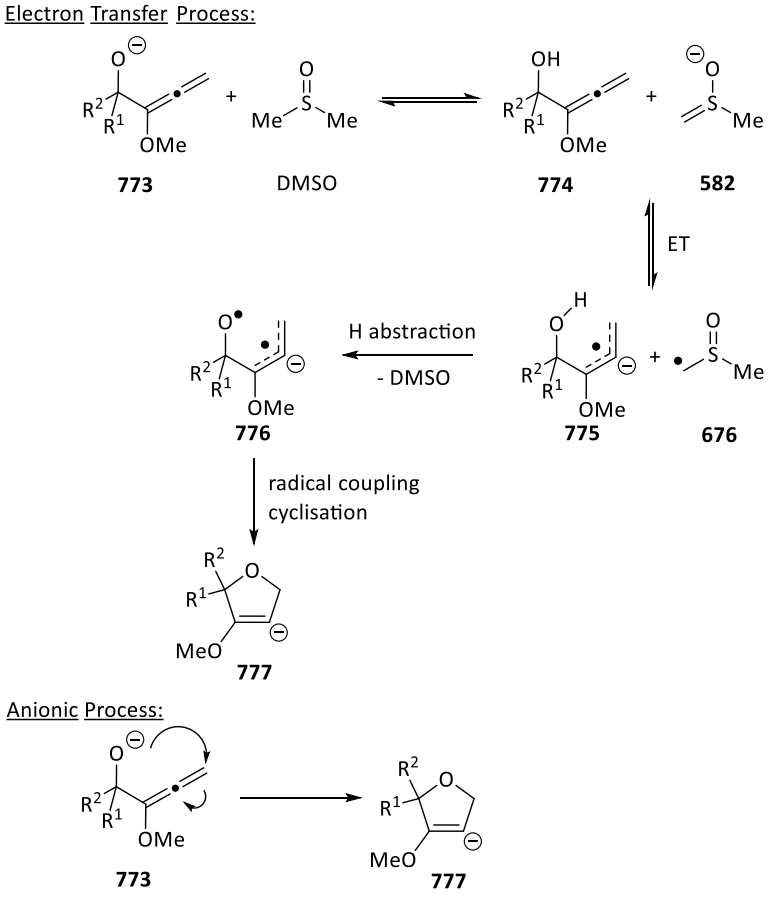
Lithiated alkoxyallenes have been found to be valuable building blocks for the synthesis of heterocycles.[214-215] these lithiated alkoxyallenes can easily be formed via deprotonation of alkoxyallenes with *n*-butyllithium **679.** [216] When adding to carbonyls, further cyclisation leads to 2,5-dihydrofuran derivatives.[217] Reissig *et al.* have led intensive investigations on the reactions of lithiated alkoxyallenes with nitrones, [218] nitriles and carboxylic acids in a three-component reaction, [219] and recently with *N*-tosylimines (see Scheme 163).[220]



Scheme 163

In 1984, Magnus and Albaugh-Robertson reported a mechanistic study of intramolecular alkoxide-allene cyclisations (see Scheme 164). [221] Their report considered two different processes for the cyclisation: 1) an intramolecular attack of

potassium alkoxide **773** to the terminus of the allene unit, which was believed to lead to a too strained transition state and be forbidden by Baldwin's rules,[222-223] although the flexibility of the allene could overcome geometrical issues,[224-225] 2) an electron transfer from dimsyl anion **582**, as the cyclisation was made in DMSO in the presence of potassium *tert*-butoxide **17**.

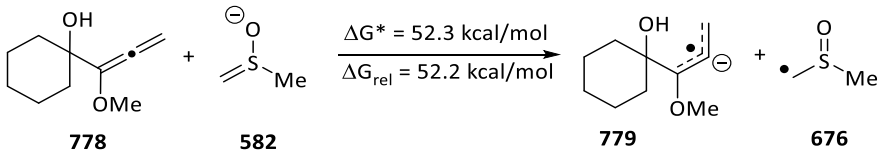


Scheme 164

The aim of the study described here was to investigate the energies of both the anionic and electron transfer processes and check which would be energetically favourable. The study will focus on the cyclisation of both alkoxide-allenes and amide-allenes.

5.1 Cyclisation of alkoxide-allenes

All the optimisations were made using Gaussian 09,[164] with the MO6-2X functional,[165] the 6-31++G(d,p) basis set,[226] and modelled implicit solvation using the Conductor-like Polarizable Continuum Model with the associated parameters of DMSO as solvent.[167-168] Before focusing on the anionic process, it is worth mentioning that the electron transfer process, as described in Scheme 163 with dimsyl anion **582** as an electron donor, was firstly investigated with the electron transfer step itself with substrate **778** (see Scheme 165). The energies found clearly suggested that this process would not even be feasible as the energy barrier found was ΔG^{*} = 52.3 kcal/mol and the relative energy found was ΔG_{rel} = 52.2 kcal/mol (the optimisation of this electron transfer was also made including potassium cation and the energies found were even higher: ΔG^{*} = 58.5 kcal/mol, ΔG_{rel} = 57.1 kcal/mol).

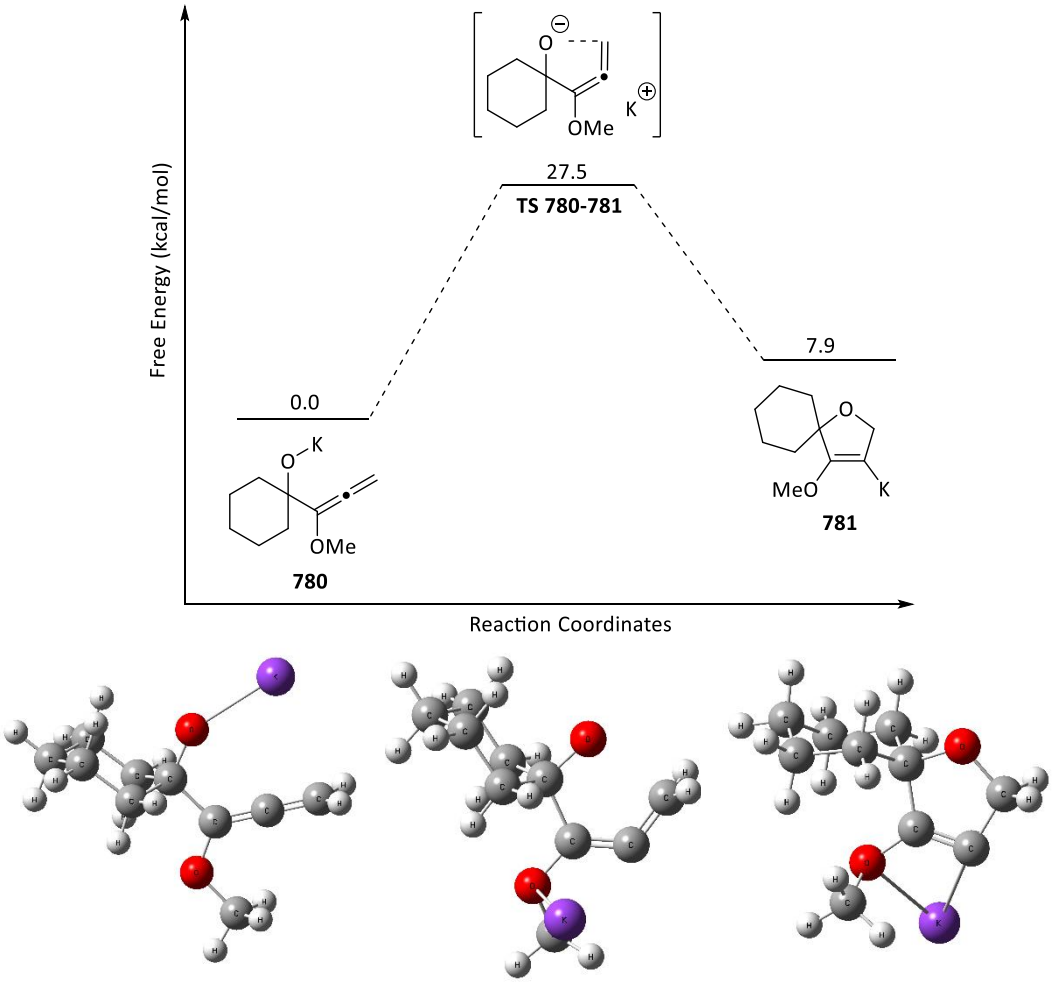


Scheme 165

Optimisations of the starting complex, transition state and product complex involved in the anionic cyclisation afforded more reasonable energies for this process (see Scheme 166). Although the reaction is exergonic (ΔG_{rel} = 7.9 kcal/mol), it has a small energy barrier (ΔG^{*} = 27.5 kcal/mol) which is achievable especially since this cyclisation is usually made upon heating.

The reaction was optimised to lead to a five-membered ring via a 5-*endo-trig* cyclisation by attack of the oxygen on the terminus of the allene unit. The 4-*exo-dig* cyclisation of **780** was also studied and two outcomes show that it is a disfavoured process compared to the 5-*endo-trig* cyclisation. Firstly, the modelled HOMO of **780** shows that it is delocalised on the carbon of the allene that would lead to a four-membered ring if it were attacked by the oxygen (see Scheme 167), meaning that this

carbon is unlikely to be electrophilic. Plus, the LUMO is delocalised on the terminal carbon of the allene unit meaning that this carbon is likely to be electrophilic.

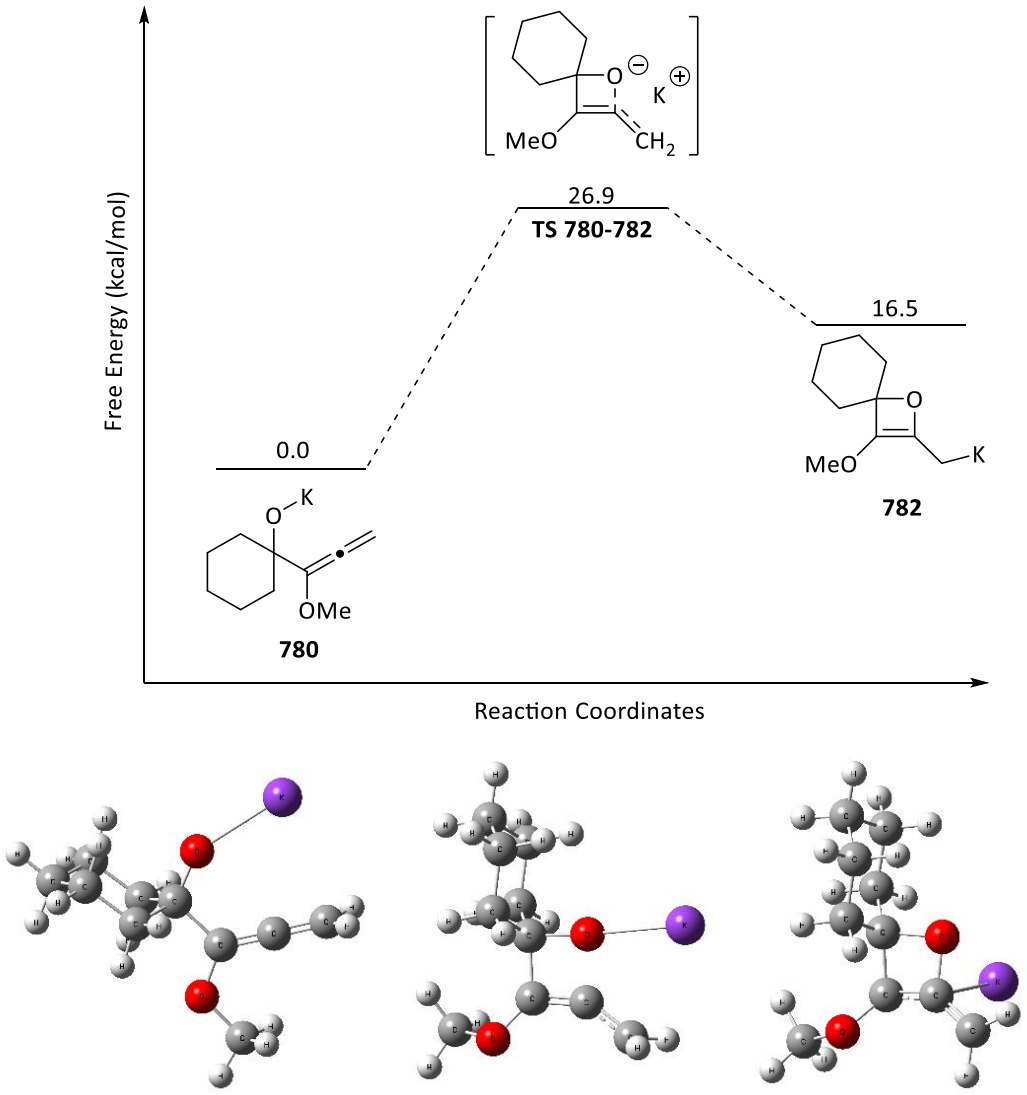


Scheme 166

HOMO of 780 **LUMO of 781**

Scheme 167

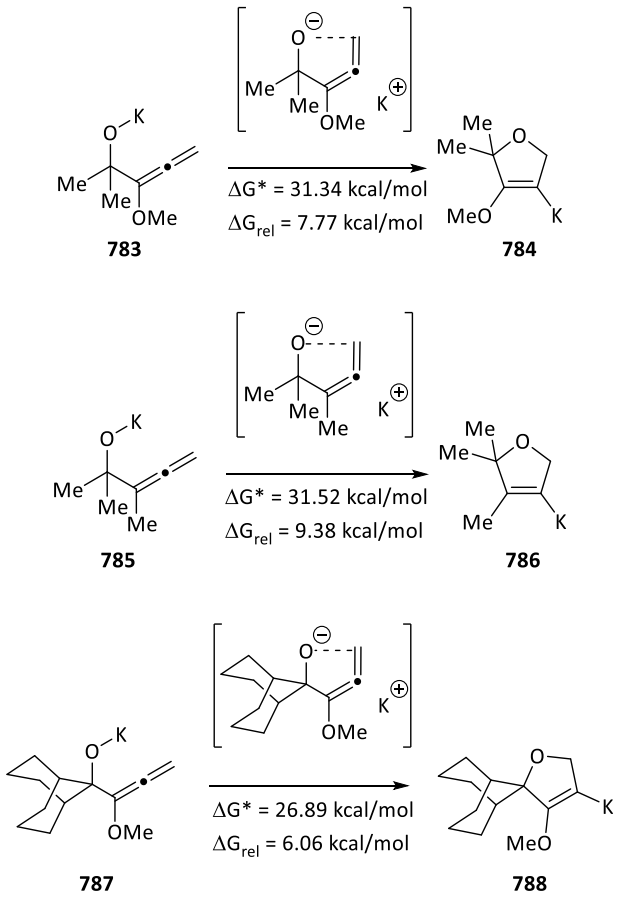
Secondly, while the energy barrier found for the 4-*exo-dig* cyclisation (ΔG* = 26.9 kcal/mol) is similar to the barrier of the 5-*endo-trig* cyclisation (ΔG* = 27.5 kcal/mol), the relative energy found for the 4-*exo-dig* cyclisation (ΔG_{rel} = 16.5 kcal/mol) is higher than the relative energy of the 5-*endo-trig* cyclisation (ΔG_{rel} = 7.9 kcal/mol) (see Scheme 168 for the energy profile of the 4-*exo-dig* cyclisation and the optimised structures). Of the two processes, the 5-*endo-trig* cyclisation will be favoured, as it was experimentally seen by Magnus,[219] since the reverse reaction from **782** to **780** requires less energy than from **781** to **780**.

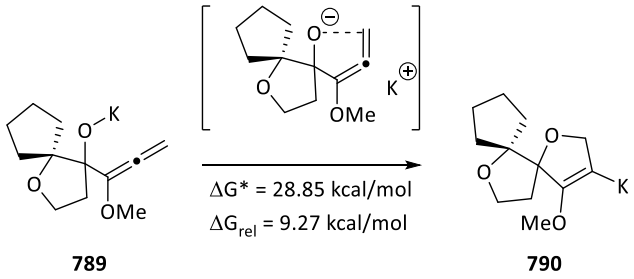


Scheme 168

Several other intramolecular anionic 5-*endo-trig* cyclisations of alkoxide-allenes were optimised and showed similar energies to the ones found for the cyclisation of **780**

(see Scheme 169). Interestingly, the optimisation of the cyclisation of **785** led to Gibbs free energies that were similar to the cyclisation of **783** meaning that the methoxy group of the allene is not bringing a particular stabilization to the reaction (although chelation of potassium with the oxygen of the methoxy group was usually observed during optimisation of the cyclized products as for **781** in Scheme 165). Also, increasing the size of the groups attached to the carbon α to the alkoxide did not result in increased free energies but rather tended to lower them. All the calculations that were made for the cyclisation of alkoxide-allenes strongly suggest an intramolecular anionic cyclisation as the energies involved in that process are achievable experimentally.



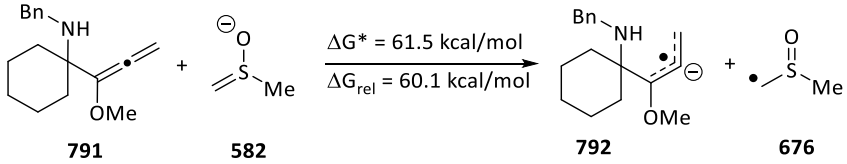


789 **790**

Scheme 169

5.2 Cyclisation of amide-allenes

The cyclisation of amide-allenes, formed by reaction of imines with lithiated methoxyallenes,[218] were investigated by focusing on the nature of the *N*-substituent. For example, amide-allene **791** (see Scheme 170) was chosen to investigate the energies of an electron transfer from dimsyl anion **582** and the energies of the anionic cyclisation.

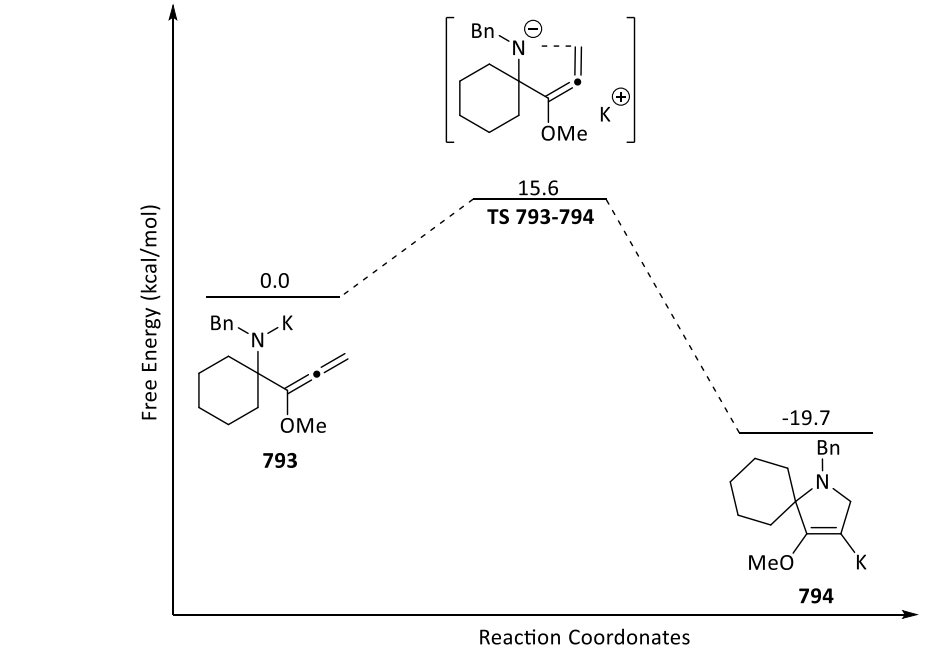


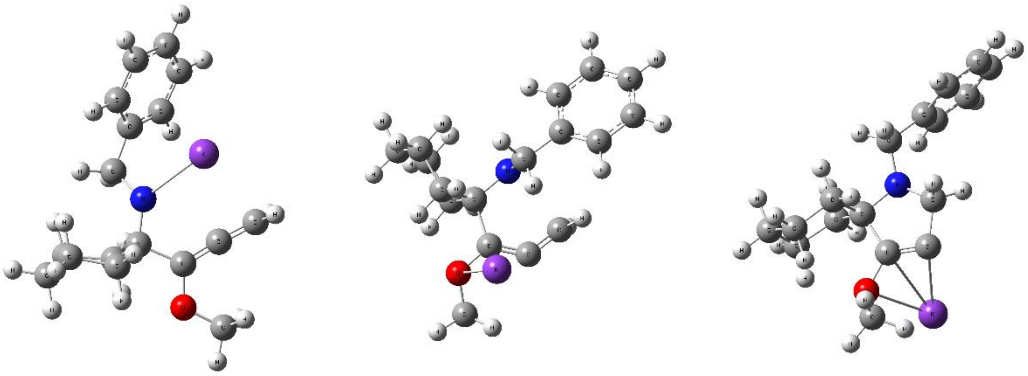
791 **582** **792** **676**

Scheme 170

The energies found for the electron transfer process, once again, did not suggest that this process was feasible as the reaction would be too endergonic (optimisation of the electron transfer including potassium cation also led to even higher energies, ΔG* = 70.8 kcal/mol, ΔG_{rel} = 64.9 kcal/mol).

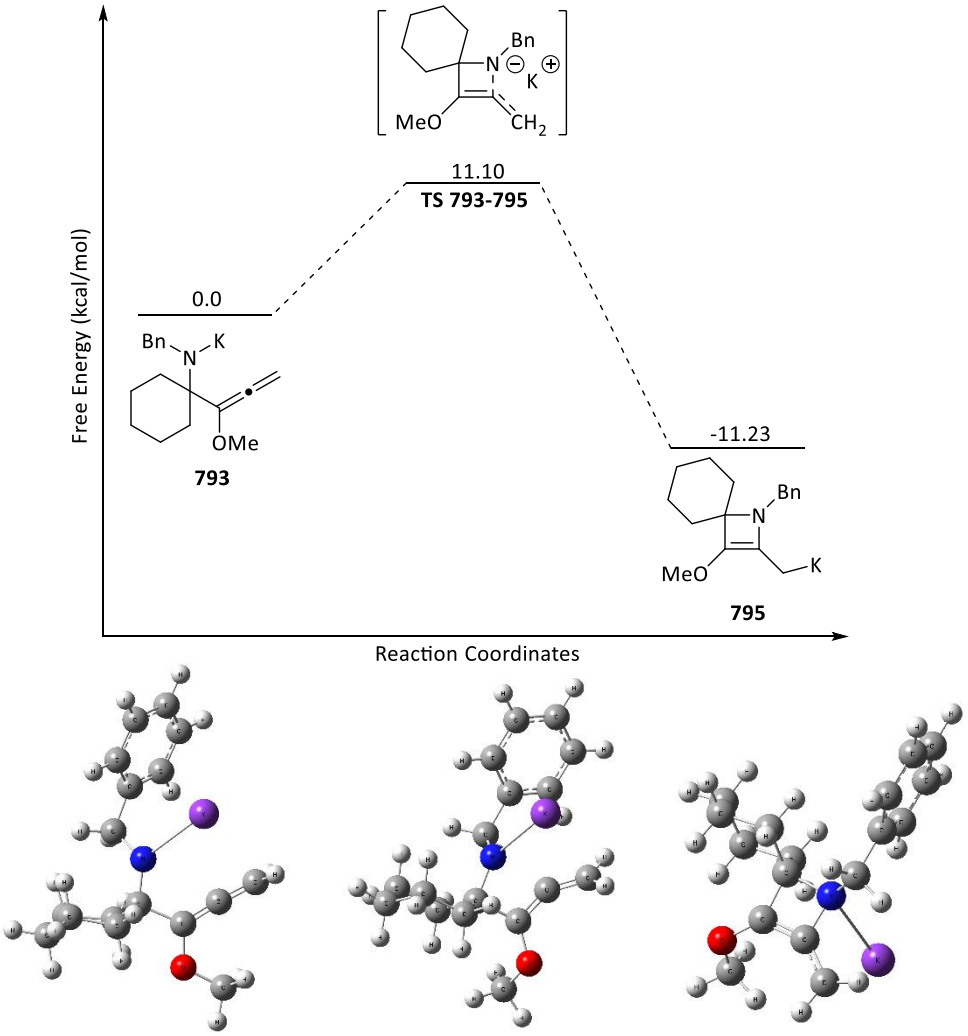
The 5-*endo*-*trig* cyclisation, via an anionic process, was found to be an easy process for amide-allene **793** as the energy barrier is ΔG* = 15.6 kcal/mol and the relative energy is negative ΔG_{rel} = -19.7 kcal/mol meaning that this cyclisation is exergonic and the barrier can easily be achievable (see Scheme 171).





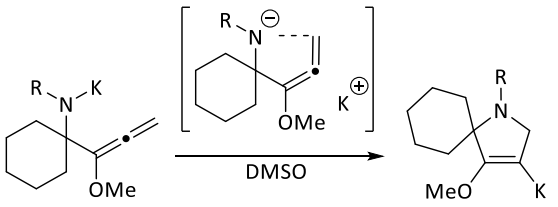
Scheme 171

It was interesting to observe such a favourable relative energy for this cyclisation and further calculations on other amide-allenes with various *N*-substituents showed that electron-donating substituents lead to similar exergonic cyclisations while electron-withdrawing substituents led to endergonic (but feasible) cyclisations. The 4-*exo*-*dig* cyclisation of **793** was also optimised and found to be an achievable process with an energy barrier of 11.10 kcal/mol and a relative energy of -11.23 kcal/mol (see Scheme 172).



Scheme 172

The other amide-allenes for which the 5-*endo-trig* cyclisations were tested were chosen with various *N*-substituents (various in size and in electronic effect, see Scheme 173 and Table 26).



796, R = Ph
798, R = Ts
800, R = ^{i}Pr
802, R = ^{t}Bu

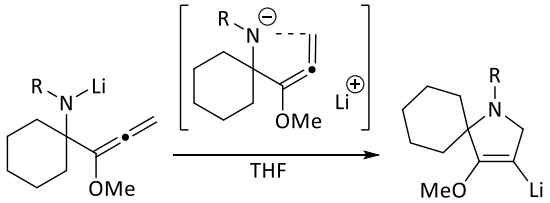
797, R = Ph
799, R = Ts
801, R = ^{i}Pr
803, R = ^{t}Bu

Scheme 173

Entry	R	ΔG* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	Ph	26.30	2.34
2	Ts	28.42	13.09
3	^{i}Pr	21.39	-19.39
4	^{t}Bu	21.10	-16.52

Table 26: Gibbs free energies of the 5-*endo-trig* cyclisation of various amide-allenes.

The cyclisations of these amides were also optimised modelling THF as solvent and using lithium salts (see Scheme 174 and Table 27).



804, R = Ph
806, R = Bn
808, R = Ts
810, R = ^{i}Pr
812, R = ^{t}Bu

805, R = Ph
807, R = Bn
809, R = Ts
811, R = ^{i}Pr
813, R = ^{t}Bu

Scheme 174

Entry	R	ΔG* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	Ph	33.20	-1.15
2	Bn	28.35	-19.34
3	Ts	30.89	6.05
4	^{i}Pr	24.94	-26.13
5	^{t}Bu	33.88	-13.91

Table 27: Gibbs free energies of the 5-*endo-trig* cyclisation of various lithium salts amide-allenes in THF.

These results show that the cyclisation is easier when the nitrogen is more nucleophilic (electron rich) than when it is poorer in electrons. The cyclisation of **796**

and **804** (R = Ph, attractive inductive effect) is easier than the cyclisation of **798** and **808** (R = Ts, attractive mesomeric effect) which is in accordance with the electronic properties of these substituents and their effect on the nucleophilicity of the nitrogen.

5.3 Conclusions and future work

Computational calculations have shown that the cyclisation of alkoxide-allenes and amide-allenes is an anionic process going through a 5-*endo-trig* cyclisation by direct attack of the alkoxide/amide on the terminus of the allene unit. The energies calculated for this study ruled out the possibility of an electron transfer process from dimsyl anion **582** to the allene, as the required energy would be far too high, as well as the possibility for a 4-*exo-dig* cyclisation which would be too disfavoured compared to the 5-*endo-trig* cyclisation. Further study could be made to calculate the energies involved when the cyclisation is catalysed by a metal complex (of palladium or gold), as seen experimentally,[227] and compare them with metal-free conditions.

Chapter 6: Experimental Details

6.1 Experimental details of chapter 2

All the reactions were performed in oven-dried apparatus and preparation of the diketopiperazines was carried out under argon atmosphere using dry solvents. Tetrahydrofuran, dichloromethane and hexane were dried with a Pure-Solv 400 solvent purification system by Innovative Technology Inc., U.S.A. A glove box (Innovative Technology Inc., U.S.A.) was used, for metal-free cross-coupling reactions, to introduce all the reactants into a pressure tube. All the reagents were bought from commercial suppliers and used without further purification, unless stated otherwise. A Büchi rotary evaporator was used to concentrate the reaction mixtures. Thin layer chromatography (TLC) was performed using aluminium-backed sheets of silica gel and visualized under a UV lamp (254 nm). Column chromatography was performed to purify compounds by using silica gel 60 (200-400 mesh).

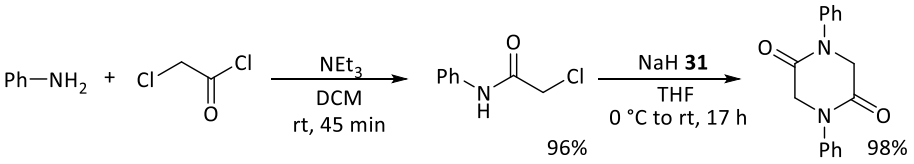
Proton NMR (^{1}H) spectra were recorded at 400 MHz on a Bruker DPX 400 spectrometer. Carbon NMR (^{13}C) spectra were recorded at 100 MHz. The chemical shifts are quoted in parts per million (ppm) by taking tetramethylsilane as a reference (δ = 0) but calibrated on the residual non-deuterated solvent signal. Signal multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; bs, broad singlet; coupling constants are given in Hertz (Hz).

Infra-Red spectra were recorded using a Shimadzu FT-IR Spectrophotometer (Model IRAffinity-1) with a MIRacle Single Reflection Horizontal ATR Accessory. Melting points were determined on a Gallenkamp Melting point apparatus. High resolution mass spectra were recorded at EPSRC National Mass Spectrometry Service Centre, Swansea. The spectra were recorded by GCMS or HRMS using electron ionization (EI), atmospheric pressure chemical ionisation (APCI), atmospheric solids analysis probe

(ASAP), electrospray ionization (ESI), nanospray ionization (NSI) techniques as stated for each compound.

Synthesis of Diketopiperazines 1-4

Preparation of 1,4-diphenylpiperazine-2,5-dione 618



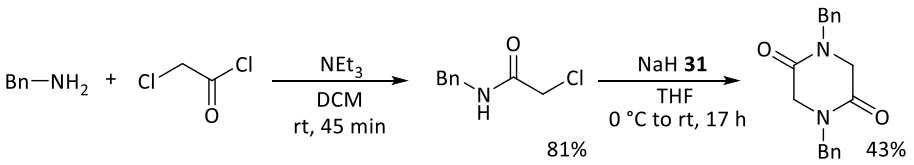
35 **617** **618** **1**

To a solution of freshly distilled aniline **35** (6.0 g, 64.43 mmol) and triethylamine (9.87 ml, 70.87 mmol) in DCM (100 mL) was slowly added chloroacetyl chloride **617** (5.64 ml, 70.87 mmol). After addition, the mixture was stirred at RT for 45 min, quenched with water (70 mL) and extracted with DCM (3 x 40 mL). The combined organic phases were washed with hydrochloric acid (2M, 100 mL) and with a saturated solution of $NaHCO_3$ (100 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to afford 2-chloro-*N*-phenylacetamide **618** as a brown/yellow solid (10.52 g, 62.02 mmol, 96.25%). M.Pt: 118-120 °C (lit. 122-125 °C).[228] δ_H (400 MHz, $CDCl_3$): 4.19 (2H, s, C*H*$_2$), 7.21-7.17 (1H, m, Ar*H*), 7.41-7.36 (2H, m, Ar*H*), 7.57-7.55 (2H, m, Ar*H*), 8.23 (1H, bs, N*H*). δ_C (101MHz, $CDCl_3$): 43.0, 120.3, 125.4, 129.3, 136.8, 163.9. IR (NEAT) ν (cm^{-1}) = 688, 748, 856, 1249, 1342, 1442, 1496, 1556, 1600, 1668, 3097, 3143, 3207, 3265. *m/z* (NSI) calcd for $C_8H_9{}^{35}ClNO$ $[M+H]^+$: 170.0367, found: 170.0366.

Sodium hydride **31** (60% in oil, 2.47 g, 62.02 mmol) was washed with dry hexane (2 x 20 mL) and the hexane was removed via cannula. Dry THF (50 mL) was added to the sodium hydride and the mixture was cooled to 0 °C. A solution of **618** (10.52 g, 62.02 mmol) in dry THF (150 mL) was slowly added. The resulting mixture was stirred from 0 °C to RT for 17 h. Water (200 mL) was added and the resulting mixture was filtered

on a funnel to isolate the product as a solid, which was washed with DCM. The filtrate was extracted three times with DCM. The organic phase and the isolated solid were combined and concentrated to afford the product 1,4-diphenylpiperazine-2,5-dione **1** as a pale brown solid (8.09 g, 30.38 mmol, 97.9%). M.Pt: 262-264 °C (lit. 266-267 °C).[229] δ_H (400 MHz, $CDCl_3$): 4.55 (4H, s, C*H*$_2$), 7.38-7.32 (6H, m, Ar*H*), 7.49-7.44 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 53.6, 125.1, 127.7, 129.6, 139.7, 164.1. IR (NEAT) ν (cm^{-1}) = 690, 754, 1141, 1251, 1334, 1431, 1450, 1469, 1496, 1591, 1651, 2947, 3059. *m/z* (NSI) calcd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1128, found: 267.1130.

Preparation of 1,4-dibenzylpiperazine-2,5-dione 2



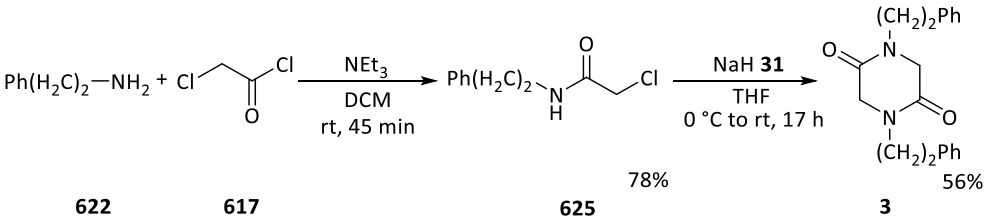
621 **617** **624** **2**

To a solution of benzylamine **621** (1.0 g, 9.33 mmol) and triethylamine (1.43 mL, 10.27 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride (0.82 mL, 10.27 mmol). After addition, the mixture was stirred at RT for 45 min, quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with hydrochloric acid (2M, 20 mL) and with a saturated solution of $NaHCO_3$ (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to afford the product *N*-benzyl-2-chloroacetamide **624** as a yellow solid (1.380 g, 7.52 mmol, 80.5%). M.Pt: 87-90 °C (lit. 91-92 °C).[230] δ_H (400 MHz, $CDCl_3$): 4.12 (2H, s, C*H*$_2$), 4.50 (2H, d, *J* = 5.6 Hz, C*H*$_2$), 6.87 (1H, bs, N*H*), 7.38-7.29 (5H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 42.7, 44.0, 127.9, 127.9, 129.0, 137.3, 165.9. IR (NEAT) ν (cm^{-1}) = 723, 744, 783, 1060, 1234, 1550, 1645, 3275. *m/z* (APCI) calcd for $C_9H_{11}{}^{35}ClNO$ $[M+H]^+$: 184.0524, found: 184.0524.

Sodium hydride **31** (60% in oil, 1.1 equiv, 0.33 g, 8.25 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (15 mL) was added to the

sodium hydride and cooled down to 0 °C and a solution of **624** (1.380 g, 7.52 mmol) in dry THF (25 mL) was slowly added. The resulting mixture was stirred from 0 °C to RT for 17 h. The mixture was quenched with water (50 ml). The non-soluble solid in water was filtered and the filtrate was extracted with DCM (2 x 30 ml). The combined organic phases and solid previously filtered were concentrated. The crude product was dissolved into DCM and purified by column chromatography on silica gel using MeOH (3%) in DCM. 1,4-Dibenzylpiperazine-2,5-dione **2** was obtained as an off-white solid (0.476 g, 1.62 mmol, 43%). M.Pt: 94-95 °C (lit. 95-97 °C).[231] δ_H (400 MHz, $CDCl_3$): 3.96 (4H, s, C*H*$_2$), 4.58 (4H, s, C*H*$_2$), 7.28-7.26 (4H, m, Ar*H*), 7.37-7.31 (6H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 49.3, 49.4, 128.3, 128.7, 129.1, 135.1, 163.4. IR (NEAT) ν (cm^{-1}) = 717, 933, 1065, 1160, 1275, 1328, 1483, 1643. *m/z* (APCI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$: 295.1441, found: 295.1442.

Preparation of 1,4-diphenethylpiperazine-2,5-dione 3

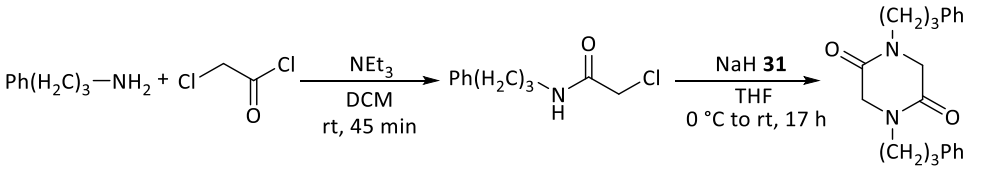


To a solution of 2-phenylethan-1-amine **622** (1.0 g, 8.25 mmol) and triethylamine (1.4 mL, 9.08 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride (0.73 mL, 9.08 mmol). After addition, the mixture was stirred at RT for 45 min, quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with hydrochloric acid (2M, 20 mL) and with a saturated solution of $NaHCO_3$ (20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated to afford the product 2-chloro-N-phenylacetamide **625** as a brown solid (1.275 g, 6.45 mmol, 78.2%). M.Pt.: 60-61 °C (lit. 66-67 °C).[232] δ_H (400 MHz, $CDCl_3$): 2.85 (2H, t, *J* = 6.8 Hz, C*H*$_2$), 3.57 (2H, q, *J* = 6.8 Hz, C*H*$_2$), 4.02 (2H, s, C*H*$_2$), 6.60 (1H, bs, N*H*), 7.27-7.19 (3H, m, Ar*H*), 7.35-7.30 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 35.6, 41.1, 42.8, 126.9,

128.8, 128.9, 138.5, 165.86. IR (NEAT) ν (cm^{-1}) = 696, 750, 1040, 1188, 1260, 1541, 1643, 3335. *m/z* (NSI) calcd for $C_{10}H_{13}{}^{35}ClNO$ $[M+H]^+$: 198.0680, found: 198.0680.

Sodium hydride **31** (60% in oil, 258 mg, 6.45 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (20 mL) was added to the sodium hydride and cooled down to 0 °C and a solution of **625** (1.275 g, 6.45 mmol) in dry THF (30 mL) was slowly added. The resulting mixture was stirred from 0 °C to rt for 17 h. The mixture was quenched with water (30 ml) and extracted with DCM (4 x 30 ml). The combined organic phases were concentrated with a Büchi rotary evaporator. The crude product was dissolved into DCM and purified by column chromatography on silica gel using DCM/MeOH (98%/2%). 1,4-diphenethylpiperazine-2,5-dione **3** was obtained as a beige solid (588 mg, 1.82 mmol, 56.4%). M.Pt.: 205-207 °C (lit. 210 °C).[233] δ_H (400 MHz, $CDCl_3$): 2.88 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.60 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.78 (4H, s, C*H*$_2$), 7.26-7.18 (6H, m, Ar*H*), 7.33-7.28 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 33.3, 48.1, 50.9, 127.0, 128.8, 128.9, 138.1, 163.5. IR (NEAT) ν (cm^{-1}) = 696, 739, 1169, 1244, 1298, 1339, 1429, 1485, 1643, 2938. *m/z* (NSI) calcd for $C_{20}H_{23}N_2O_2$ $[M+H]^+$: 323.1754, found: 323.1758.

Preparation of 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



To a solution of 3-phenylpropan-1-amine **623** (1.0 g, 7.40 mmol) and triethylamine (1.14 mL, 8.12 mmol) in DCM (30 mL) was slowly added chloroacetyl chloride **617** (0.65 mL, 8.12 mmol). After addition, the mixture was stirred at rt for 30 min and quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The combined organic phases were washed with a 2M solution of HCl in water (20 mL) and with a saturated solution of $NaHCO_3$ (20 mL). The organic phase was dried over Na_2SO_4,

filtered and concentrated to afford the product 2-chloro-*N*-(3-phenylpropyl)acetamide[234] **626** as an orange oil (1.167 g, 5.51 mmol, 74.5%). δ_H (400 MHz, $CDCl_3$): 1.90 (2H, quin, *J* = 7.6 Hz, C*H*$_2$), 2.68 (2H, t, *J* = 7.6 Hz, C*H*$_2$), 3.50 (2H, q, *J* = 6.0 Hz, C*H*$_2$), 4.02 (2H, s, C*H*$_2$), 6.56 (1H, bs, N*H*), 7.22-7.17 (3H, m, Ar*H*), 7.31-7.27 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 30.9, 33.3, 39.6, 42.8, 126.3, 128.5, 128.7, 141.2, 166.0. IR (NEAT) ν (cm^{-1}) = 698, 745, 1260, 1537, 1653, 2938, 3292. *m*/*z* (NSI) calcd for $C_{11}H_{15}{}^{35}ClNO$ $[M+H]^+$: 212.0837, found: 212.0835.

Sodium hydride (60% in oil, 220.5 mg, 5.51 mmol) was washed with dry hexane (2 x 10 mL) and the hexane was removed. Dry THF (20 mL) was added to the sodium hydride and cooled down to 0 °C and a solution of **626** (1.167 g, 5.51 mmol) in dry THF (30 mL) was slowly added. The resulting mixture was stirred from 0 °C to RT for 22 h. The mixture was quenched with water (30 ml) and extracted with DCM (4 x 30 ml). The combined organic phases were concentrated with a Büchi rotary evaporator. The crude product was dissolved into DCM and purified by column chromatography on silica gel using DCM/MeOH (98%/2%). 1,4-bis(3-phenepropyl)piperazine-2,5-dione **4** was obtained as a pale yellow solid (604 mg, 1.72 mmol, 62.6%). M.Pt.: 115-118 °C (no lit. value). δ_H (400 MHz, $CDCl_3$): 1.90 (4H, quin, *J* = 7.2 Hz, C*H*$_2$), 2.64 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.42 (4H, t, *J* = 7.6 Hz, C*H*$_2$), 3.85 (4H, s, C*H*$_2$), 7.20-7.16 (6H, m, Ar*H*), 7.30-7.26 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 28.1, 33.2, 45.9, 50.1, 126.3, 128.4, 128.6, 141.0, 163.5. IR (NEAT) ν (cm^{-1}) = 608, 694, 723, 754, 1024, 1487, 1647, 2932, 3292. *m*/*z* (NSI) calcd for $C_{22}H_{27}N_2O_2$ $[M+H]^+$: 351.2067, found: 351.2064.

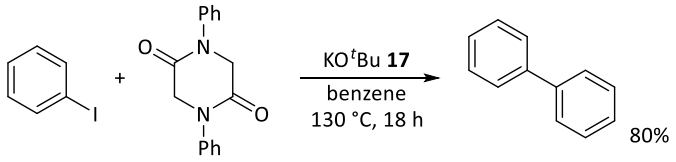
Cross-coupling reaction of aryl iodides with benzene promoted by DKPs

General Experimental Procedure 1

Inside a glovebox under nitrogen atmosphere, an oven-dried pressure tube was loaded with dry benzene (10 mL), DKP (0.1 mmol), KO^{t}Bu **17** (3.0 mmol) and aryl

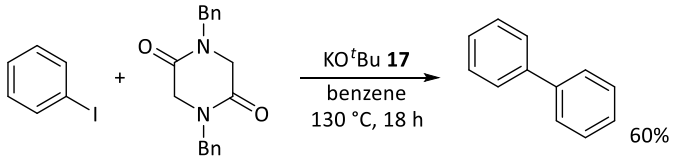
iodide (1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C. The mixture was stirred for 18 h at 130 °C, cooled to room temperature, quenched with water (30 mL) and extracted with Et_2O (3 X 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude product. Pure products were isolated by column chromatography using hexane when the reaction substrate was iodobenzene **5** or an iodotoluene **9**, **10** and **11**, and using Et_2O (3%) in hexane when the reaction substrate was an iodoanisole **6**, **7** and **8**.

Substrate: iodobenzene 5, Additive: 1,4-diphenylpiperazine-2,5-dione 1



Using General Procedure 1, iodobenzene **5** (0.204 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (123.4 mg, 0.800 mmol, 80.0%). M.Pt: 69-71 °C (lit. 70-71 °C).[235] δ_H (400 MHz, $CDCl_3$): 7.37-7.32 (2H, m, Ar*H*), 7.46-7.42 (4H, m, Ar*H*), 7.61-7.58 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 127.3, 127.4, 128.9, 141.4. IR (NEAT) v (cm^{-1}) = 694, 725, 902, 1004, 1429, 1475, 2924, 3034, 3061. *m/z* (APCI) calcd for $C_{12}H_{11}$ $[M+H]^+$: 155.0855, found: 155.0851.

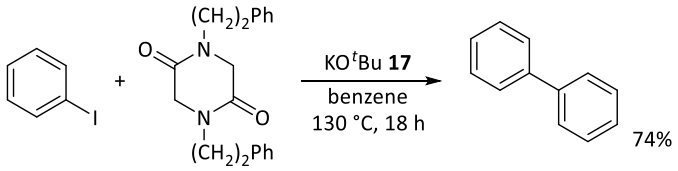
Substrate: iodobenzene 5, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



Using General Procedure 1, iodobenzene **5** (0.204 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in

benzene (10 mL) and afforded biphenyl **18** as a white solid (92.5 mg, 0.600 mmol, 60.0%). NMR spectra details as above.

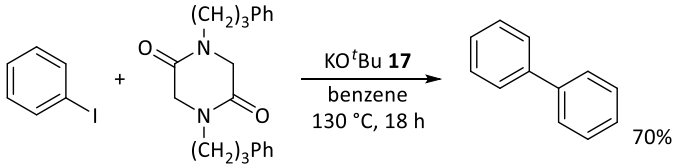
Substrate: iodobenzene 5, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



5 **3** **18**

Using General Procedure 1, iodobenzene **5** (0.204 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (114.1 mg, 0.740 mmol, 74.0%). NMR spectra details as above.

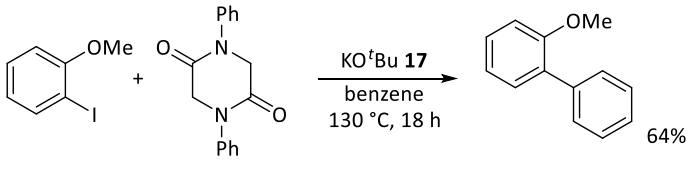
Substrate: iodobenzene 5, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 4



5 **4** **18**

Using General Procedure 1, iodobenzene **5** (0.204 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (107.9 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

Substrate: 2-iodoanisole 6, Additive: 1,4-diphenylpiperazine-2,5-dione 1

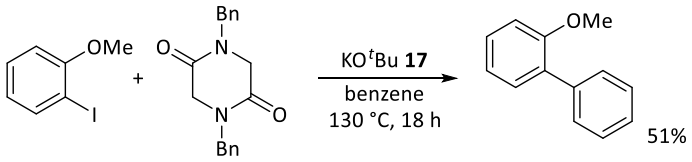


6 **1** **19**

Using General Procedure 1, 2-iodoanisole **6** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in

benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl[236] **19** as a colourless oil (118.1 mg, 0.640 mmol, 64.0%). δ_H (400 MHz, $CDCl_3$): 3.87 (3H, s, C*H*$_3$), 7.05 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.13-7.08 (1H, m, Ar*H*), 7.42-7.37 (3H, m, Ar*H*), 7.50-7.46 (2H, m, Ar*H*), 7.63-7.60 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 55.6, 111.4, 120.9, 127.0, 128.0, 128.7, 129.6, 130.8, 131.0, 138.6, 156.6. IR (NEAT) ν (cm^{-1}) = 696, 731, 752, 1026, 1122, 1234, 1257, 1429, 1481, 2833, 3059. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878.

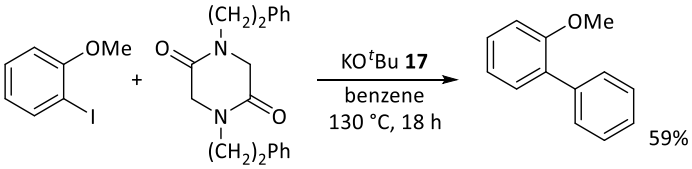
Substrate: 2-iodoanisole 6, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



6 **2** **19**

Using General Procedure 1, 2-iodoanisole **6** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (94.0 mg, 0.510 mmol, 51.0%). NMR spectra details as above.

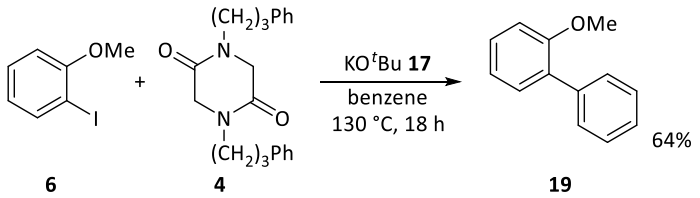
Substrate: 2-iodoanisole 6, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



6 **3** **19**

Using General Procedure 1, 2-iodoanisole **6** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (108.7 mg, 0.590 mmol, 59.0%). NMR spectra details as above.

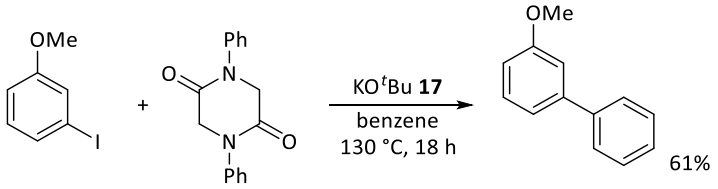
Substrate: 2-iodoanisole 6, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 4



6 4 19

Using General Procedure 1, 2-iodoanisole **6** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (117.9 mg, 0.640 mmol, 64.0%). NMR spectra details as above.

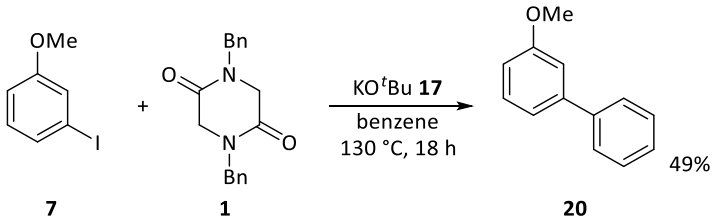
Substrate: 3-iodoanisole 7, Additive: 1,4-diphenylpiperazine-2,5-dione 1



7 1 20

Using General Procedure 1, 3-iodoanisole **7** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl[237] **20** as a colourless oil (111.6 mg, 0.610 mmol, 61.0%). δ_H (400 MHz, $CDCl_3$): 3.88 (3H, s, C*H*$_3$), 6.93-6.90 (1H, m, Ar*H*), 7.15 (1H, t, *J* = 2.4, Ar*H*), 7.21-7.19 (1H, m, Ar*H*), 7.39-7.34 (2H, m, Ar*H*), 7.47-7.43 (2H, m, Ar*H*), 7.62-7.59 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 55.4, 112.8, 113.0, 119.8, 127.3, 127.5, 128.8, 129.8, 141.2, 142.9, 160.1. IR (NEAT) ν (cm^{-1}) = 694, 754, 850, 862, 1018, 1037, 1053, 1211, 1294, 1419, 1477, 1571, 1597, 2833, 3057. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878.

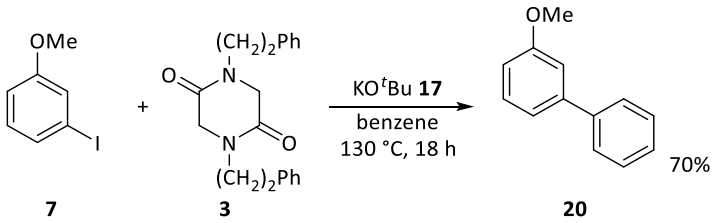
Substrate: 3-iodoanisole 7, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



7 **1** **20**

Using General Procedure 1, 3-iodoanisole **7** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (90.3 mg, 0.490 mmol, 49.0%). NMR spectra details as above.

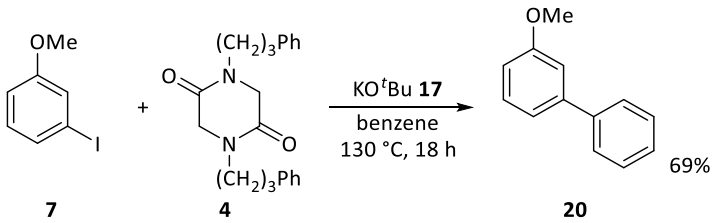
Substrate: 3-iodoanisole 7, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



7 **3** **20**

Using General Procedure 1, 3-iodoanisole **7** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (129.0 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

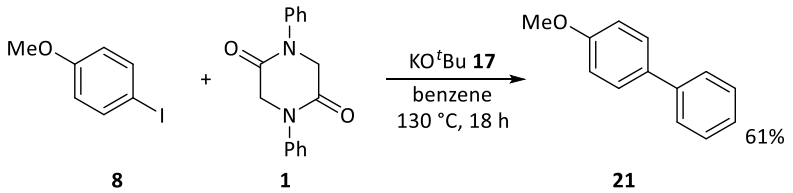
Substrate: 3-iodoanisole 7, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



7 **4** **20**

Using General Procedure 1, 3-iodoanisole **7** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (127.1 mg, 0.690 mmol, 69.0%). NMR spectra details as above.

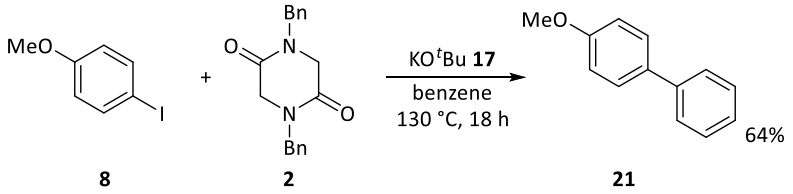
Substrate: 4-iodoanisole 8, Additive: 1,4-diphenylpiperazine-2,5-dione 1



8 **1** **21**

Using General Procedure 1, 4-iodoanisole **8** (0.234 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (112.4 mg, 0.610 mmol, 61.0%). M.Pt: 84-85 °C (lit. 84-85 °C).[238] δ_H (400 MHz, $CDCl_3$): 3.86 (3H, s, C*H*$_3$), 6.99-6.97 (2H, m, Ar*H*), 7.32-7.28 (1H, m, Ar*H*), 7.43-7.39 (2H, m, Ar*H*), 7.57-7.52 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 55.5, 114.4, 126.8, 126.9, 128.3, 128.9, 133.9, 141.0, 159.3. IR (NEAT) ν (cm^{-1}) = 686, 758, 833, 1033, 1184, 1199, 1247, 1483, 1604, 2835, 2962, 3003, 3034, 3066. *m/z* (APCI) calcd for $C_{13}H_{12}O$ $[M]^+$: 184.0883, found: 184.0878.

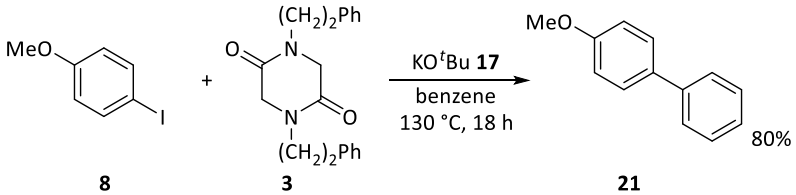
Substrate: 4-iodoanisole 8, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



8 **2** **21**

Using General Procedure 1, 4-iodoanisole **8** (0.234 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (117.9 mg, 0.640 mmol, 64.0%). NMR spectra details as above.

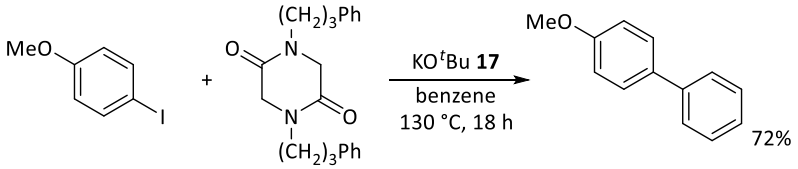
Substrate: 4-iodoanisole 8, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



8 **3** **21**

Using General Procedure 1, 4-iodoanisole **8** (0.234 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (147.4 mg, 0.800 mmol, 80.0%). NMR spectra details as above.

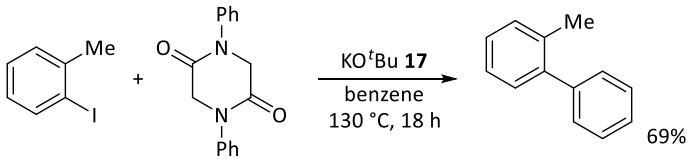
Substrate: 4-iodoanisole 8, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



8 **4** **21**

Using General Procedure 1, 4-iodoanisole **8** (0.234 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **21** as a white solid (132.6 mg, 0.720 mmol, 72.0%). NMR spectra details as above.

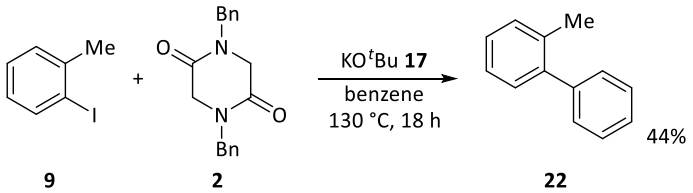
Substrate: 2-iodotoluene 9, Additive: 1,4-diphenylpiperazine-2,5-dione 1



9 **1** **22**

Using General Procedure 1, 2-iodotoluene **9** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1'-biphenyl[239] **22** as a colourless oil (116.0 mg, 0.690 mmol, 69.0%). δ_H (400 MHz, $CDCl_3$): 2.33 (3H, s, C*H*$_3$), 7.31-7.29 (3H, m, Ar*H*), 7.38-7.36 (3H, m, Ar*H*), 7.66-7.44 (3H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 20.6, 125.9, 126.9, 127.3, 128.2, 129.3, 129.9, 130.4, 135.5, 142.1, 142.2. IR (NEAT) ν (cm^{-1}) = 700, 725, 746, 773, 1439, 1479. *m/z* (APCI) calcd for $C_{13}H_{12}$ $[M]^+$: 168.0934, found: 168.0930.

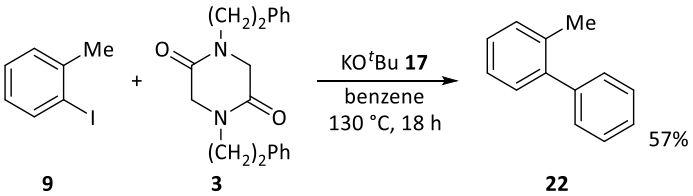
Substrate: 2-iodotoluene 9, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



9 **2** **22**

Using General Procedure 1, 2-iodotoluene **9** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1'-biphenyl **22** as a colourless oil (74.0 mg, 0.440 mmol, 44.0%). NMR spectra details as above.

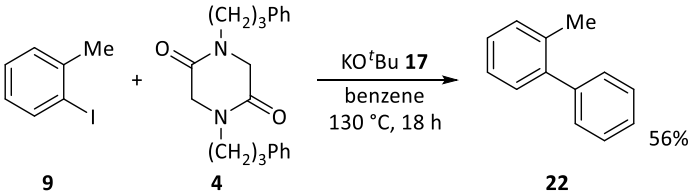
Substrate: 2-iodotoluene 9, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



9 **3** **22**

Using General Procedure 1, 2-iodotoluene **9** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1'-biphenyl **22** as a colourless oil (95.9 mg, 0.570 mmol, 57.0%). NMR spectra details as above.

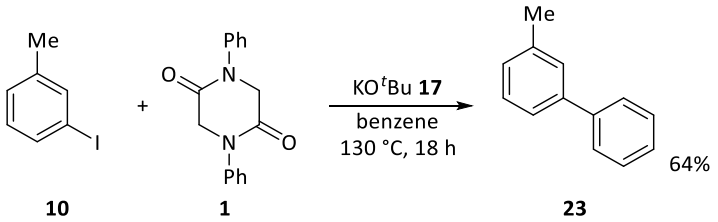
Substrate: 2-iodotoluene 9, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 4



9 **4** **22**

Using General Procedure 1, 2-iodotoluene **9** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methyl-1,1'-biphenyl **22** as a colourless oil (94.2 mg, 0.560 mmol, 56.0%). NMR spectra details as above.

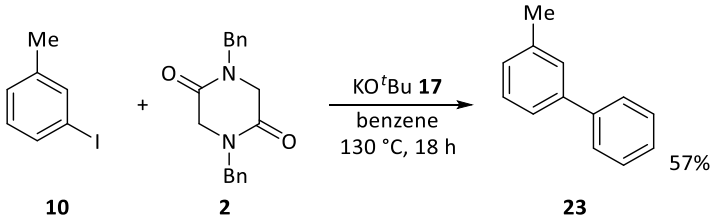
Substrate: 3-iodotoluene 10, Additive: 1,4-diphenylpiperazine-2,5-dione 1



10 **1** **23**

Using General Procedure 1, 3-iodotoluene **10** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1'-biphenyl[240] **23** as a colourless oil (107.7 mg, 0.640 mmol, 64%). δ_H (400 MHz, $CDCl_3$): 2.48 (3H, s, C*H*$_3$), 7.23-7.21 (1H, m, Ar*H*), 7.41-7.37 (2H, m, Ar*H*), 7.50-7.45 (4H, m, Ar*H*), 7.66-7.63 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 21.7, 124.4, 127.3, 128.1, 128.7, 128.8, 128.9, 129.0, 138.5, 141.4, 141.5. IR (NEAT) ν (cm^{-1}) = 615, 696, 750, 1481, 1599, 2918, 3030. *m/z* (APCI) calcd for $C_{13}H_{12}$ $[M]^+$: 168.0934, found: 168.0930.

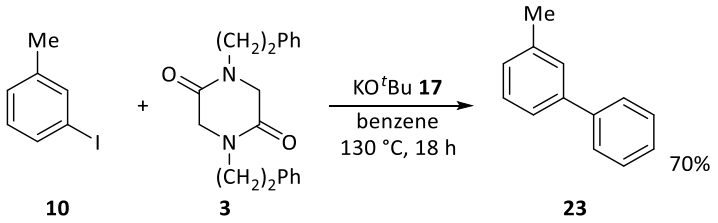
Substrate: 3-iodotoluene 10, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



10 **2** **23**

Using General Procedure 1, 3-iodotoluene **10** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1'-biphenyl **23** as a colourless oil (95.9 mg, 0.570 mmol, 57.0%). NMR spectra details as above.

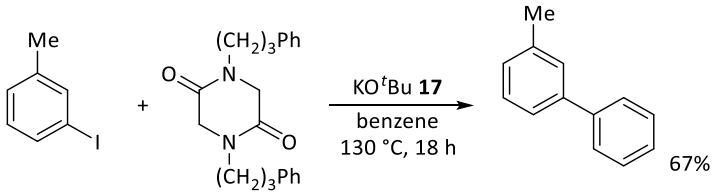
Substrate: 3-iodotoluene 10, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



10 **3** **23**

Using General Procedure 1, 3-iodotoluene **10** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1'-biphenyl **23** as a colourless oil (117.8 mg, 0.700 mmol, 70.0%). NMR spectra details as above.

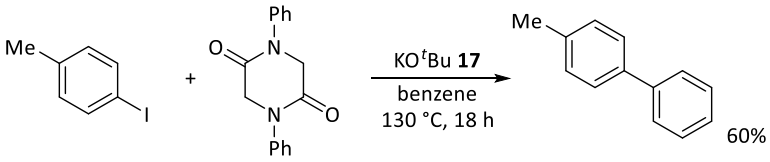
Substrate: 3-iodotoluene 10, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 4



10 **4** **23**

Using General Procedure 1, 3-iodotoluene **10** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methyl-1,1'-biphenyl **23** as a colourless oil (112.7 mg, 0.670 mmol, 67.0%). NMR spectra details as above.

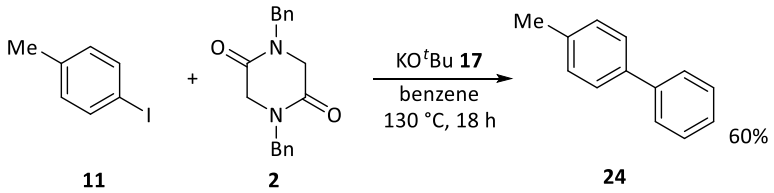
Substrate: 4-iodotoluene 11, Additive: 1,4-diphenylpiperazine-2,5-dione 1



11 **1** **24**

Using General Procedure 1, 4-iodotoluene **11** (0.218 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 mg, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (100.9 mg, 0.060 mmol, 60%). M.Pt: 45-47 °C (lit. 46-47 °C).[241] δ_H (400 MHz, $CDCl_3$): 2.41 (3H, s, C*H*$_3$), 7.28-7.25 (2H, m, Ar*H*), 7.36-7.31 (1H, m, Ar*H*), 7.46-7.42 (2H, m, Ar*H*), 7.52-7.50 (2H, m, Ar*H*), 7.61-7.58 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 21.2, 127.1, 127.2, 128.8, 129.6, 137.2, 138.5, 141.3. IR (NEAT) ν (cm^{-1}) = 688, 752, 821, 1037, 1377, 1485, 2856, 2916, 3030. *m/z* (APCI) calcd for $C_{13}H_{13}$ $[M+H]^+$: 169.1012, found: 169.1011.

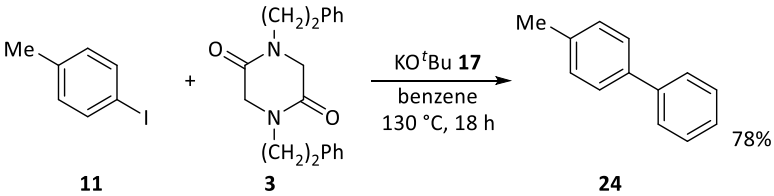
Substrate: 4-iodotoluene 11, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



11 **2** **24**

Using General Procedure 1, 4-iodotoluene **11** (0.218 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (100.9 mg, 0.600 mmol, 60.0%). NMR spectra details as above.

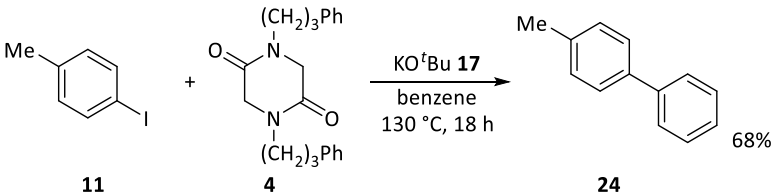
Substrate: 4-iodotoluene 11, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



11 **3** **24**

Using General Procedure 1, 4-iodotoluene **11** (0.218 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-me thyl-1,1'-biphenyl **24** as a colourless solid (131.2 mg, 0.780 mmol, 78.0%). NMR spectra details as above.

Substrate: 4-iodotoluene 11, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



11 **4** **24**

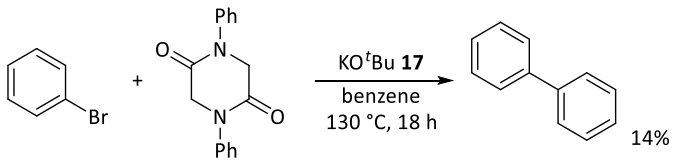
Using General Procedure 1, 4-iodotoluene **11** (0.218 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (114.4 mg, 0.680 mmol, 68.0%). NMR spectra details as above.

Cross-coupling reaction of aryl bromides with benzene promoted by DKPs

General Experimental Procedure 2

Inside a glovebox under nitrogen atmosphere, an oven-dried pressure tube was loaded with dry benzene (10 mL), DKP (0.1 mmol), KO^{t}Bu (3.0 mmol) and aryl bromide (1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C. The mixture was stirred for 18 h at 130 °C, cooled to room temperature, quenched with water (30 mL) and extracted with Et_2O (3 X 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude product. Pure products were isolated by column chromatography using hexane when the reaction substrate was bromobenzene **12** or 4-bromotoluene **16**, and using Et_2O (3%) in hexane when the reaction substrate was a bromoanisole **13**, **14** and **15**.

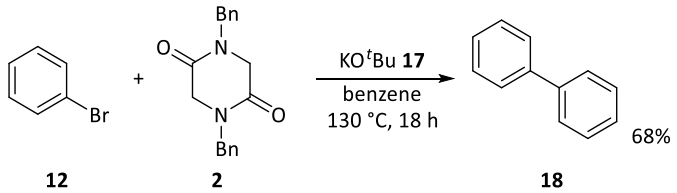
Substrate: bromobenzene 12, Additive: 1,4-diphenylpiperazine-2,5-dione 1



12 **1** **18**

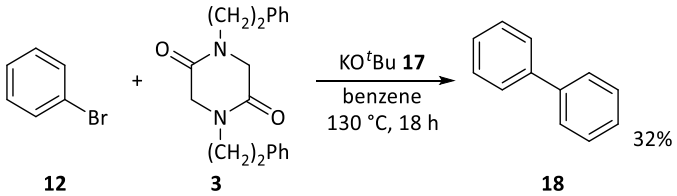
Using General Procedure 2, bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (21.6 mg, 0.140 mmol, 14.0%). NMR spectra details as above.

Substrate: bromobenzene 12, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



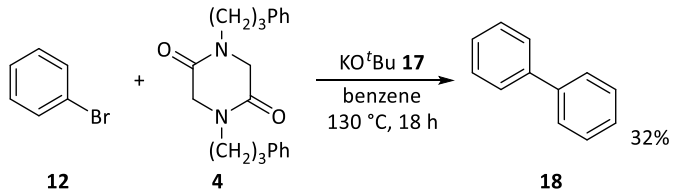
Using General Procedure 2, bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (104.9 mg, 0.680 mmol, 68.0%). NMR spectra details as above.

Substrate: bromobenzene 12, Additive: 1,4-diphenethylpiperazine -2,5-dione 3



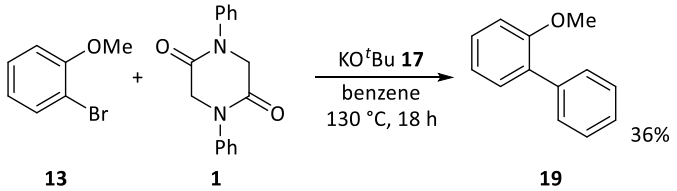
Using General Procedure 2, bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (49.3 mg, 0.320 mmol, 32.0%). NMR spectra details were as above.

Substrate: bromobenzene 12, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



Using General Procedure 2, bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (49.3 mg, 0.320 mmol, 32.0%). NMR spectra details as above.

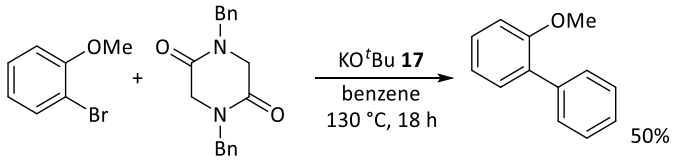
Substrate: 2-bromoanisole 13, Additive: 1,4-diphenylpiperazine-2,5-dione 1



13 **1** **19**

Using General Procedure 2, 2-bromoanisole **13** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (66.3 mg, 0.360 mmol, 36.0%). NMR spectra details as above.

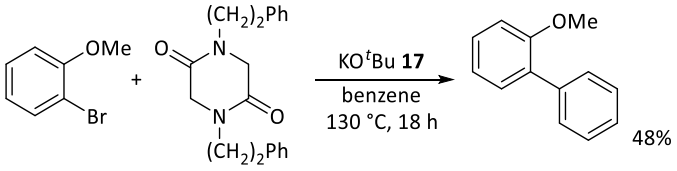
Substrate: 2-bromoanisole 13, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



13 **2** **19**

Using General Procedure 2, 2-bromoanisole **13** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (92.1 mg, 0.500 mmol, 50.0%). NMR spectra details as above.

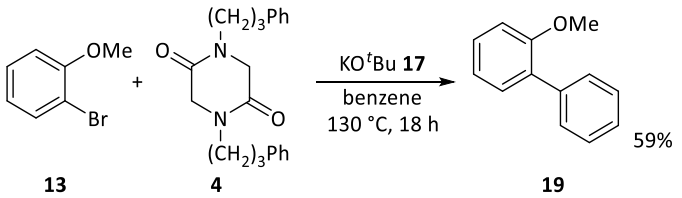
Substrate: 2-bromoanisole 13, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



13 **3** **19**

Using General Procedure 2, 2-bromoanisole **13** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (88.4 mg, 0.480 mmol, 48.0%). NMR spectra details as above.

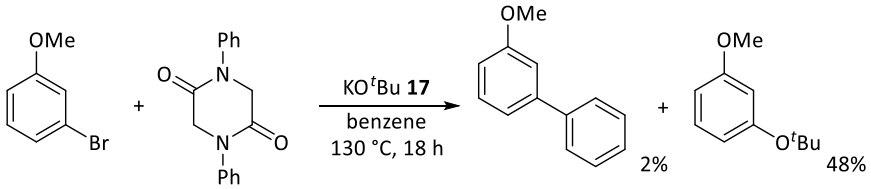
Substrate: 2-bromoanisole 13, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



13 **4** **19**

Using General Procedure 2, 2-bromoanisole **13** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-methoxy-1,1'-biphenyl **19** as a colourless oil (108.7 mg, 0.590 mmol, 59.0%). NMR spectra details as above.

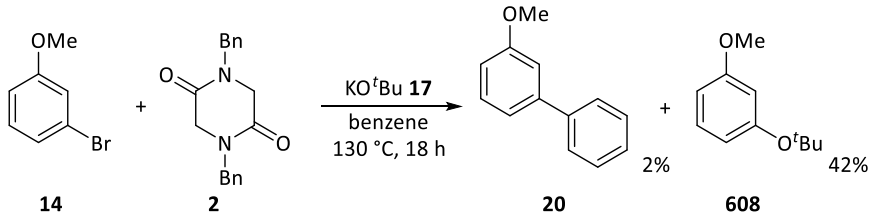
Substrate: 3-bromoanisole 14, Additive: 1,4-diphenylpiperazine-2,5-dione 1



14 **1** **20** **608**

Using General Procedure 2, 3-bromoanisole **14** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above. 1-(*tert*-Butoxy)-3-methoxybenzene[242] **608** was also afforded as a colourless oil (86.5 mg, 0.480 mmol, 48.0%), δ_H (400 MHz, $CDCl_3$): 1.36 (9H, s, OC(C*H*$_3$)$_3$), 3.78 (3H, s, OC*H*$_3$), 6.55 (1H, t, *J* = 2.0 Hz, Ar*H*), 6.65-6.59 (2H, m, Ar*H*), 7.15 (1H, t, *J* = 8.0 Hz, Ar*H*). δ_C (100 MHz, $CDCl_3$): 29.1, 55.4, 78.7, 108.9, 110.2, 116.5, 129.2, 156.8, 160.3. IR (NEAT) ν (cm^{-1}) = 691, 963, 1043, 1138, 1281, 1483, 1586, 2973. *m/z* (EI) $C_{11}H_{16}O_2$ [M]: 180.1.

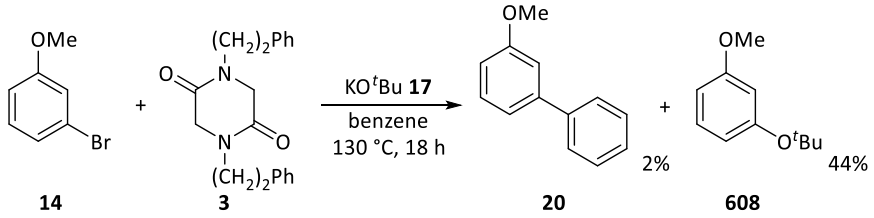
Substrate: 3-bromoanisole 14, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



14 **2** **20** **608**

Using General Procedure 2, 3-bromoanisole **14** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above. 1-(*tert*-Butoxy)-3-methoxybenzene **608** was also afforded as a colourless oil (75.7 mg, 0.420 mmol, 42.0%). NMR spectra details as above.

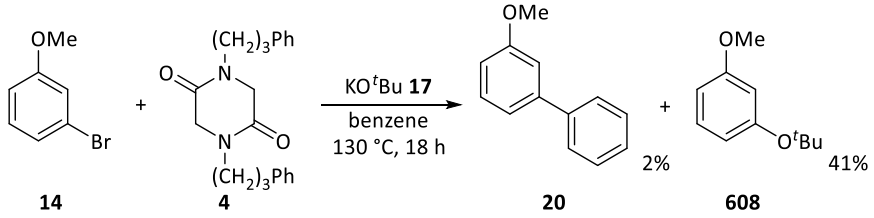
Substrate: 3-bromoanisole 14, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



14 **3** **20** **608**

Using General Procedure 2, 3-bromoanisole **14** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above. 1-(*tert*-Butoxy)-3-methoxybenzene **608** was also afforded as a colourless oil (79.3 mg, 0.440 mmol, 44.0%). NMR spectra details as above.

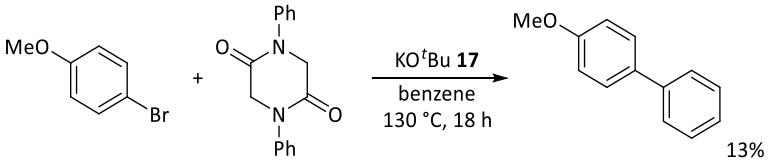
Substrate: 3-bromoanisole 14, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



14 **4** **20** **608**

Using General Procedure 2, 3-bromoanisole **14** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 3-methoxy-1,1'-biphenyl **20** as a colourless oil (3.7 mg, 0.020 mmol, 2.0%). NMR spectra details as above. 1-(*tert*-Butoxy)-3-methoxybenzene **608** was also afforded as a colourless oil (73.9 mg, 0.410 mmol, 41.0%). NMR spectra details as above.

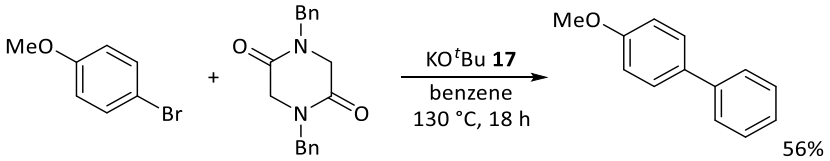
Substrate: 4-bromoanisole 15, Additive: 1,4-diphenylpiperazine-2,5-dione 1



15 **1** **21**

Using General Procedure 2, 4-bromoanisole **15** (0.184 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (23.9 mg, 0.130 mmol, 13.0%). NMR spectra details as above.

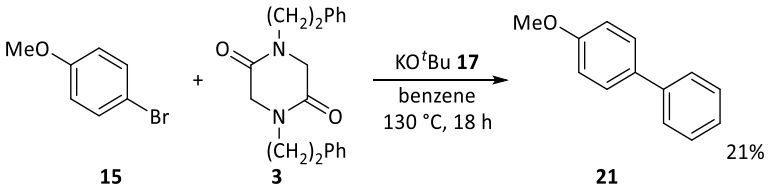
Substrate: 4-bromoanisole 15, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



15 **2** **21**

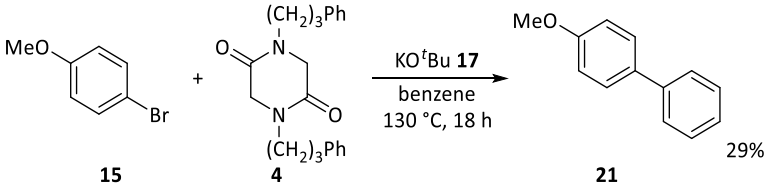
Using General Procedure 2, 4-bromoanisole **15** (0.184 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (103.2 mg, 0.560 mmol, 56.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 15, Additive: 1,4-diphenethylpiperazine-2,5-dione 3



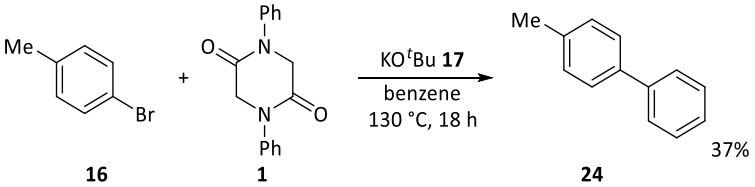
Using General Procedure 2, 4-bromoanisole **15** (0.184 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (38.7 mg, 0.210 mmol, 21.0%). NMR spectra details as above.

Substrate: 4-bromoanisole 15, Additive: 1,4-bis(3-phenylpropyl)-piperazine-2,5-dione 4



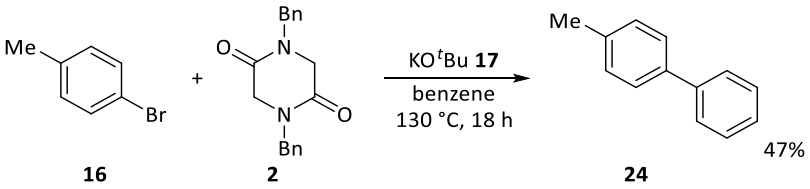
Using General Procedure 2, 4-bromoanisole **15** (0.184 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** as a white solid (53.4 mg, 0.290 mmol, 29.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 16, Additive: 1,4-diphenylpiperazine-2,5-dione 1



Using General Procedure 2, 4-bromotoluene **16** (0.171 g, 1.0 mmol) was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (62.2 mg, 0.370 mmol, 37.0%). NMR spectra details as above.

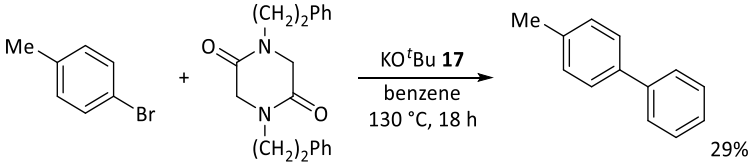
Substrate: 4-bromotoluene 16, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



16 **2** **24**

Using General Procedure 2, 4-bromotoluene **16** (0.171 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (79.1 mg, 0.470 mmol, 47.0%). NMR spectra details as above.

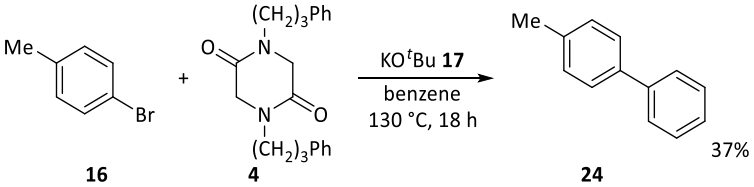
Substrate: 4-bromotoluene 16, Additive: 1,4-diphenethyl-piperazine-2,5-dione 3



16 **3** **24**

Using General Procedure 2, 4-bromotoluene **16** (0.171 g, 1.0 mmol) was treated with 1,4-diphenethylpiperazine-2,5-dione **3** (0.032 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (48.8 mg, 0.290 mmol, 29.0%). NMR spectra details as above.

Substrate: 4-bromotoluene 16, Additive: 1,4-bis(3-phenylpropyl)piperazine-2,5-dione 4



16 **4** **24**

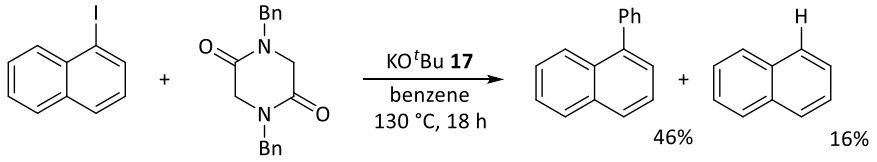
Using General Procedure 2, 4-bromotoluene **16** (0.171 g, 1.0 mmol) was treated with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4** (0.035 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methyl-1,1'-biphenyl **24** as a colourless solid (62.2 mg, 0.370 mmol, 37.0%). NMR spectra details as above.

Cross-coupling reaction of halonaphthalenes with benzene promoted by DKPs

General information

The experimental procedure for these cross-coupling reactions was the same as the procedures described above for cross-coupling experiments. The products were purified by column chromatography using hexane as eluent.

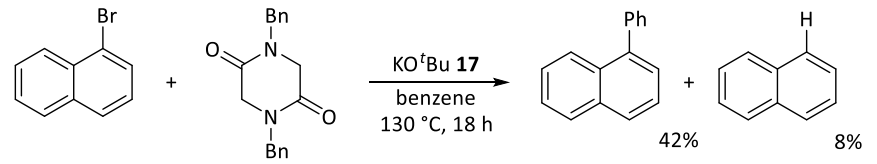
Substrate: 1-iodonaphthalene 639, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



639 **2** **642** **110**

1-Iodonaphthalene **639** (0.254 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 1-phenylnaphthalene[243] **642** as a pale-yellow oil (94.0 mg, 0.460 mmol, 46%). δ_H (400 MHz, $CDCl_3$): 7.56-7.42 (9H, m, Ar*H*), 7.93-7.87 (3H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 125.5, 125.9, 126.2, 127.1, 127.3, 127.4, 127.8, 128.4, 128.9, 130.2, 131.8, 133.9, 140.4, 140.9. IR (NEAT) ν (cm^{-1}) = 702, 762, 779, 803, 1396, 1495, 3054. *m/z* (APCI) calcd for $C_{16}H_{13}$ $[M+H]^+$: 205.1012, found: 205.1012. Naphthalene **110** was recovered as a white solid (20.5 mg, 0.16 mmol, 16%). M.Pt.: 79-81 °C (lit. 80-83 °C).[244] δ_H (400 MHz, $CDCl_3$): 7.51-7.47 (4H, m, Ar*H*), 7.88-7.84 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 126.0, 128.0, 133.6. IR (NEAT) ν (cm^{-1}) = 777, 961, 1125, 1273, 1390, 1504, 1593, 3047. *m/z* (EI) $C_{10}H_8$ [M] : 128.1.

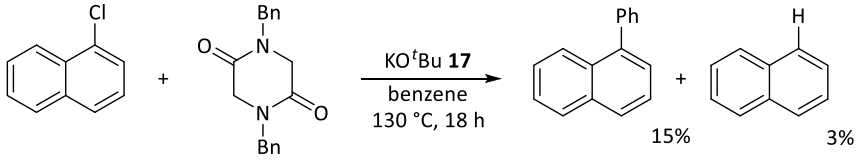
Substrate: 1-bromonaphthalene 280, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



280 **2** **642** **110**

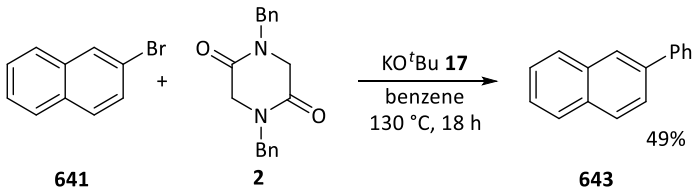
1-Bromonaphthalene **280** (0.207 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 1-phenylnaphthalene **642** as a pale-yellow oil (85.8 mg, 0.420 mmol, 42%). Naphthalene **110** was recovered as a white solid (10.3 mg, 0.08 mmol, 8%). NMR spectra details as above.

Substrate: 1-chloronaphthalene 640, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



1-Chloronaphthalene **640** (0.163 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 1-phenylnaphthalene **642** as a pale-yellow oil (30.6 mg, 0.15 mmol, 15%). Naphthalene **110** was recovered as a white solid (3.8 mg, 0.03 mmol, 3%). NMR spectra details as above.

Substrate: 2-bromonaphthalene 641, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



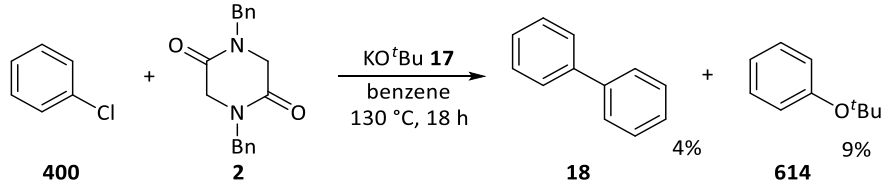
2-Bromonaphthalene **641** (0.207 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 2-phenylnaphthalene **643** as a white solid (100.1 mg, 0.49 mmol, 49%). M.Pt.: 90-92 °C (lit. 96-97 °C).[245] δ_H (400 MHz, $CDCl_3$): 7.41-7.36 (1H, m, Ar*H*), 7.53-7.46 (4H, m, Ar*H*), 7.77-7.72 (3H, m, Ar*H*), 7.93-7.86 (3H, m, Ar*H*), 8.05 (1H, s, Ar*H*). δ_C (100 MHz, $CDCl_3$): 125.8, 126.0, 126.1, 126.4, 127.5, 127.6, 127.8, 128.4, 128.6, 129.0, 132.8, 133.9, 138.7, 141.3. IR (NEAT) ν (cm^{-1}) = 688, 745, 756, 771, 859, 3034. *m/z* (APCI) calcd for $C_{16}H_{13}$ $[M+H]^+$: 205.1012, found: 205.1008.

Attempts to entrain the cross-coupling reaction of aryl chlorides and fluorides with benzene

General Procedure 3

Inside a glovebox under nitrogen atmosphere, an oven-dried pressure tube was loaded with dry benzene (10 mL), DKP (0.1 mmol), KO^{t}Bu (3.0 mmol), aryl chloride or fluoride (0.9 mmol) and aryl iodide (0.1 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C. The mixture was stirred for 18 h at 130 °C, cooled to room temperature, quenched with water (30 mL) and extracted with Et_2O (3 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude product. Pure products were isolated by column chromatography using hexane or Et_2O (2.5%) in hexane as eluent.

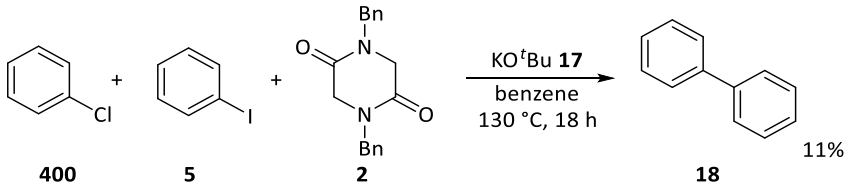
Substrate: chlorobenzene 400, **Additive: 1,4-dibenzylpiperazine-2,5-dione 2**



400 **2** **18** **614**

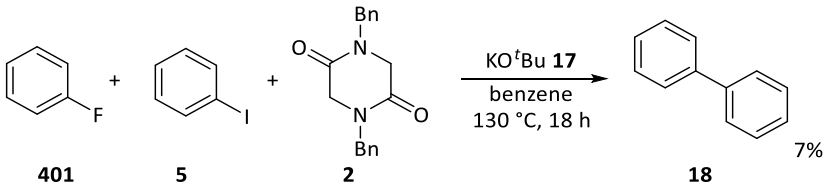
Using General Procedure 3 with chlorobenzene **400** alone (0.113 g, 1.0 mmol), 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (6.2 mg, 0.04 mmol, 4%), NMR spectra details as above, and *tert*-butoxybenzene[246] **614** as a colourless liquid (13.5 mg, 0.09 mmol, 9%). δ_H (400 MHz, $CDCl_3$): 1.35 (9H, s, OC(C*H*$_3$)$_3$), 7.01-6.98 (2H, m, Ar*H*), 7.09-7.05 (1H, m, Ar*H*), 7.28-7.24 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 29.0, 78.5, 123.4, 124.3, 128.9, 155.5. IR (NEAT) ν (cm^{-1}) = 697, 751, 781, 1158, 1234, 1366, 1485, 1593, 2974. *m/z* (EI) $C_{10}H_{14}O$ [M]: 150.1.

Substrate: chlorobenzene 400, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



Using General Procedure 3 with chlorobenzene **400** (0.101 g, 0.9 mmol), iodobenzene **5** (0.020 g, 0.1 mmol), 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (17.0 mg, 0.11 mmol, 11%). NMR spectra details as above.

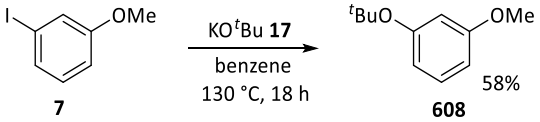
Substrate: fluorobenzene 401, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



Using General Procedure 3 with fluorobenzene **401** (0.086 g, 0.9 mmol), iodobenzene **5** (0.020 g, 0.1 mmol), 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded biphenyl **18** as a white solid (10.8 mg, 0.07 mmol, 7%). NMR spectra details as above.

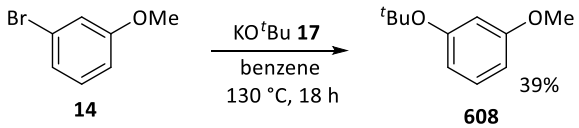
Reactions of 3-iodoanisole 7 and 3-bromoanisole 14 with KO^{t}Bu 17

Substrate: 3-iodoanisole 7



The experimental procedure was the same as for the previous cross-coupling reactions, without use of an organic additive. 3-Iodoanisole **7** (0.234 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) to selectively afford 3-*tert*-butoxyanisole **608** as a colourless oil (104.5 mg, 0.58 mmol, 58%). NMR spectra details as above.

Substrate: 3-bromoanisole 14

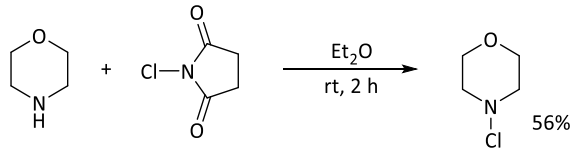


14 **608**

3-Bromoanisole **14** (0.187 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) to selectively afford 3-*tert*-butoxyanisole **608** as a colourless oil (70.3 mg, 0.39 mmol, 39%). NMR spectra details as above.

Use of 4-chloromorpholine 604 as an additive

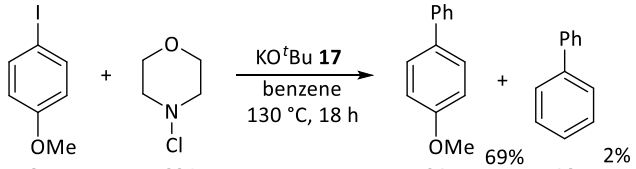
Synthesis of 4-chloromorpholine 604



602 **603** **604**

To a solution of *N*-chlorosuccinimide **603** (1.69 g, 12.7 mmol) in dry Et_2O, under argon, at room temperature, was added morpholine **602** (1.0 g, 11.5 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h, filtered, washed with water (2 x 30 mL), dried over Na_2SO_4, filtered and concentrated to afford *N*-chloromorpholine[247] **604** as a colourless oil (0.182 g, 6.42 mmol, 56%). δ_H (400 MHz, $CDCl_3$): 3.18 (4H, bs, CH_2), 3.76 (4H, bs, CH_2). δ_C (100 MHz, $CDCl_3$): 63.0, 67.7. IR (NEAT) ν (cm^{-1}) = 888, 1009, 1102, 1260, 1457, 2857, 2921, 2961. *m*/*z* (EI) C_4H_8ClNO [M]: 121.0, 123.0.

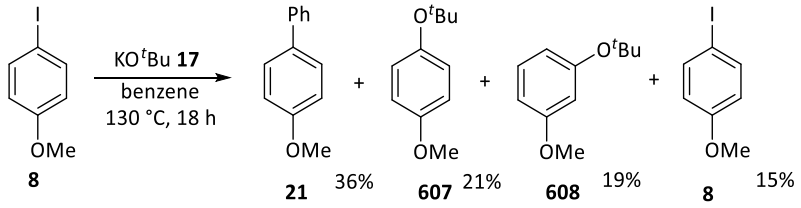
Cross coupling reaction of 4-iodoanisole 8 with benzene promoted by *N*-chloromorpholine 604



8 **604** **21** **18**

The experimental procedure was the same as for the previous cross-coupling reactions of aryl halides with benzene. 4-Iodoanisole **8** (0.234 g, 1.0 mmol) was treated with *N*-chloromorpholine **604** (0.012 g, 0.1 mmol), KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) and afforded 4-methoxy-1,1'-biphenyl **21** (127.1 mg, 0.69 mmol, 69%) and biphenyl **18** (3.1 mg, 0.02 mmol, 2%).

Cross coupling reaction of 4-iodoanisole 8 with benzene without promoter



4-Iodoanisole **8** was treated with KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) to afford 4-methoxy-1,1'-biphenyl **21** (66.3 mg, 0.36 mmol, 36%), an inseparable mixture of 4-*tert*-butoxyanisole[242] **607** (37.9 mg, 0.21 mmol, 21%) and 3-*tert*-butoxyanisole **608** (34.2 mg, 0.19 mmol, 19%), δ_H (400 MHz, $CDCl_3$): 1.31 (9H, s, OC(C*H*$_3$)$_3$), 1.36 (9H, s, OC(C*H*$_3$)$_3$), 3.78 (3H, s, OC*H*$_3$), 3.78 (3H, s, OC*H*$_3$), 6.56 (1H, t, *J* = 2.0 Hz, Ar*H*), 6.65-6.59 (2H, m, Ar*H*), 6.82-6.78 (2H, m, Ar*H*), 6.94-6.90 (2H, m, Ar*H*), 7.16 (1H, t, *J* = 8.4 Hz, Ar*H*), δ_C (100 MHz, $CDCl_3$): 28.8, 29.0, 55.4, 55.6, 78.2, 78.7, 108.9, 110.2, 113.9, 116.5, 125.5, 129.2, 148.8, 155.9, 156.8, 160.3, IR (NEAT) ν (cm^{-1}) = 693, 769, 846, 1039, 1141, 1165, 1227, 1485, 1504, 1600, 2974, *m/z* (EI) $C_{11}H_{16}O_2$ [M]: 180.1 (both isomers), and remaining 4-iodoanisole **8** (35.1 mg, 0.15 mmol, 15%).

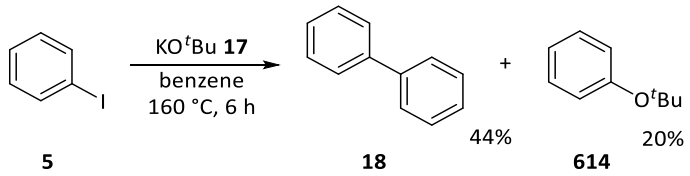
Repetition of Wilden's reactions

General Information

All reactions were prepared inside a glovebox as reported above. The reaction mixture was stirred by placing the sealed pressure tube inside a stirred oil bath at 160 °C for 6 h. After cooling to room temperature, the mixture was quenched by water (30 mL) and extracted with Et_2O (3 X 30 mL). Combined organic extracts were dried

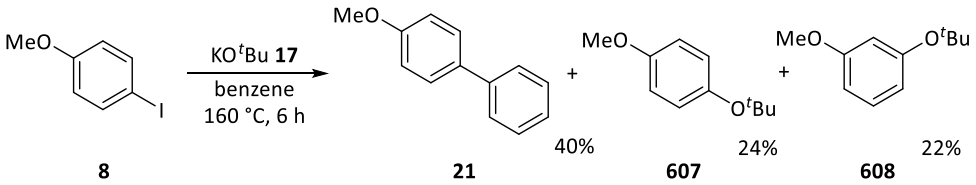
over Na_2SO_4, filtered and concentrated to afford crude products. The yields of the reaction products were quantified using 1,3,5-trimethoxybenzene as an internal standard in the ^1H NMR spectra of the crude reaction product.

Substrate: iodobenzene 5



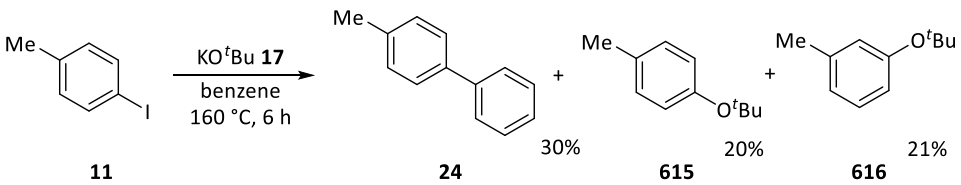
Iodobenzene **5** (0.204 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.449 g, 4.0 mmol) in benzene (10 mL) to afford biphenyl **18** (67.9 mg, 0.44 mmol, 44%) and *tert*-butoxybenzene **614** (30.0 mg, 0.20 mmol, 20%). NMR spectra details as above for all products.

Substrate: 4-iodoanisole 8



4-Iodoanisole **8** (0.204 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.449 g, 4.0 mmol) in benzene (10 mL) to afford 4-methoxy-1,1'-biphenyl **21** (73.7 mg, 0.40 mmol, 40%), 4-*tert*-butoxyanisole **607** (43.3 mg, 0.24 mmol, 24%) and 3-*tert*-butoxyanisole **608** (39.7 mg, 0.22 mmol, 22%). NMR spectra details as above for all products.

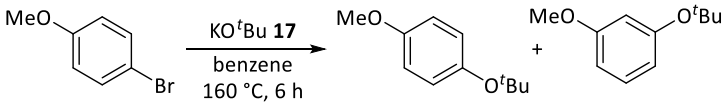
Substrate: 4-iodotoluene 11



4-Iodotoluene **11** (0.218 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.449 g, 4.0 mmol) in benzene (10 mL) to afford 4-methyl-1,1'-biphenyl **24** (50.5 mg, 0.30 mmol, 30%), NMR spectra details as above, and a mixture of 4-*tert*-butoxytoluene **615** (32.8 mg,

0.20 mmol, 20%) and 3-*tert*-butoxytoluene **616** (34.5 mg, 0.21 mmol, 21%), δ_H (400 MHz, $CDCl_3$): 1.33 (9H, s, OC(CH_3)$_3$), 1.35 (9H, s, OC(CH_3)$_3$), 2.31 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.81-6.79 (2H, m, Ar*H*), 6.90-6.87 (3H, m, Ar*H*), 7.07-7.04 (2H, m, Ar*H*), 7.16-7.11 (1H, m, Ar*H*), δ_C (100 MHz, $CDCl_3$): 20.9, 21.5, 29.0, 29.1, 78.2, 78.3, 121.2, 124.2, 124.3, 125.1, 128.6, 129.5, 132.9, 138.9, 153.0, 155.5, IR (NEAT) ν (cm^{-1}) = 695, 792, 898, 950, 1149, 1236, 1370, 1485, 1506, 1606, 2976, *m/z* (EI) $C_{11}H_{16}O$ [M]: 164.1 (both isomers).

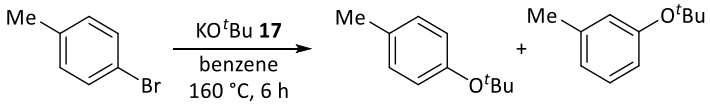
Substrate: 4-bromoanisole 15



15 **607** **608**

4-Bromoanisole 15 (0.187 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.449 g, 4.0 mmol) in benzene (10 mL) to afford a mixture of 4-*tert*-butoxyanisole **607** (75.7 mg, 0.42 mmol, 42%) and 3-*tert*-butoxyanisole **608** (70.3 mg, 0.39 mmol, 39%). NMR spectra details as above.

Substrate: 4-bromotoluene 16

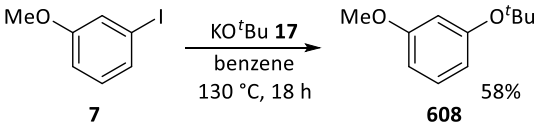


16 **615** **616**

4-Bromotoluene **16** (0.171 g, 1.0 mmol) was treated with KO^{t}Bu **17** (0.449 g, 4.0 mmol) in benzene (10 mL) to afford a mixture of 4-*tert*-butoxytoluene **615** (55.8 mg, 0.34 mmol, 34%) and 3-*tert*-butoxytoluene **616** (57.5 mg, 0.35 mmol, 35%). NMR spectra details as above.

Selective benzyne formation followed by *tert*-butoxide addition on 3-haloanisoles

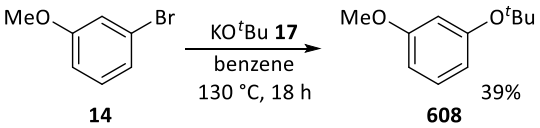
Substrate: 3-iodoanisole 7



7 **608**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (10 mL), 3-iodoanisole **7** (0.234 g, 1.0 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 X 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude product. Purification of the crude was made by column chromatography using Et_2O (2.5%) in hexane as eluent to afford 3-*tert*-butoxyanisole **608** (104.5 mg, 0.58 mmol, 58%). NMR spectra details as above.

Substrate: 3-bromoanisole 14



14 **608**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (10 mL), 3-bromoanisole **14** (0.187 g, 1.0 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 X 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude product. Purification of the crude was made by column chromatography using Et_2O (2.5%) in hexane as eluent to afford 3-*tert*-butoxyanisole **608** (70.3 mg, 0.39 mmol, 39%). NMR spectra details as above.

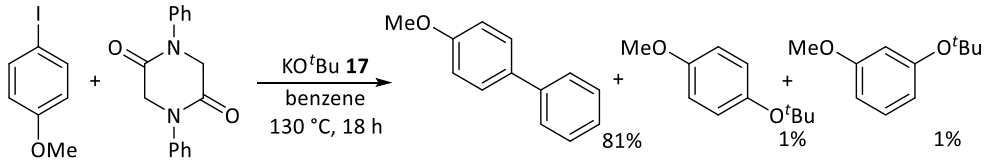
Tracking of benzyne adducts when an efficient organic additive is present in a transition metal-free cross-coupling reaction

General information

The following experiments were made to check if the benzyne formation from aryl halides under the usual metal-free cross-coupling conditions was efficiently shut down or still a non-negligible process.

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (10 mL), aryl halide (1.0 mmol), a DKP (0.1 mmol) and KO^{t}Bu **17** (indicated amount). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at indicated temperature for indicated amount of time. Yields of the reaction products were quantified using 1,3,5-trimethoxybenzene as an internal standard.

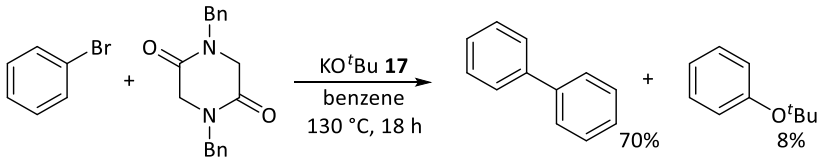
Substrate: 4-iodoanisole 8, Additive: 1,4-diphenylpiperazine-2,5-dione 1



8 **1** **21** **607** **608**

4-Iodoanisole **8** was treated with 1,4-diphenylpiperazine-2,5-dione **1** (0.026 g, 0.1 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) at 130 °C for 18 h to afford 4-methoxy-1,1'-biphenyl **21** (149.2 mg, 0.81 mmol, 81%), 4-*tert*-butoxyanisole **607** (1.8 mg, 0.01 mmol, 1%) and 3-*tert*-butoxyanisole **608** (1.8 mg, 0.01 mmol, 1%). NMR spectra details as above.

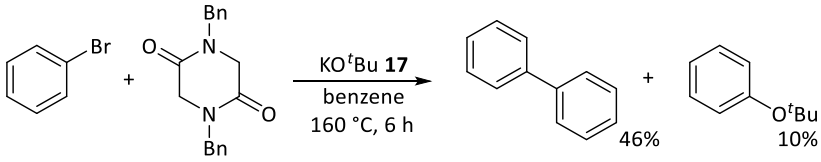
Substrate: bromobenzene 12, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



12 **2** **18** **614**

Bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) at 130 °C for 18 h to afford biphenyl **18** (107.9 mg, 0.70 mmol, 70%) and *tert*-butoxybenzene **614** (12.0 mg, 0.08 mmol, 8%). NMR spectra details as above.

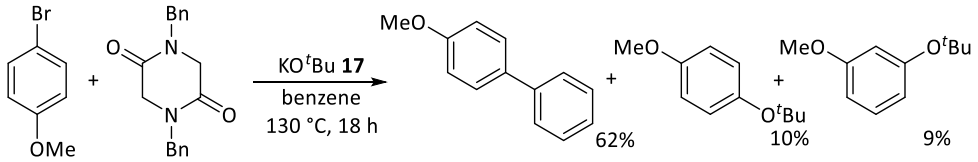
Substrate: bromobenzene 12, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



12 **2** **18** **614**

Bromobenzene **12** (0.157 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) at 160 °C for 6 h to afford biphenyl **18** (70.9 mg, 0.46 mmol, 46%) and *tert*-butoxybenzene **614** (15.0 mg, 0.10 mmol, 10%). NMR spectra details as above.

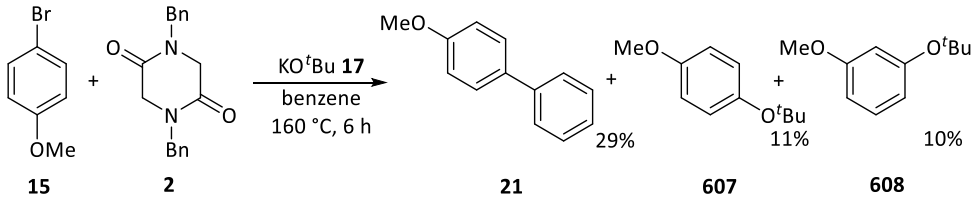
Substrate: 4-bromoanisole 15, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



15 **2** **21** **607** **608**

4-Bromoanisole **15** (0.187 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) at 130 °C for 18 h to afford 4-methoxy-1,1'-biphenyl **21** (114.2 mg, 0.62 mmol, 62%), 4-*tert*-butoxyanisole **607** (18.0 mg, 0.10 mmol, 10%) and 3-*tert*-butoxyanisole **608** (16.2 mg, 0.09 mmol, 9%). NMR spectra details as above.

Substrate: 4-bromoanisole 15, Additive: 1,4-dibenzylpiperazine-2,5-dione 2



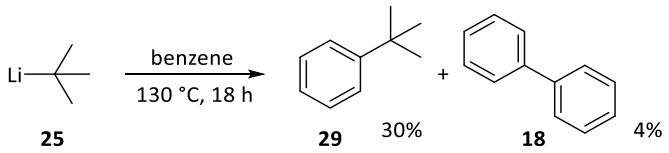
15 **2** **21** **607** **608**

4-Bromoanisole **15** (0.187 g, 1.0 mmol) was treated with 1,4-dibenzylpiperazine-2,5-dione **2** (0.029 g, 0.1 mmol) and KO^{t}Bu **17** (0.337 g, 3.0 mmol) in benzene (10 mL) at 160 °C for 6 h to afford 4-methoxy-1,1'-biphenyl **21** (53.4 mg, 0.29 mmol, 29%), 4-*tert*-butoxyanisole **607** (19.8 mg, 0.11 mmol, 11%) and 3-*tert*-butoxyanisole **608** (18.0 mg, 0.10 mmol, 10%). NMR spectra details as above.

6.2 Experimental details of Chapter 3

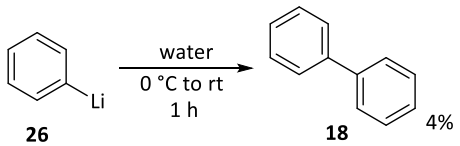
Reactions of ^{t}BuLi 25 and phenyl lithium 26 with benzene and benzene-d_6

Reaction of ^{t}BuLi 25 with benzene



Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (3 mL) and ^{t}BuLi **25** (1.7 M in hexanes, 0.59 mL, 1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography using hexane as eluent to afford *tert*-butylbenzene[248] **29** as a colourless oil (40.3 mg, 0.30 mmol, 30%), δ_H (400 MHz, $CDCl_3$): 1.35 (9H, s, C(C*H*$_3$)), 7.19 (1H, m, Ar*H*), 7.32 (2H, m, Ar*H*), 7.41 (2H, m, Ar*H*), δ_C (100 MHz, $CDCl_3$): 31.6, 34.9, 127.3, 127.4, 128.9, 141.4, IR (NEAT) ν (cm^{-1}) = 690, 1156, 1242, 1537, 1651, 2876, 2935, 2965, 3290, *m/z* (APCI) calcd for $C_{10}H_{15}$ $[M+H]^+$: 135.1168, found: 135.1165. Biphenyl **18** (6.2 mg, 0.04 mmol, 4%) was also recovered, NMR spectra details as above.

Quenching of phenyllithium 26 in water



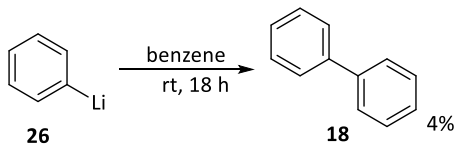
Phenyllithium **26** (1.9 M in dibutyl ether, 0.53 mL, 1.0 mmol) was added to an oven-dried round-bottom flask under argon. The flask was cooled to 0 °C with an ice bath and water (3 mL) was slowly added to the flask. The resulting mixture was stirred from 0 °C to room temperature for one hour, extracted with Et_2O (3 x 5 mL), combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification was made by column chromatography using hexane as eluent to afford biphenyl **18** (6.2 mg, 0.04 mmol, 4%). NMR spectra details as above.

Reactions of phenyllithium 26 in benzene at various temperatures

General reaction

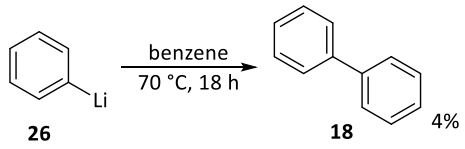
Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (3 mL) and phenyllithium **26** (1.9 M in dibutyl ether, 0.53 mL, 1.0 mmol). The tube was sealed, taken outside the glovebox and the mixture was stirred at the indicated temperature for 18 h. The mixture was quenched with water (3 mL), extracted with Et_2O (3 x 5 mL), combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification was made by column chromatography on silica using hexane as eluent to afford pure biphenyl **18**.

Reaction conducted at room temperature



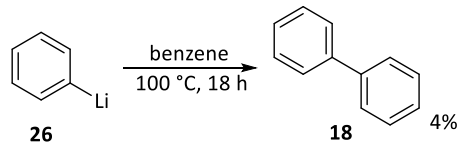
Reaction of phenyllithium **26** with benzene at room temperature afforded biphenyl **18** (6.2 mg, 0.04 mmol, 4%). NMR spectra details as above.

Reaction conducted at 70 °C



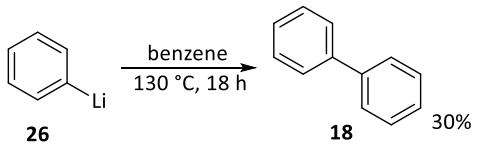
Reaction of phenyllithium **26** with benzene at 70 °C afforded biphenyl **18** (6.2 mg, 0.04 mmol, 4%). NMR spectra details as above.

Reaction conducted at 100 °C



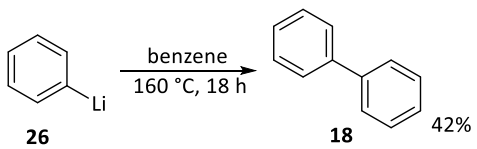
Reaction of phenyllithium **26** with benzene at 100 °C afforded biphenyl **18** (6.2 mg, 0.04 mmol, 4%). NMR spectra details as above.

Reaction conducted at 130 °C



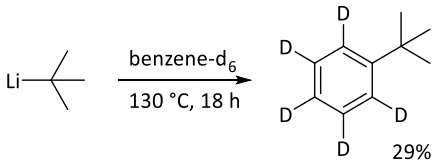
Reaction of phenyllithium **26** with benzene at 130 °C afforded biphenyl **18** (46.3 mg, 0.30 mmol, 30%). NMR spectra details as above.

Reaction conducted at 160 °C



Reaction of phenyllithium **26** with benzene at 160 °C afforded biphenyl **18** (64.8 mg, 0.42 mmol, 42%). NMR spectra details as above.

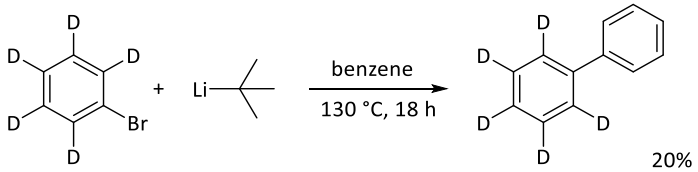
Reaction of ^{t}BuLi 25 in benzene-d_6



25 **686**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene-d_6 (3 mL) and ^{t}BuLi **25** (1.7 M in hexanes, 0.59 mL, 1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography using hexane as eluent to afford *tert*-butylbenzene-d_5[249] **686** as a colorless oil (40.9 mg, 0.29 mmol, 29%), δ_H (400 MHz, $CDCl_3$): 1.34 (9H, s, C(CH_3)$_3$). δ_D (61 MHz, $CHCl_3$): 7.20, 7.31, 7.40. δ_C (100 MHz, $CDCl_3$): 31.5, 34.8. 124.8 (t, *J* (^{13}C-D) = 10Hz), 125.2, (t, *J* (^{13}C-D) = 15 Hz), 125.7 (t, *J* (^{13}C-D) = 25 Hz), 141.4. IR (NEAT) ν (cm^{-1}) = 1238, 1364, 1465, 2275, 2867, 2924, 2960. *m*/*z* (EI) calcd for $C_{10}H_9D_5$ [M]: 139.1409, found: 139.1416.

Reaction of bromobenzene-d_5 687 with ^{t}BuLi 25 in benzene

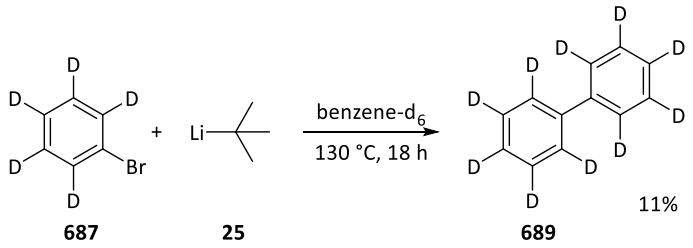


687 **25** **688**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (3 mL), bromobenzene-d_5 **687** (0.162 g, 1.0 mmol) and ^{t}BuLi **25** (1.7 M in

hexanes, 0.59 mL, 1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography using hexane as eluent to afford biphenyl-d_5 **688** as a white solid (31.8 mg, 0.20 mmol, 20%). M.Pt: 60-62 °C (lit. 63-66 °C).[250] δ_H (400 MHz, $CDCl_3$): 7.36-7.33 (1H, m, Ar*H*), 7.45-7.43 (2H, m, Ar*H*), 7.61-7.58 (2H, m, Ar*H*). δ_D (61 MHz, $CHCl_3$): 7.39, 7.49, 7.64. δ_C (100 MHz, $CDCl_3$): 127.3, 127.4, 128.9, 141.4, the signals of the carbons attached to a deuterium were hidden behind the signals of the carbons attached to a proton. IR (NEAT) ν (cm^{-1}) = 691, 736, 788, 834, 2272, 3036, 3058. *m/z* (ASAP) calcd for $C_{12}H_5D_5$ [M]: 159.1096, found: 159.1091.

Reaction of bromobenzene-d_5 687 with ^{t}BuLi 25 in benzene-d_6



687 **25** **689**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene-d_6 (3 mL), bromobenzene-d_5 **687** (0.162 g, 1.0 mmol) and ^{t}BuLi **25** (1.7 M in hexanes, 0.59 mL, 1.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was quenched with water (30 mL) and extracted with Et_2O (3 x 30 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography using hexane as eluent to afford biphenyl-d_{10} **689** as a white solid (18.1 mg, 0.11 mmol, 11%). M.Pt: 67-69 °C (lit. 69-70 °C).[251] δ_D (61 MHz, $CHCl_3$): 7.39, 7.49, 7.64. δ_C (100 MHz, $CDCl_3$): 126.9 (t, *J* (^{13}C-D) = 20 Hz), 127.2 (foreign signal that might arise from a

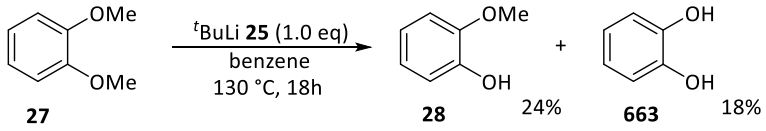
contamination with benzene-d_5), 128.4 (t, *J* (^{13}C-D) = 20 Hz), 141.2. IR (NEAT) ν (cm^{-1}) = 745, 810, 848, 983, 1322, 1342, 1567, 2272, 2290. *m/z* (ASAP) calcd for $C_{12}D_{10}$ [M]: 164.1410, found: 164.1412.

Alkyl aryl ethers deprotection by ^{t}BuLi 25

General deprotection procedure

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with benzene (5 mL), alkyl aryl ether (0.5 mmol) and ^{t}BuLi **25** (0.5 mmol or 1.0 mmol as specified). The pressure tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 130 °C for 18 h. After cooling to room temperature, the mixture was carefully quenched with water (30 mL). The aqueous layer was acidified to pH = 6-7 (controlled by pH paper) using sulfuric acid and extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purifications were made by column chromatography using EtOAc (10-20%) in hexane as eluent.

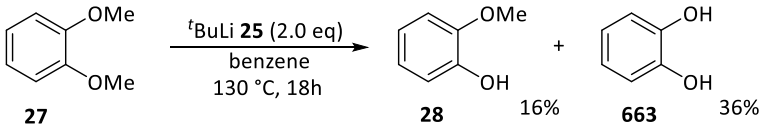
Substrate: 1,2-dimethoxybenzene 27 with 1.0 eq of ^{t}BuLi 27



Using deprotection procedure, 1,2-dimethoxybenzene **27** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford 2-methoxyphenol **28** as a colourless solid (14.9 mg, 0.12 mmol, 24%), M.Pt: 29-30 °C (lit. 28-29 °C),[252] δ_H (400 MHz, $CDCl_3$): 3.89 (3H, s, OC*H*$_3$), 5.61 (1H, s, OH), 6.95-6.85 (4H, m, Ar*H*), δ_C (100 MHz, $CDCl_3$): 56.0, 110.9, 114.7, 120.3, 121.6, 145.8, 146.7, IR (NEAT) ν (cm^{-1}) = 736, 829,

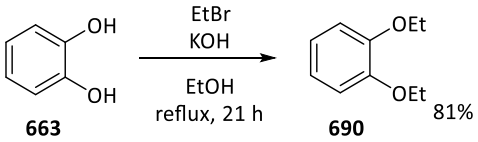
1037, 1232, 1511, 3391. *m/z* (ASAP) calcd for $C_7H_8O_2$ [M]: 124.0524, found: 124.0517, and catechol **663** as a colourless solid (9.9 mg, 0.09 mmol, 18%), M.Pt.: 100-102 °C (lit. 104 °C),[253] δ_H (400 MHz, $CDCl_3$): 5.40 (2H, bs, OH), 6.83-6.79 (2H, m, Ar*H*), 6.89-6.85 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 115.7, 121.5, 143.5, IR (NEAT) ν (cm^{-1}) = 742, 1043, 1097, 1186, 1240, 1362, 1470, 1515, 1619, 3318, 3445, *m/z* (EI) $C_6H_6O_2$ [M]: 110.0.

Substrate: 1,2-dimethoxybenzene 27 with 2.0 eq of ^{t}BuLi 25



Using deprotection procedure, 1,2-dimethoxybenzene **27** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford 2-methoxyphenol **28** (9.9 mg, 0.08 mmol, 16%) and catechol **663** (19.8 mg, 0.18 mmol, 36%). NMR spectra details as above.

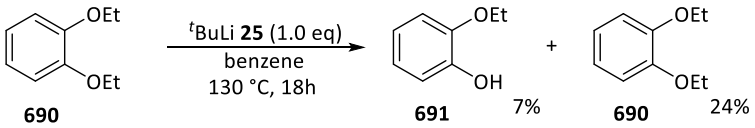
Synthesis of 1,2-diethoxybenzene 690



To a 100 mL 3-necked flask were added ethanol (40 mL) and catechol **663** (2.0 g, 18.2 mmol). The flask was equipped with a condenser and placed under argon. Potassium hydroxide (2.24 g, 39.9 mmol) and bromoethane (3.97 g, 36.4 mmol) were added to the mixture which was then stirred at reflux for 5 h. Further potassium hydroxide (1.02 g, 18.2 mmol) and bromoethane (1.99 g, 18.2 mmol) were added to the mixture which was stirred for another 16 h at reflux. The solvent was evaporated using a Büchi rotary evaporator and water (40 mL) was added to the mixture. The resulting water phase was extracted with DCM (3 x 40 mL). The combined organic extracts were dried

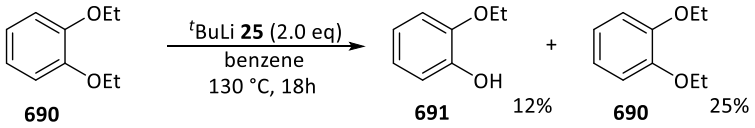
over Na_2SO_4, filtered and concentrated to afford the crude product which was purified by column chromatography on silica using EtOAc (5%) in hexane as eluent to afford 1,2-diethoxybenzene[254] **690** as a colourless oil (2.45 g, 14.74 mmol, 81%). δ_H (400 MHz, $CDCl_3$): 1.45 (6H, t, *J* = 6.8 Hz, C*H*$_3$), 4.09 (4H, q, *J* = 7.2 Hz, C*H*$_2$), 6.89 (4H, s, Ar*H*). δ_C (100 MHz, $CDCl_3$): 15.0, 64.6, 113.8, 121.1, 149.0. IR (NEAT) ν (cm^{-1}) = 735, 927, 1041, 1126, 1217, 1246, 1392, 1452, 1475, 1500, 1591, 2978. *m/z* (NSI) calcd for $C_{10}H_{15}O_2$ $[M+H]^+$: 167.1067, found: 167.1067.

Substrate: 1,2-diethoxybenzene 690 with 1.0 eq of ^{t}BuLi 25



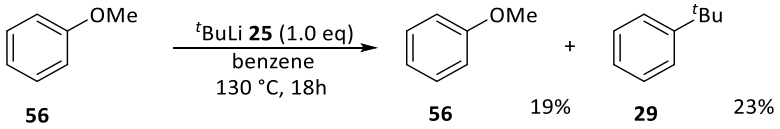
Using deprotection procedure, 1,2-diethoxybenzene **690** (83.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford 2-ethoxyphenol **691** as a colourless solid (4.8 mg, 0.04 mmol, 7%). M.Pt. 24-26 °C (lit. 20-22 °C).[255] δ_H (400 MHz, $CDCl_3$): 1.45 (3H, t, *J* = 6.8 Hz, C*H*$_3$), 4.11 (2H, q, *J* = 6.8 Hz, C*H*$_2$), 6.80-6.95 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 15.1, 64.6, 111.8, 114.6, 120.2, 121.5, 145.9, 146.0. IR (NEAT) ν = 742, 927, 1041, 1119, 1221, 1258, 1502, 2926, 3532. *m/z* (EI) $C_8H_{10}O_2$ [M]: 138.1. Remaining starting material **690** was also isolated (19.9 mg, 0.12 mmol, 24%).

Substrate: 1,2-diethoxybenzene 690 with 2.0 eq of ^{t}BuLi 25



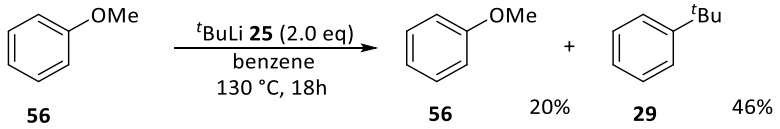
Using deprotection procedure, 1,2-diethoxybenzene **690** (83.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford 2-ethoxyphenol **691** (8.3 mg, 0.06 mmol, 12%) and remaining starting material **690** (20.8 mg, 0.13 mmol, 25%). NMR spectra details as above.

Substrate: anisole 56 with 1.0 eq of ^{t}BuLi 25



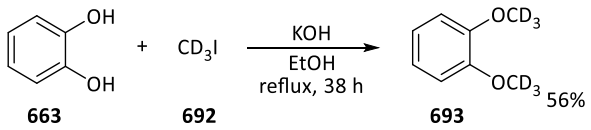
Using deprotection procedure, anisole **56** (54.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford remaining starting material **56** (10.3 mg, 0.095 mmol, 19%) and *tert*-butylbenzene **29** (15.4 mg, 0.12 mmol, 23%). NMR spectra details as above.

Substrate: anisole 56 with 2.0 eq of ^{t}BuLi 25



Using deprotection procedure, anisole **56** (54.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford remaining starting material **56** (10.8 mg, 0.10 mmol, 20%) and *tert*-butylbenzene **29** (61.7 mg, 0.46 mmol, 46%). NMR spectra details as above.

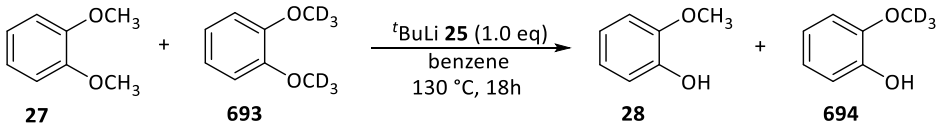
Synthesis of 1,2-dimethoxybenzene-d_6 693



To a 100 mL 3-necked flask were added ethanol (25 mL) and catechol **663** (1.0 g, 9.1 mmol). The flask was equipped with a condenser and placed under argon. Potassium hydroxide (1.12 g, 20.0 mmol) and iodomethane-d_3 **692** (2.90 g, 20.0 mmol) were added to the mixture which was then stirred at reflux for 17 h. Further potassium hydroxide (1.12 g, 20.0 mmol) and iodomethane-d_3 **692** (2.90 g, 20.0 mmol) were added to the mixture which was stirred for another 17 h. After another addition of

potassium hydroxide (0.56 g, 10.0 mmol) and iodomethane-d_3 **692** (1.45 g, 10.0 mmol), the mixture was stirred for an additional 4 h. The resulting mixture was concentrated on a Büchi rotary evaporator, water (30 mL) was added and the mixture was extracted with DCM (3 x 30 mL), combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford 1,2-dimethoxybenzene-d_6[256] **693** as a pale-yellow oil (0.57 g, 5.1 mmol, 56%). δ_H (400 MHz, $CDCl_3$): 6.94-6.87 (4H, m, Ar*H*). δ_D (61 MHz, $CHCl_3$): 3.85, δ_C (100 MHz, $CDCl_3$): 55.1 (t, *J* (^{13}C-D) = 10 Hz), 111.4, 120.9, 149.1. IR (NEAT) ν (cm^{-1}) = 723, 737, 956, 995, 1051, 1108, 1128, 1236, 1259, 1452, 1502, 1589, 2069. *m/z* (APCI) calcd for $C_8H_4D_6O_2$ [M]: 144.1057, found: 144.1063.

Substrates: 1:1 mixture of 1,2-dimethoxybenzene 27 and 1,2-dimethoxybenzene-d_6 693 with 1.0 eq of ^{t}BuLi 25

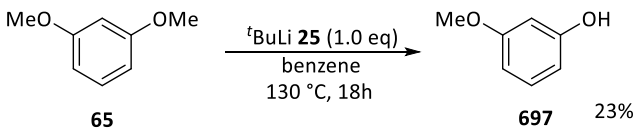


27 **693** **28** **694**

1:0.5 ratio

Using deprotection procedure, a mixture of 1,2-dimethoxybenzene **27** (69.1 mg, 0.5 mmol) and 1,2-dimethoxybenzene-d_6 **694** (72.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene. For this reaction, the reaction mixture was extracted with Et_2O before acidification. Extraction of the acidified water phase led to recovery of a mixture of 2-methoxyphenol **28** and 2-methoxyphenol-d_3[257] **694** with a 1:0.5 ratio. δ_H (400 MHz, $CDCl_3$): 3.89 (3H, s, OC*H*$_3$), 5.61 (1.5H, bs, OH), 6.85-6.94 (6H, m, Ar*H*). δ_D (61 MHz, $CHCl_3$): 3.86. δ_C (100 MHz, $CDCl_3$): 56.0, 110.9, 114.7, 120.3, 121.6, 145.8, 146.7. *m/z* (EI) $C_7H_8O_2$ **27** [M]: 124.2, *m/z* (EI) $C_7H_5D_3O_2$ **694** [M]: 127.2.

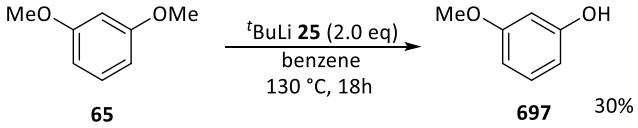
Substrate: 1,3-dimethoxybenzene 65 with 1.0 eq of ^{t}BuLi 25



65 **697** 23%

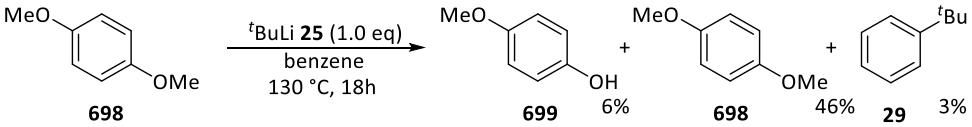
Using deprotection procedure, 1,3-dimethoxybenzene **65** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford 3-methoxyphenol[258] **697** as a colourless oil (14.3 mg, 0.12 mmol, 23%). δ_H (400 MHz, $CDCl_3$): 3.78 (3H, s, OCH_3), 6.44-6.40 (2H, m, Ar*H*), 6.51-6.48 (1H, m, Ar*H*), 7.15-7.11 (1H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 55.4, 101.7, 106.6, 107.9, 130.3, 156.9, 161.1. IR (NEAT) ν (cm^{-1}) = 686, 764, 843, 944, 1039, 1145, 1284, 1455, 1493, 1595, 3365. *m/z* (EI) $C_7H_8O_2$ [M]: 124.0.

Substrate: 1,3-dimethoxybenzene 65 with 2.0 eq of ^{t}BuLi 25



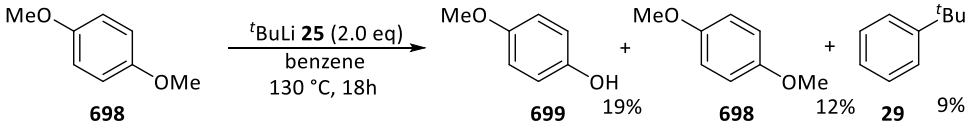
Using deprotection procedure, 1,3-dimethoxybenzene **65** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford 3-methoxyphenol **697** (18.6 mg, 0.15 mmol, 30%). NMR spectra details as above.

Substrate: 1,4-dimethoxybenzene 698 with 1.0 eq of ^{t}BuLi 25



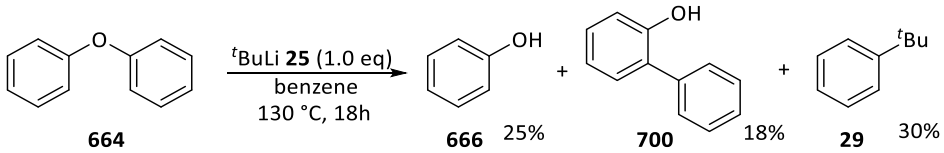
Using deprotection procedure, 1,4-dimethoxybenzene **698** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford 4-methoxyphenol **699** as a colourless solid (3.7 mg, 0.03 mmol, 6%). M.Pt. 56-58 °C (lit. 57-58 °C).[259] δ_H (400 MHz, $CDCl_3$): 3.76 (3H, s, OCH_3), 4.51 (1H, bs, O*H*), 6.81-6.75 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 56.0, 115.0, 116.2, 149.6, 153.9. IR (NEAT) ν (cm^{-1}) = 736, 827, 1041, 1236, 1455, 1509, 3398. *m/z* (EI) calcd for $C_7H_8O_2$ [M]: 124.0524, found: 124.0524. Remaining starting material **698** (31.8 mg, 0.23 mmol, 46%) and *tert*-butylbenzene **29** (2.0 mg, 0.015 mmol, 3%) were also recovered. NMR spectra details as above.

Substrate: 1,4-dimethoxybenzene 698 with 2.0 eq of ^{t}BuLi 25



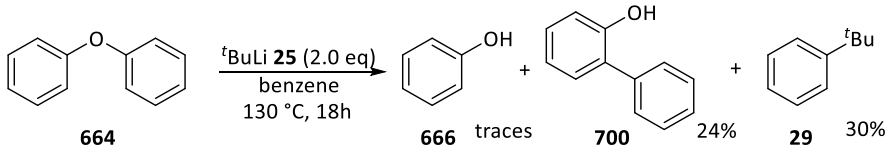
Using deprotection procedure, 1,4-dimethoxybenzene **698** (69.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford 4-methoxyphenol **699** (11.8 mg, 0.095 mmol, 19%), remaining starting material **698** (8.3 mg, 0.06 mmol, 12%) and *tert*-butylbenzene **29** (12.1 mg, 0.09 mmol, 9%). NMR spectra details as above.

Substrate: diphenyl ether 664 with 1.0 eq of ^{t}BuLi 25



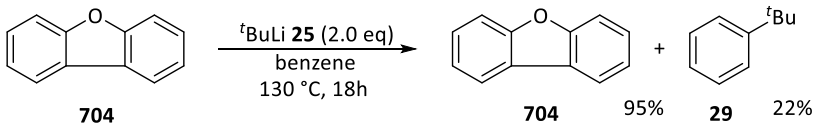
Using deprotection procedure, diphenyl ether **664** (85.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford: i) phenol **666** as a colourless solid (11.8 mg, 0.125 mmol, 25%), M.Pt. 38-40 °C (lit. 38.5-41.5 °C),[260] δ_H (400 MHz, $CDCl_3$): 4.72 (1H, s, O*H*), 6.85-6.81 (2H, m, Ar*H*), 6.95-6.92 (1H, m, Ar*H*), 7.25-7.23 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 115.4, 121.0, 129.8, 155.5., IR (NEAT) ν (cm^{-1}) = 691, 751, 1223, 1472, 1595, 3229, *m/z* (EI) C_6H_6O [M]: 94.0; ii) 2-phenylphenol **700** as a colourless solid (15.3 mg, 0.09 mmol, 18%), M.Pt.: 54-56 °C (lit. 56-57 °C),[261] δ_H (400 MHz, $CDCl_3$): 5.20 (1H, s, O*H*), 7.02-6.98 (2H, m, Ar*H*), 7.30-7.24 (2H, m, Ar*H*), 7.43-7.39 (1H, m, Ar*H*), 7.52-7.47 (4H, m, Ar*H*), δ_C (100 MHz, $CDCl_3$): 116.0, 121.0, 128.0, 128.2, 129.2, 129.3, 129.4, 130.4, 137.2, 152.6. IR (NEAT) ν (cm^{-1}) = 701, 753, 1178, 1435, 1480, 3532, *m/z* (EI) $C_{12}H_{10}O$ [M]: 170.1; iii) *tert*-butylbenzene **29** (20.1 mg, 0.15 mmol, 30%). NMR spectra details as above.

Substrate: diphenyl ether 664 with 2.0 eq of ^{t}BuLi 25



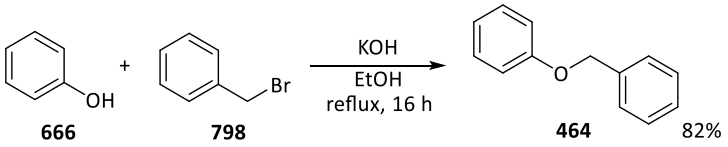
Using deprotection procedure, diphenyl ether **664** (85.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford 2-phenylphenol **700** (20.4 mg, 0.12 mmol, 24%) and *tert*-butylbenzene **29** (40.3 mg, 0.3 mmol, 30%). A trace amount of phenol **666** was observed in the ^{1}H NMR spectrum of the crude product. NMR spectra details as above.

Substrate: dibenzofuran 704 with 2.0 eq of ^{t}BuLi 25



Using deprotection procedure, dibenzofuran **704** (84.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (1.0 mmol) in benzene to afford *tert*-butylbenzene **29** (14.8 mg, 0.11 mmol, 22%) and remaining starting material (79.9 mg, 0.48 mmol, 95%). NMR spectra details as above.

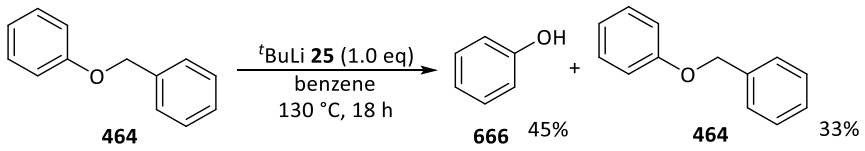
Synthesis of (benzyloxy)benzene 464



To a 100 mL 2-necked flask were added phenol **666** (2.0 g, 21.3 mmol) and EtOH (30 mL). A condenser was attached to the flask which was put under argon. Potassium hydroxide (1.20 g, 21.4 mmol) and benzyl bromide **798** (2.53 mL, 21.3 mmol) were added to the mixture which was then stirred at reflux for 3 h. Further potassium

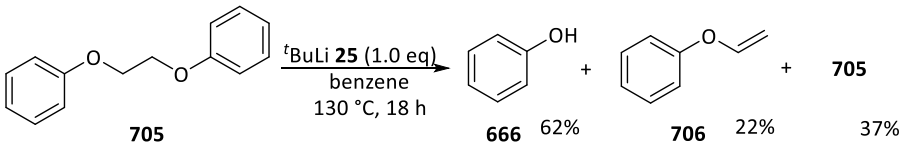
hydroxide (1.20 g, 21.4 mmol) and benzyl bromide **798** (2.53 mL, 21.3 mmol) were added to the mixture at reflux. After stirring for another 16 h at reflux, the mixture was cooled to room temperature, concentrated on a Büchi rotary evaporator and water (40 mL) was added to the crude mixture. The water phase was extracted with DCM (3 x 40 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography on silica using Et_2O (2.5%) in hexane to afford benzyl phenyl ether **464** as a white solid (3.23 g, 17.5 mmol, 82%). M. Pt. 36-37 °C (lit. 37-38 °C).[262] δ_H (400 MHz, $CDCl_3$): 5.08 (2H, s, C*H*$_2$), 6.99-6.96 (3H, m, Ar*H*), 7.46-7.28 (7H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 70.1, 115.0, 121.1, 127.6, 128.1, 128.7, 129.6, 137.2, 158.9. IR (NEAT) ν (cm^{-1}) = 739, 1010, 1236, 1375, 1454, 1492, 1583, 1597. *m/z* (EI) calcd for $C_{13}H_{12}O$ [M]: 184.0888, found: 184.0890.

Substrate: (benzyloxy)benzene 464 with 1.0 eq of ^{t}BuLi 25



Using deprotection procedure, (benzyloxy)benzene **464** (92.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene to afford phenol **666** (21.2 mg, 0.23 mmol, 45%) and remaining starting material **464** (30.4 mg, 0.17 mmol, 33%). NMR spectra details as above.

Substrate: 1,2-diphenoxyethane 705 with 1.0 eq of ^{t}BuLi 25

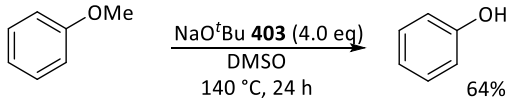


Using deprotection procedure, 1,2-diphenoxyethane **705** (107.1 mg, 0.5 mmol) was treated with ^{t}BuLi **25** (0.5 mmol) in benzene. For this reaction, the water phase was

extracted with Et_2O before acidification, and after, to isolate phenol **25** from the other products. Purification of the first crude (resulting from extraction before acidification) was made by column chromatography using hexane (100%) until (vinyloxy)benzene **706** was eluted then, with EtOAc (15%) in hexane. The reaction afforded phenol **666** (29.0 mg, 0.31 mmol, 62%) and (vinyloxy)benzene[263] **706** (13.2 mg, 0.11 mmol, 22%) as a colourless oil. δ_H (400 MHz, $CDCl_3$): 4.43 (1H, dd, *J* = 6.0, 1.6 Hz, C=C*H*), 4.76 (1H, dd, *J* = 14.0, 1.6 Hz, C=C*H*), 6.70 (1H, dd, *J* = 13.6, 6.0 Hz, C=C*H*), 7.02-6.98 (2H, m, Ar*H*), 7.10-7.07 (1H, m, Ar*H*), 7.35-7.30 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 95.2, 117.3, 123.3, 129.8, 148.4, 157.0. IR (NEAT) ν (cm^{-1}) = 800, 1028, 1262, 1561, 1654, 2024, 2911, *m*/*z* (EI) C_8H_8O [M]: 120.0. Remaining starting material **705** was also recovered (39.6 mg, 0.19 mmol, 37%).

Reproduction of Teck-Peng-Loh's reactions

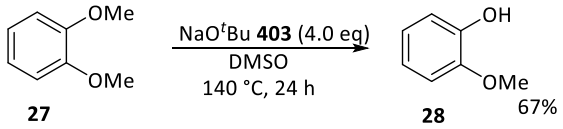
Substrate: anisole 56 with 4.0 eq of NaO^{t}Bu 403



56 **666**

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with DMSO (5 mL), anisole **56** (54.1 mg, 0.5 mmol) and NaO^{t}Bu **403** (0.192 g, 2.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 140 °C for 24 h. After cooling to room temperature, the mixture was diluted in water (20 mL), acidified to pH 5-6 with hydrochloric acid (2 M) and extracted with DCM (3 x 20 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification by column chromatography on silica using EtOAc (10%) in hexane as eluent afforded phenol **666** (30.1 mg, 0.32 mmol, 64%). NMR spectra details as above.

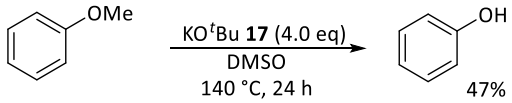
Substrate: 1,2-dimethoxybenzene 27 with 4.0 eq of NaO^{t}Bu 403



27 **28**

1,2-Dimethoxybenzene **27** (69.1 mg, 0.5 mmol) was used with the same procedure described above for the reaction of anisole **56**. The reaction afforded 2-methoxyphenol **28** (41.6 mg, 0.34 mmol, 67%). NMR spectra details as above.

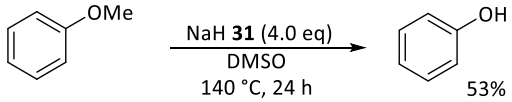
Substrate: anisole 56 with 4.0 eq of KO^{t}Bu 17



56 **666**

Anisole **56** (54.1 mg, 0.5 mmol) was used with the same procedure described above using KO^{t}Bu **17** (224.4 mg, 2.0 mmol). The reaction afforded phenol **666** (22.1 mg, 0.24 mmol, 47%). NMR spectra details as above.

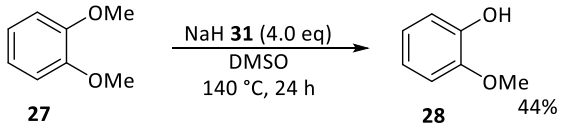
Substrate: anisole 56 with 4.0 eq of NaH 31



56 **666**

Anisole **56** (54.1 mg, 0.5 mmol) was used with the same procedure described above using NaH **31** (60% in oil, 80.0 mg, 2.0 mmol). The reaction afforded phenol **666** (25.4 mg, 0.27 mmol, 47%). NMR spectra details as above.

Substrate: 1,2-dimethoxybenzene 27 with 4.0 eq of NaH 31

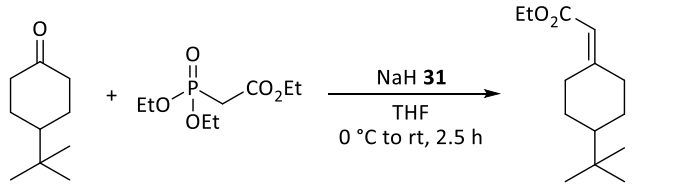


27 **28**

1,2-Dimethoxybenzene **27** (69.1 mg, 0.5 mmol) was used with the same procedure described above using NaH **31** (60% in oil, 80.0 mg, 2.0 mmol). The reaction afforded 2-methoxyphenol **28** (27.3 mg, 0.22 mmol, 44%). NMR spectra details as above.

Multi-step synthesis of 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane 707 from 4-(*tert*-butyl)cyclohexan-1-one 710

Synthesis of ethyl 2-(4-(*tert*-butyl)cyclohexylidene)acetate 712

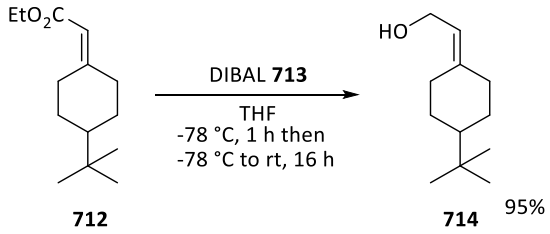


710 **711** **712**

Sodium hydride **31** (60% in oil, 1.04 g, 26.0 mmol) was added to a 100 mL three-necked round-bottomed flask under argon and was washed with dry hexane (3 x 20 mL). Dry THF (20 mL) was added to the washed sodium hydride **31** and the mixture was cooled to 0 °C. Ethyl 2-(diethoxyphosphoryl)acetate **711** (5.66 mL, 28.5 mmol) was slowly added to the mixture. After stirring for 5 min at 0 °C, a solution of 4-(*tert*-butyl)cyclohexan-1-one **710** (4.01 g, 26.0 mmol) in dry THF (20 mL) was added to the mixture at 0 °C. The resulting mixture was stirred from 0 °C to room temperature for 2.5 h. Water (40 mL) was added to the mixture which was then extracted with Et_2O (3 x 40 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica using Et_2O (10%) in hexane as eluent to afford ethyl 2-(4-(*tert*-

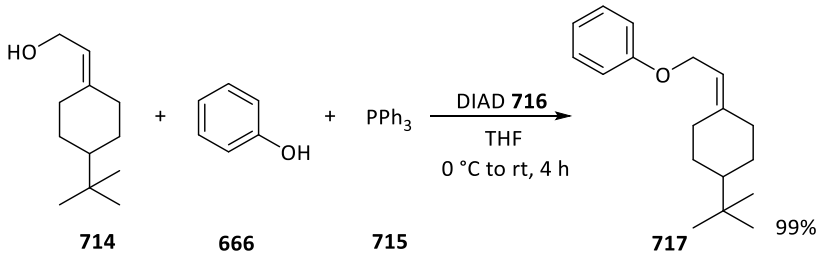
butyl)cyclohexylidene)acetate[264] **712** as a colourless oil (5.37 g, 23.92 mmol, 92%). δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, C(C*H*$_3$)$_3$), 1.26-1.11 (3H, m, C*H*), 1.27 (3H, t, *J* = 7.2 Hz, C*H*$_3$), 1.87-1.79 (1H, m, C*H*), 1.96-1.91 (2H, m, C*H*), 2.19-2.12 (1H, m, C*H*), 2.32-2.28 (1H, m, C*H*), 3.89-3.84 (1H, m, C*H*), 4.13 (2H, q, *J* = 7.2 Hz, C*H*$_2$), 5.60 (1H, s, C=C*H*). δ_C (100 MHz, $CDCl_3$): 14.5, 27.7, 28.6, 29.4, 29.7, 32.6, 38.0, 48.0, 59.6, 112.9, 163.7, 167.0. IR (NEAT) ν (cm^{-1}) = 860, 1037, 1150, 1163, 1182, 1246, 1647, 1712, 2943. *m/z* (NSI) calcd for $C_{14}H_{25}O_2$ $[M+H]^+$: 225.1849, found: 225.1849.

Synthesis of 2-(4-(*tert*-butyl)cyclohexylidene)ethan-1-ol 714



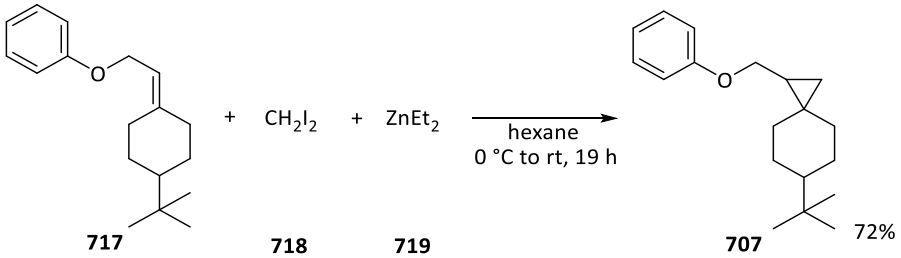
To a stirred solution of ethyl 2-(4-(*tert*-butyl)cyclohexylidene)acetate **712** (5.35 g, 23.8 mmol) in dry THF (80 mL) under argon at -78 °C, was added DIBAL **713** (1 M in toluene, 52.5 mL, 52.5 mmol). The resulting mixture was stirred at -78 °C for 1 h and then from -78 °C to room temperature for 16 h. The mixture was quenched with water (70 mL) and acidified with hydrochloric acid (2.0 M) to pH 6-7. The white salt form was filtered and the filtrate was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford 2-(4-(*tert*-butyl)cyclohexylidene)ethan-1-ol[264] **714** as a pale yellow oil (4.12 g, 22.61 mmol, 95%). δ_H (400 MHz, $CDCl_3$): 0.85 (9H, s, C(C*H*$_3$)$_3$), 1.22-0.97 (4H, m, C*H* + O*H*), 1.78-1.71 (1H, m, C*H*), 1.91-1.84 (2H, m, C*H*), 2.07-2.02 (1H, m, C*H*), 2.27-2.22 (1H, m, C*H*), 2.71-2.66 (1H, m, C*H*), 4.13 (2H, d, *J* = 7.2 Hz, C*H*$_2$), 5.37 (1H, tt, *J* = 7.6, 2.0 Hz, C=C*H*). δ_C (100 MHz, $CDCl_3$): 27.7, 28.7, 28.8, 29.2, 32.6, 37.1, 48.4, 58.8, 120.1, 144.7. IR (NEAT) ν (cm^{-1}) = 995, 1006, 1363, 2939, 3292. *m/z* (APCI) calcd for $C_{12}H_{21}O_1$ $[M-H]^+$: 181.1587, found: 181.1587.

Synthesis of (2-(4-(*tert*-butyl)cyclohexylidene)ethoxy)benzene 717

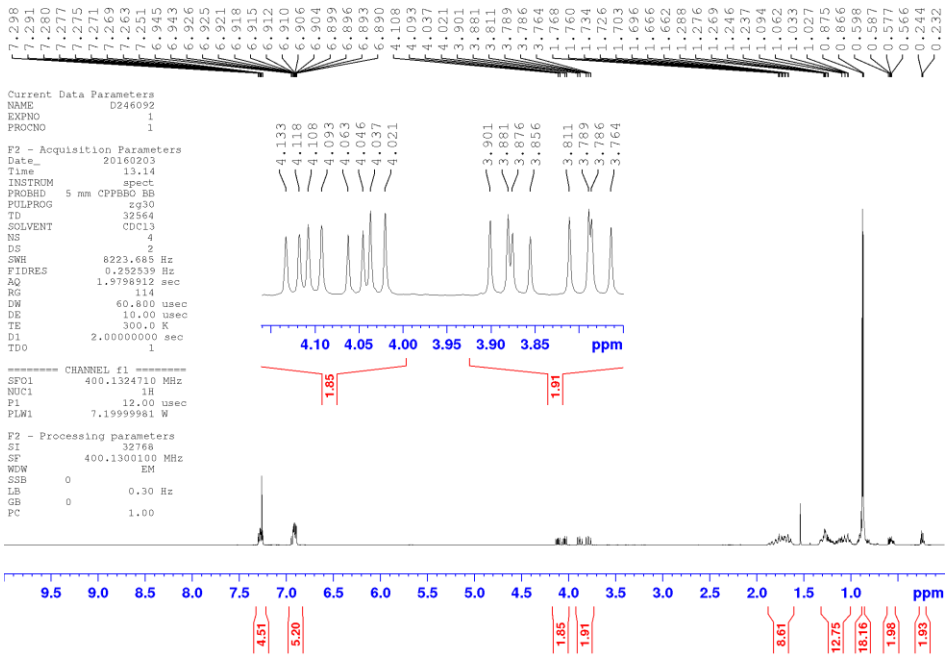


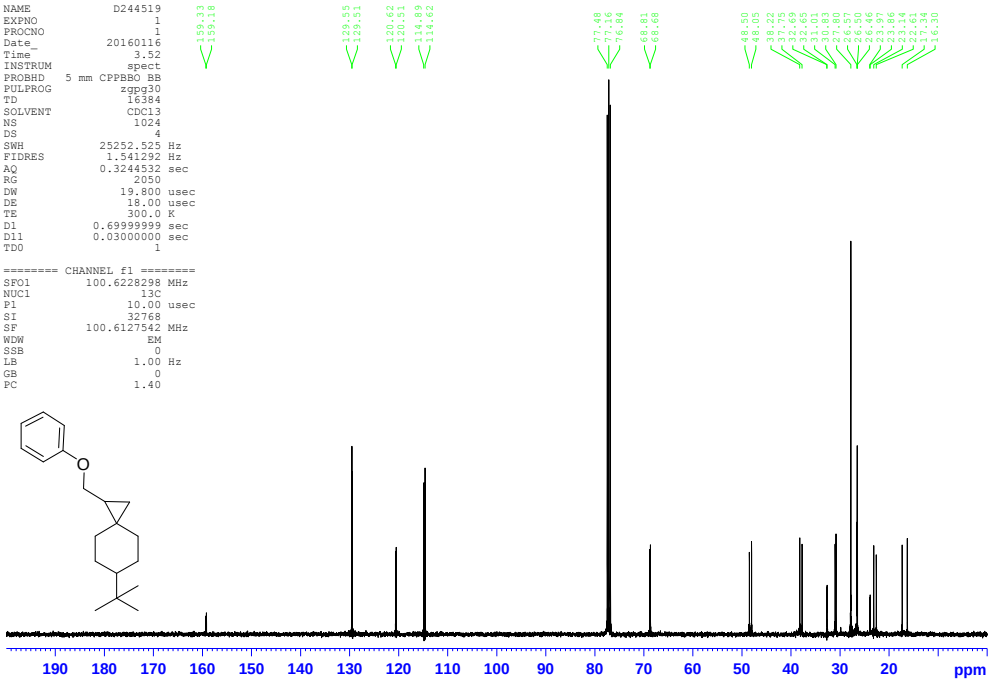
To a 250 mL round-bottomed flask were added phenol **666** (688.0 mg, 7.31 mmol) and triphenylphosphine **715** (2.3 g, 8.77 mmol). The flask was put under argon atmosphere and dry THF (50 mL) was added followed by a solution of 2-(4-(*tert*-butyl)cyclohexylidene)ethan-1-ol **714** (2.0 g, 10.97 mmol) in dry THF (50 mL). The mixture was cooled to 0 °C and DIAD **716** (2.3 mL, 2.36 g, 11.68 mmol) was slowly added. The resulting yellow mixture was stirred from 0 °C to room temperature for 4 h. The solvent was evaporated at Büchi rotary evaporator and the resulting yellow oil was purified by column chromatography on silica using EtOAc (3%) in hexane as eluent to afford (2-(4-(*tert*-butyl)cyclohexylidene)ethoxy)benzene[265] **717** as a pale yellow oil (compound not yet reported in the literature) (1.88 g, 7.28 mmol, 99%). δ_H (400 MHz, $CDCl_3$): 0.86 (9H, s, C(C*H*$_3$)$_3$), 1.24-1.02 (3H, m, C*H*), 1.91-1.81 (3H, m, C*H*), 2.12-2.08 (1H, m, C*H*), 2.34-2.30 (1H, m, C*H*), 2.74-2.69 (1H, m, C*H*), 4.53 (2H, d, *J* = 6.8 Hz, C*H*$_2$), 5.43 (1H, t, *J* = 6.8 Hz, C=C*H*), 6.95-6.90 (3H, m, Ar*H*), 7.30-7.26 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 27.8, 28.5, 29.1, 29.2, 32.6, 37.1, 40.4, 64.2, 114.9, 116.2, 120.7, 129.5, 145.9, 159.0. IR (NEAT) ν (cm^{-1}) = 688, 755, 987, 1006, 1028, 1236, 1492, 1598, 2941. *m*/*z* (EI) $C_{18}H_{26}O$ [M]: 258.2.

Synthesis of 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane 707



To a 100 mL round-bottomed flask, containing (2-(4-(*tert*-butyl)cyclohexylidene)-ethoxy)benzene **717** (1.88 g, 7.28 mmol) in dry hexane (25 mL) at 0 °C under argon, was added diethyl zinc **719** (1 M in hexane, 17.5 mL, 17.5 mmol). The resulting mixture was stirred at 0 °C for 5 min and diiodomethane **718** (1.4 mL, 4.66 g, 17.4 mmol) was added. The resulting mixture was stirred from 0 °C to room temperature for 19 h, quenched with water (40 mL), extracted with hexane (3 x 40 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford a mixture of diasteroisomers of 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane **707** as a colourless oil (compounds not yet reported in the literature, the NMR spectra have been added for information only) (1.42 g, 5.21 mmol, 72%). δ_H (400 MHz, $CDCl_3$): 0.23 (2H, m, CH_2), 0.57 (2H, m, CH_2), 0.87 (18H, s, C(CH_3)$_3$), 1.03-1.32 (12H, m, C*H*), 1.66-1.86 (8H, m, C*H*), 3.76-3.90 (2H, m, CH_2), 4.02-4.14 (2H, m, CH_2), 6.91 (6H, m, Ar*H*), 7.28 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 16.3, 17.3, 22.6, 23.1, 23.9, 24.0, 26.4, 26.5, 26.6, 27.8, 30.8, 31.0, 32.6, 32.7, 37.8, 38.2, 48.1, 48.5, 68.7, 68.8, 114.6, 114.9, 120.5, 120.6, 129.5, 129.6, 159.2, 159.3. IR (NEAT) ν (cm^{-1}) = 690, 754, 1010, 1031, 1240, 1363, 1494, 1598, 2937. *m/z* (APCI) calcd for $C_{19}H_{29}O$ $[M+H]^+$: 273.2213, found: 273.2216.



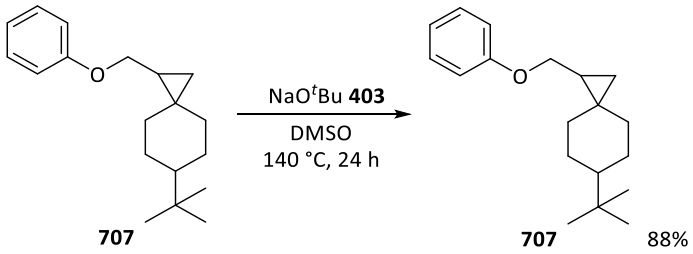


Test of Teck Peng Loh's conditions with 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane 707

General reaction conditions

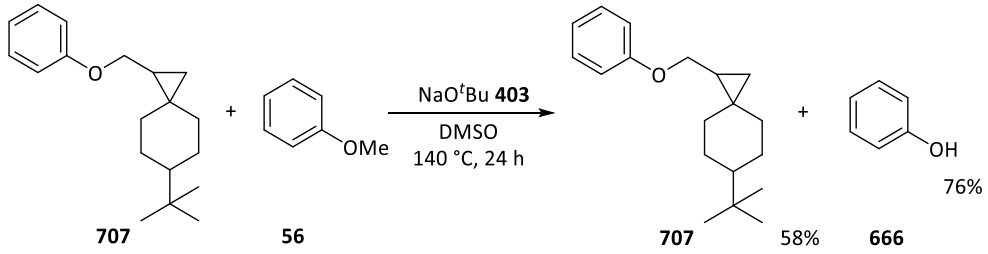
Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with DMSO (5 mL), substrate (0.5 mmol) and NaO^{t}Bu **403** (0.192 g, 2.0 mmol). The tube was sealed, taken outside the glovebox and placed in a stirred oil bath at 140 °C for 24 h. After cooling to room temperature, the mixture was diluted in water (20 mL), acidified to pH 5-6 with hydrochloric acid (2 M) and extracted with DCM (3 x 20 mL). Combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Yields of the reaction products were quantified by use of 1,3,5-trimethoxybenzene as an internal standard.

Substrate: 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane 707



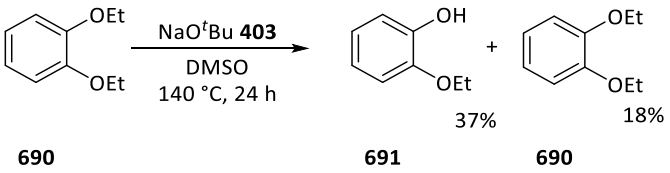
6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane **707** (136.2 mg, 0.5 mmol) was treated with NaO^{t}Bu **403** (2.0 mmol) in DMSO to afford unreacted starting material **707** (119.9 mg, 0.44 mmol). No formation of phenol **666** was observed.

Substrates: 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane 707 and anisole 56



6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane **707** (136.2 mg, 0.5 mmol) and anisole **56** (54.1 mg, 0.5 mmol) were treated with NaO^{t}Bu **403** (2.0 mmol) in DMSO to afford phenol **666** (35.8 mg, 0.38 mmol, 76%) and unreacted 6-(*tert*-butyl)-1-(phenoxymethyl)spiro[2.5]octane **707** (79.0 mg, 0.29 mmol, 58%). No other species derived from **707** was seen.

Substrate: 1,2-diethyoxybenzene 690



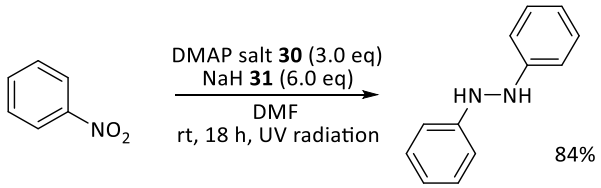
1,2-Diethoxybenzene **690** (83.1 mg, 0.5 mmol) was treated with NaO^{t}Bu **403** (2.0 mmol) in DMSO to afford 2-ethoxyphenol **691** (25.6 mg, 0.19 mmol, 37%) and unreacted starting material **690** (15.0 mg, 0.09 mmol, 18%).

6.3 Experimental details of Chapter 4

General reduction procedure

Inside a glovebox under nitrogen atmosphere, a pressure tube was loaded with DMAP salt **30** (specified amount), dry DMF (5 mL), NaH **31** (specified amount) and reduction substrate (0.33 mmol). The tube was sealed, taken outside the glovebox and the mixture was stirred for 18 h at room temperature under UV light OR at 130 °C without UV light, as indicated. The mixture was quenched at room temperature with water (30 mL), extracted with Et_2O (2 x 25 mL), combined organic extracts were washed with water (3 x 25 mL), dried over Na_2SO_4, filtered and concentrated. Crude products were purified by column chromatography on silica using EtOAc (5%) in hexane, for isolation of azobenzene **36** and azoxybenzene **731**, and EtOAc (20%) in hexane for isolation of hydrazine **37**.

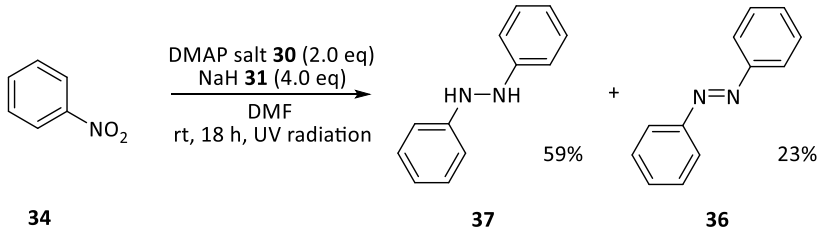
Substrate: nitrobenzene 34 with 3.0 eq of DMAP salt 30



34 **37**

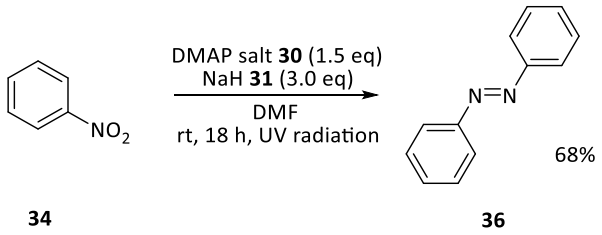
Nitrobenzene **34** (41 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-diphenylhydrazine **37** as a white solid (25.8 mg, 0.14 mmol, 84%). M.Pt. 123-125 °C (lit. 124-125 °C).[266] δ_H (400 MHz, $CDCl_3$): 5.62 (2H, bs, N*H*), 6.87-6.82 (6H, m, Ar*H*), 7.24-7.19 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 112.5, 120.1, 129.5, 149.0. IR (NEAT) ν (cm^{-1}) = 689, 775, 927, 1072, 1454, 1483. *m/z* (NSI) calcd for $C_{12}H_{13}N_2$ $[M+H]^+$: 185.1073, found: 185.1073.

Substrate: nitrobenzene 34 with 2.0 eq of DMAP salt 30



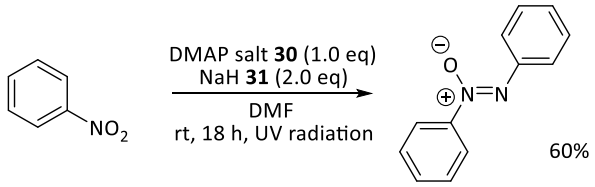
Nitrobenzene **34** (41 mg, 0.33 mmol) was treated with DMAP salt **30** (356.6 mg, 0.66 mmol) and sodium hydride **31** (31.7 mg, 1.32 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-diphenylhydrazine **37** (17.9 mg, 0.10 mmol, 59%), NMR spectra details as above, and azobenzene **36** as an orange solid (6.9 mg, 0.04 mmol, 23%). M. Pt. 65-66 °C (lit. 65-66 °C).[267] δ_H (400 MHz, $CDCl_3$): 7.55-7.46 (6H, m, Ar*H*), 7.94-7.90 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 123.0, 129.2, 131.1, 152.8. IR (NEAT) ν (cm^{-1}) = 688, 775, 927, 1072, 1454, 1483. *m/z* (EI) $C_{12}H_{10}N_2$ [M]: 182.1.

Substrate: nitrobenzene 34 with 1.5 eq of DMAP salt 30



Nitrobenzene **34** (41 mg, 0.33 mmol) was treated with DMAP salt **30** (267.4 mg, 0.50 mmol) and sodium hydride **31** (23.8 mg, 0.99 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford azobenzene **36** (20.4 mg, 0.11 mmol, 68%). NMR spectra details as above.

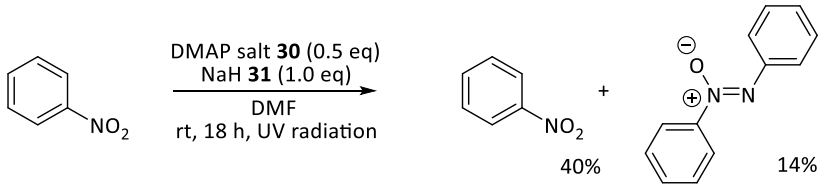
Substrate: nitrobenzene 34 with 1.0 eq of DMAP salt 30



34 **731**

Nitrobenzene **34** (41 mg, 0.33 mmol) was treated with DMAP salt **30** (178.3 mg, 0.33 mmol) and sodium hydride **31** (15.8 mg, 0.66 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford azoxybenzene[268] **731** as a yellow oil (19.6 mg, 0.10 mmol, 60%). δ_H (400 MHz, $CDCl_3$): 7.39 (1H, tt, *J* = 6.8, 1.2 Hz, Ar*H*), 7.59-7.47 (5H, m, Ar*H*), 8.18-8.15 (2H, m, Ar*H*), 8.33-8.30 (2H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 122.5, 125.7, 128.9, 129.0, 129.8, 131.7, 144.2, 148.5. IR (NEAT) ν (cm^{-1}) = 686, 764, 1277, 1301, 1441, 1476. *m/z* (NSI) calcd for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0866, found: 199.0865. A trace amount of azobenzene **36** was also observed in the ^1H NMR spectra of the crude product.

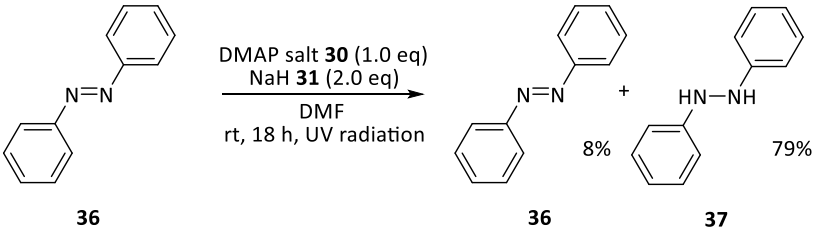
Substrate: nitrobenzene 34 with 0.5 eq of DMAP salt 30



34 **34** **731**

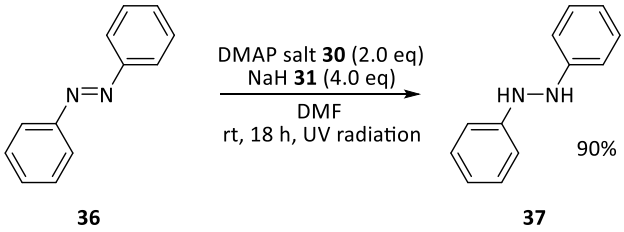
Nitrobenzene **34** (41 mg, 0.33 mmol) was treated with DMAP salt **30** (89.1 mg, 0.17 mmol) and sodium hydride **31** (7.9 mg, 0.33 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford azoxybenzene **731** (4.6 mg, 0.02 mmol, 14%), NMR spectra details as above, and unreacted starting material **34** (16.3 mg, 0.13 mmol, 40%). Yields were quantified by use of 1,3,5-trimethoxybenzene as an internal standard.

Substrate: azobenzene 36 with 1.0 eq of DMAP salt 30



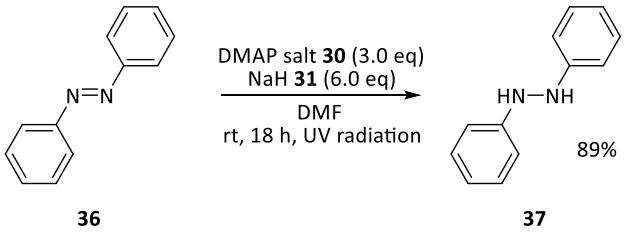
Azobenzene **36** (60.1 mg, 0.33 mmol) was treated with DMAP salt **30** (178.3 mg, 0.33 mmol) and sodium hydride **31** (15.8 mg, 0.66 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-diphenylhydrazine **37** (48.0 mg, 0.26 mmol, 79%) and remaining starting material **36** (4.8 mg, 0.026 mmol, 8%). NMR spectra details as above.

Substrate: azobenzene 36 with 2.0 eq of DMAP salt 30



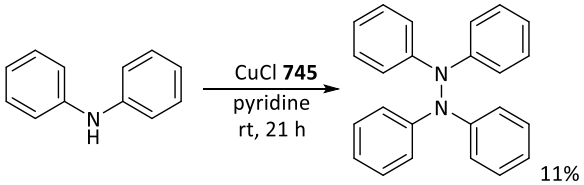
Azobenzene **36** (60.1 mg, 0.33 mmol) was treated with DMAP salt **30** (356.6 mg, 0.66 mmol) and sodium hydride **31** (31,7 mg, 1.32 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-diphenylhydrazine **37** (54.1 mg, 0.30 mmol, 90%). NMR spectra details as above.

Substrate: azobenzene 36 with 3.0 eq of DMAP salt 30



Azobenzene **36** (60.1 mg, 0.33 mmol) was treated with DMAP salt **37** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-diphenylhydrazine **37** (54.1 mg, 0.29 mmol, 89%). NMR spectra details as above.

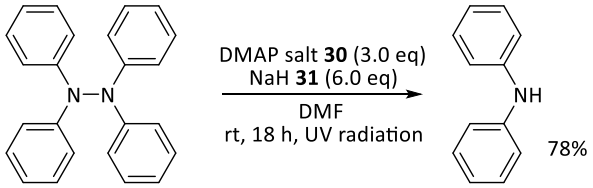
Synthesis of tetraphenylhydrazine 746



744 **746**

To a 250 mL 3-necks round-bottomed flask under argon were added copper chloride **745** (1.98 g, 20.0 mmol) and pyridine (50 mL). The atmosphere of the flask was replaced by oxygen and a solution of diphenylamine **744** (1.69 g, 9.99 mmol) in pyridine (10 mL) was added to the flask upon vigorous stirring and oxygen flow. After addition, the mixture was stirred at room temperature for 21 h under oxygen atmosphere. Pyridine was removed by distillation and the resulting residue was extracted with Et_2O (4 x 25 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification was made by column chromatography on silica using DCM (25%) in hexane to afford tetraphenylhydrazine **746** as a white powder (184.9 mg, 0.55 mmol, 11%). M. Pt. 144-146 °C (lit. 144-147 °C).[269] δ_H (400 MHz, $CDCl_3$): 6.90 (4H, tt, *J* = 7.2, 1.2 Hz, Ar*H*), 7.22-7.17 (8H, m, Ar*H*), 7.32-7.29 (8H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 118.3, 122.2, 129.2, 143.7. IR (NEAT) ν (cm^{-1}) = 689, 740, 1030, 1273, 1294, 1485, 1586. *m*/*z* (APCI) calcd for $C_{24}H_{21}N_2$ $[M+H]^+$: 337.1699, found: 337.1696.

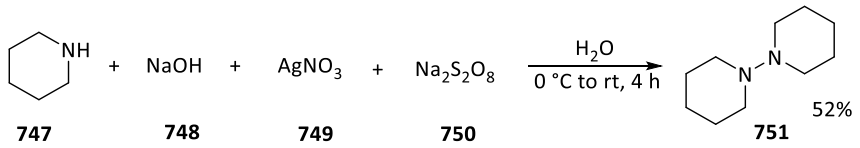
Substrate: tetraphenylhydrazine 746 with 3.0 eq of DMAP salt 30



746 **744**

Tetraphenylhydrazine **746** (111.0 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h. The crude product was purified by column chromatography on silica using EtOAc (7%) in hexane to afford diphenylamine **744** as an off-white solid (87.1 mg, 0.51 mmol, 78%). M. Pt. 51-53 °C (lit. 52-54 °C).[270] δ_H (400 MHz, $CDCl_3$): 5.69 (1H, bs, N*H*), 6.93 (2H, tt, *J* = 7.6, 0.8 Hz, Ar*H*), 7.09-7.06 (4H, m, Ar*H*), 7.29-7.24 (4H, m, Ar*H*). δ_C (100 MHz, $CDCl_3$): 118.0, 121.2, 129.5, 143.3. IR (NEAT) ν (cm^{-1}) = 689, 743, 877, 1175, 1318, 1495, 1515, 1589, 3382. *m/z* (EI) $C_{12}H_{11}N$ [M]: 169.1.

Synthesis of bipiperidine 751

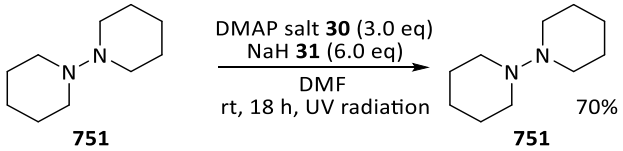


747 **748** **749** **750** **751**

To a 100 mL round-bottomed flask at 0 °C were added H_2O (15 mL), piperidine **747** (2.5 g, 29.4 mmol), NaOH **748** (2.35 g, 58.8 mmol) and $AgNO_3$ **749** (250.0 mg, 1.47 mmol). After stirring for 15 min, a solution of $Na_2S_2O_8$ **750** (6.99 g, 29.4 mmol) in H_2O (20 mL) was added to the mixture which was then stirred from 0 °C to room temperature for 4 h. The mixture was extracted with EtOAc (3 x 30 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica using EtOAc (10%) in hexane to afford bipiperidine[271] **751** as a yellow oil (1.29 g, 7.64 mmol, 52%). δ_H (400 MHz, $CDCl_3$): 1.34 (4H, m, CH_2), 1.59 (8H, quin, *J* = 6.0 Hz, CH_2), 2.66 (8H, t, *J* = 5.2 Hz,

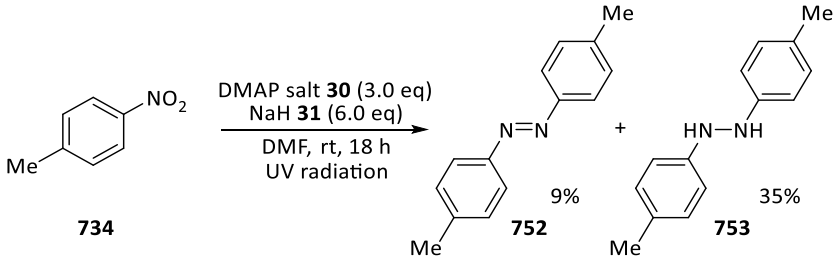
C*H*$_2$). δ_C (100 MHz, $CDCl_3$): 24.9, 26.7, 49.3. IR (NEAT) ν (cm^{-1}) = 875, 1442, 2731, 2800, 2852, 2930. *m/z* (EI) $C_{10}H_{20}N_2$ [M]: 168.1.

Substrate: bipiperidine 751 with 3.0 eq of DMAP salt 30



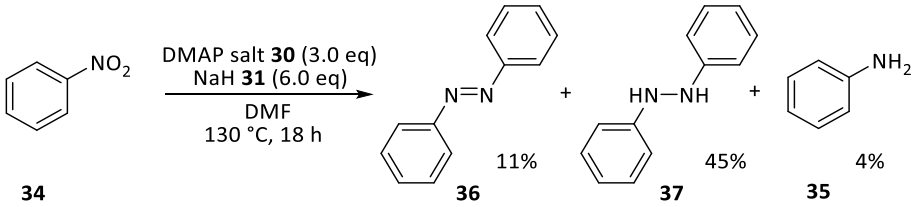
Bipiperidine **751** (55.5 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h. ^{1}H NMR of the crude reaction mixture showed only remaining starting material (38.9 mg, 0.23 mmol, 70%), yield was quantified by use of 1,3,5-trimethoxybenzene as an internal NMR standard.

Substrate: *p*-nitrotoluene 734 with 3.0 eq of DMAP salt 30



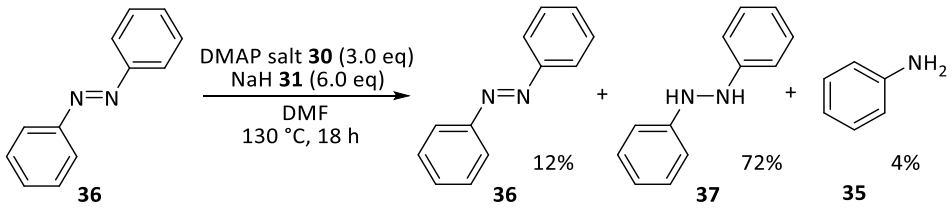
p-Nitrotoluene **734** (45.3 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at room temperature under UV light for 18 h to afford 1,2-di-*p*-tolyldiazene **752** (3.1 mg, 0.01 mmol, 9%) and 1,2-di-*p*-tolylhydrazine **753** (12.3 mg, 0.06 mmol, 35%). Yields were quantified using 1,3,5-trimethoxybenzene as an internal standard. δ_H (400 MHz, $CDCl_3$) for **752**: 2.43 (6H, s, C*H*$_3$), 7.31-7.29 (4H, m, Ar*H*), 7.82-7.79 (4H, m, Ar*H*), data in accordance with literature.[272] δ_H (400 MHz, $CDCl_3$) for **753**: 2.25 (6H, s, C*H*$_3$), 5.50 (2H, bs, N*H*), 6.77-6.74 (4H, m, Ar*H*), 7.02-7.00 (4H, m, Ar*H*), data in accordance with literature.[273]

Substrate: nitrobenzene 34 with 3.0 eq of DMAP salt 30 (thermal conditions)



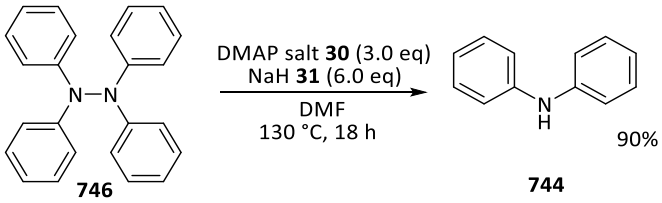
Nitrobenzene **34** (40.6 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at 130 °C for 18 h to afford azobenzene **36** (3.3 mg, 0.02 mmol, 11%), 1,2-diphenylhydrazine **37** (13.7 mg, 0.07 mmol, 45%), NMR spectra details as above, and aniline **35** (1.2 mg, 0.01 mmol, 4%), yields were quantified by use of 1,3,5-trimethoxybenzene as an internal standard. Observed ^{1}H NMR for aniline **35**: δ_H (400 MHz, $CDCl_3$): 3.05 (2H, s, NH_2), 6.70-6.67 (2H, m, Ar*H*), 6.76 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.17-7.13 (2H, m, Ar*H*), data in accordance with literature.[274]

Substrate: azobenzene 36 with 3.0 eq of DMAP salt 30 (thermal conditions)



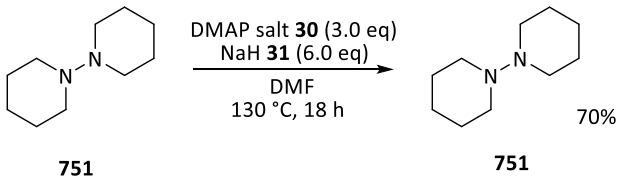
Azobenzene **36** (60.1 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at 130 °C for 18 h to afford remaining starting material **36** (7.2 mg, 0.04 mmol, 12%), 1,2-diphenylhydrazine **37** (43.8 mg, 0.24 mmol, 72%) and aniline **35** (2.5 mg, 0.026 mmol, 4%). NMR spectra details as above.

Substrate: tetraphenylhydrazine 746 with 3.0 eq of DMAP salt 30 (thermal conditions)



Tetraphenylhydrazine **746** (111.0 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at 130 °C for 18 h to afford diphenylamine **744** (100.5 mg, 0.59 mmol, 90%) after purification (chromatography on silica using EtOAc (7%) in hexane as eluent). NMR spectra details as above.

Substrate: bipiperidine 751 with 3.0 eq of DMAP salt 30 (thermal conditions)



Bipiperidine **751** (55.5 mg, 0.33 mmol) was treated with DMAP salt **30** (540.2 mg, 1.0 mmol) and sodium hydride **31** (48.0 mg, 2.0 mmol) in dry DMF (5 mL) at 130 °C for 18 h. ^{1}H NMR of the crude product showed only remaining starting material (38.9 mg, 0.23 mmol, 70%), yield was quantified by use of 1,3,5-trimethoxybenzene as an internal standard.

7 Appendixes

7.1 Marcus theory calculations with 1,4-Diphenylpiperazine-2,5-dione **1**

Substrates: halobenzenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	iodobenzene	31.3	22.9
2	bromobenzene	35.7	27.7
3	chlorobenzene	79.2	54.2
4	fluorobenzene	92.4	58.4

Substrate: 2-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodoanisole	26.1	16.7
2	2-bromoanisole	30.6	22.5
3	2-chloroanisole	84.4	55.6
4	2-fluoroanisole	89.6	59.1

Substrates: 3-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodoanisole	30.9	22.7
2	3-bromoanisole	34.8	26.2
3	3-chloroanisole	38.3	31.2
4	3-fluoroanisole	86.0	60.5

Substrates: 4-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodanisole	31.1	22.8
2	4-bromoanisole	34.3	24.9
3	4-chloroanisole	91.1	54.8
4	4-fluoroanisole	81.5	57.0

Substrates: 2-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodotoluene	30.8	21.8
2	2-bromotoluene	35.7	28.2
3	2-chlorotoluene	87.7	56.8
4	2-fluorotoluene	93.1	59.7

Substrates: 3-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodotoluene	30.8	23.1
2	3-bromotoluene	35.9	27.6
3	3-chlorotoluene	41.1	35.3
4	3-fluorotoluene	88.2	58.7

Substrates: 4-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodotoluene	30.8	23.7
2	4-bromotoluene	35.6	27.5
3	4-chlorotoluene	84.1	55.5
4	4-fluorotoluene	90.2	58.0

7.2 Marcus theory calculations with 1,4-dibenzylpiperazine-2,5-dione **2**

Substrates: halobenzenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	iodobenzene	28.6	18.5
2	bromobenzene	32.9	23.4
3	chlorobenzene	68.0	49.9
4	fluorobenzene	79.5	54.0

Substrate: 2-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodoanisole	23.6	12.3
2	2-bromoanisole	27.9	18.1
3	2-chloroanisole	72.4	51.2
4	2-fluoroanisole	77.5	54.7

Substrates: 3-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodoanisole	28.3	18.4
2	3-bromoanisole	32.1	21.9
3	3-chloroanisole	35.5	26.9
4	3-fluoroanisole	75.2	56.2

Substrates: 4-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodoanisole	28.4	18.5
2	4-bromoanisole	31.7	20.5
3	4-chloroanisole	77.1	50.4
4	4-fluoroanisole	70.7	52.6

Substrates: 2-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodotoluene	28.2	17.5
2	2-bromotoluene	32.9	23.8
3	2-chlorotoluene	75.3	52.4
4	2-fluorotoluene	80.5	55.3

Substrates: 3-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodotoluene	28.1	18.7
2	3-bromotoluene	33.2	23.2
3	3-chlorotoluene	38.2	30.9
4	3-fluorotoluene	76.4	54.4

Substrates: 4-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodotoluene	28.1	19.4
2	4-bromotoluene	32.9	23.2
3	4-chlorotoluene	72.2	51.2
4	4-fluorotoluene	77.7	53.6

7.3 Marcus theory calculations with 1,4-diphenethylpiperazine-2,5-dione **3**

Substrates: halobenzenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	iodobenzene	27.7	17.0
2	bromobenzene	31.9	21.8
3	chlorobenzene	65.0	48.3
4	fluorobenzene	76.2	52.5

Substrates: 2-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodoanisole	22.7	10.8
2	2-bromoanisole	27.0	16.6
3	2-chloroanisole	69.3	49.7
4	2-fluoroanisole	74.4	53.2

Substrates: 3-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodoanisole	27.3	16.8
2	3-bromoanisole	31.1	20.4
3	3-chloroanisole	36.0	27.5
4	3-fluoroanisole	72.3	54.6

Substrates: 4-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodoanisole	27.4	16.9
2	4-bromoanisole	30.7	19.0
3	4-chloroanisole	73.7	48.9
4	4-fluoroanisole	67.8	51.1

Substrates: 2-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodotoluene	27.2	15.9
2	2-bromotoluene	31.9	22.3
3	2-chlorotoluene	72.2	50.9
4	2-fluorotoluene	77.2	53.8

Substrates: 3-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodotoluene	27.2	17.2
2	3-bromotoluene	32.2	21.7
3	3-chlorotoluene	37.1	29.4
4	3-fluorotoluene	73.3	52.8

Substrates: 4-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodotoluene	27.1	17.8
2	4-bromotoluene	31.8	21.7
3	4-chlorotoluene	69.1	49.6
4	4-fluorotoluene	74.5	52.1

7.4 Marcus theory calculations with 1,4-bis(3-phenylpropyl)piperazine-2,5-dione **4**

Substrates: halobenzenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	iodobenzene	27.0	15.1
2	bromobenzene	31.2	20.0
3	chlorobenzene	57.9	46.8
4	fluorobenzene	67.4	50.6

Substrates: 2-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodoanisole	22.1	8.9
2	2-bromoanisole	26.3	14.7
3	2-chloroanisole	61.4	47.8
4	2-fluoroanisole	66.4	51.3

Substrates: 3-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodoanisole	26.6	15.0
2	3-bromoanisole	30.4	18.5
3	3-chloroanisole	35.2	25.6
4	3-fluoroanisole	65.4	52.7

Substrates: 4-haloanisoles

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodoanisole	26.8	15.0
2	4-bromoanisole	30.0	17.1
3	4-chloroanisole	64.1	47.0
4	4-fluoroanisole	60.9	49.2

Substrates: 2-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodotoluene	26.6	14.0
2	2-bromotoluene	31.2	20.4
3	2-chlorotoluene	63.9	49.0
4	2-fluorotoluene	68.7	51.9

Substrates: 3-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodotoluene	26.5	15.3
2	3-bromotoluene	31.5	19.8
3	3-chlorotoluene	36.3	27.5
4	3-fluorotoluene	65.5	51.0

Substrates: 4-halotoluenes

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodotoluene	26.4	16.0
2	4-bromotoluene	31.1	19.8
3	4-chlorotoluene	61.3	47.7
4	4-fluorotoluene	66.0	50.2

7.5 Marcus theory calculations with biaryl radical anions

Substrate: halobenzenes, donor: biphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	iodobenzene	8.2	-20.9
2	bromobenzene	11.2	-16.1
3	chlorobenzene	10.5	10.4
4	fluorobenzene	15.0	14.6

Substrates: 2-haloanisoles, donor: 2-methoxybiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodoanisole	3.8	-32.0
2	2-bromoanisole	6.1	-26.2
3	2-chloroanisole	7.3	6.9
4	2-fluoroanisole	10.4	10.4

Substrates: 3-haloanisoles, donor: 3-methoxybiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodoanisole	7.5	-22.3
2	3-bromoanisole	10.4	-18.8
3	3-chloroanisole	13.4	-11.7
4	3-fluoroanisole	15.5	15.5

Substrates: 4-haloanisoles, donor: 4-methoxybiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodoanisole	6.8	-25.5
2	4-bromoanisole	9.3	-23.5
3	4-chloroanisole	6.7	6.4
4	4-fluoroanisole	9.2	8.7

Substrates: 2-halotoluenes, donor: 2-methylbiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	2-iodotoluene	6.4	-27.7
2	2-bromotoluene	9.1	-21.3
3	2-chlorotoluene	7.7	7.3
4	2-fluorotoluene	10.2	10.2

Substrates: 3-halotoluenes, donor: 3-methylbiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	3-iodotoluene	7.2	-22.4
2	3-bromotoluene	11.0	-17.9
3	3-chlorotoluene	14.0	-10.2
4	3-fluorotoluene	13.2	13.2

Substrates: 4-halotoluenes, donor: 4-methylbiphenyl radical anion

Entry	Substrate	ΔG^* (kcal/mol)	ΔG_{rel} (kcal/mol)
1	4-iodotoluene	6.2	-23.7
2	4-bromotoluene	9.8	-19.9
3	4-chlorotoluene	8.2	8.1
4	4-fluorotoluene	10.5	10.5

8 References

[1] A. J. Birch, *J. Chem. Soc.* **1944**, 430-436.

[2] C. A. Kraus, *J. Amer. Chem. Soc.* **1921**, *43*, 749-770.

[3] B. A. Averill, P. Eldredge, **2011**, *General Chemistry: Principles, Patterns and Applications*, Saylor Academy.

[4] A. J. Birch, *J. Chem. Soc.* **1945**, 809-813.

[5] A. J. Birch, *J. Chem. Soc.* **1946**, 593-597.

[6] A. J. Birch, D. Nasipuri, *Tetrahedron* **1959**, *6*, 148-153.

[7] N. L. Holy, *Chem. Rev.* **1974**, *74*, 243-277.

[8] A. P. Krapcho, A. A. Bothner-By, *J. Am. Chem. Soc.* **1959**, *81*, 3658

[9] H. E. Zimmerman, *Tetrahedron* **1961**, *16*, 169.

[10] A. J. Birch, A. L. Hinde, L. Radom, *J. Am. Chem. Soc.* **1980**, *102*, 3370.

[11] H. E. Zimmerman, P. A. Wang, *J. Am Chem. Soc.* **1990**, *112*, 1281-1283.

[12] V. D. Parker, M. Tilset, O. Hammerich, *J. Am. Chem. Soc.* **1987**, *109*, 7905.

[13] H. E. Zimmerman, P. A. Wang, *J. Am. Chem. Soc.* **1993**, *115*, 2205.

[14] H. E. Zimmerman, *Acc. Chem. Res.* **2012**, *45*, 164.

[15] T. J. Donohoe, P. M. Guyo, *J. Org. Chem.* **1996**, *61*, 7664.

[16] T. J. Donohoe, P. M. Guyo, R. L. Beddoes, M. Helliwell, *J. Chem. Soc.*, *Perkin Trans.* **1998**, *1*, 667.

[17] A. J. Birch, J. Slobbe, *J. Heterocycles* **1976**, *5*, 905.

[18] T. J. Donohoe, P. M. Guyo, R. R. Harji, M. Helliwell, *Tetrahedron. Lett.* **1998**, *39*, 3075.

[19] T. J. Donohoe, R. R. Harji, R. P. C. Cousins, *Chem. Commun.* **1999**, 141.

[20] T. J. Donohoe, R. R. Harji, R. P. C. Cousins, *Tetrahedron Lett.* **2000**, *41*, 1327.

[21] T. J. Donohoe, R. R. Harji, R. P. C. Cousins, *Tetrahedron Lett.* **2000**, *41*, 1331.

[22] M. Yus, D. J. Ramon, *J. Chem. Soc.*, *Chem. Commun.* **1991**, 398.

[23] T. J. Donohoe, D. House, *J. Org. Chem.* **2002**, *67*, 5015.

[24] P. K. Freeman, L. L. Hutchinson, *Tetrahedron Lett.* **1976**, 1849.

[25] P. K. Freeman, L. L. Hutchinson, *J. Org. Chem.* **1980**, *45*, 1924.

[26] L. Bouveault, G. Blanc, *C. R. Séances hebd. Ac. Sc.* **1903**, *136*, 1676.

[27] L. Bouveault, R. Loquin, *Compt. Rend.* **1905**, *140*, 1593.

[28] P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693.

[29] J. L. Namy, J. Souppe, H. B. Kagan, *Tetrahedron Lett.* **1983**, *24*, 765.

[30] J. Souppe, L. Danon, J. L. Namy, H. B. Kagan, *J. Organometal. Chem.* ***1989,*** 50, 227.

[31] P. Barbier, *C. R. Séances hebd. Ac. Sc.* **1899**, *128*, 110.

[32] T. P. Ananthanarayan, T. Gallagher, P. Magnus, *J. Chem. Soc.*, *Chem. Commun.* **1982**, 709.

[33] C. Exon, T. Gallagher, P. Magnus, *J. Am. Chem. Soc.* **1983**, *105*, 4739.

[34] T. P. Ananthanarayan, P. Magnus, A. W. Norman, *J. Chem. Soc.*, *Chem. Commun.* **1983**, 1096.

[35] G. A. Molander, J. B. Etter, *J. Org. Chem.* **1986**, *51*, 1778.

[36] G. A. Molander, G. J. Hahn, *J. Org. Chem.* **1986**, *51*, 1135.

[37] G. A. Molander, G. J. Hahn, *J. Org. Chem.* **1986**, *51*, 2596.

[38] J. Inanaga, O. Ujikawa, M. Yamaguchi, *Tetrahedron Lett.* **1991**, *32*, 1737.

[39] S. M. Bennett, D. Larouche, *Synlett* **1991**, 805.

[40] G. A. Molander, J. A. McKie, *J. Org. Chem.* **1994**, *59*, 3186.

[41] E. Nandanan, C. U. Dinesh, H.-U. Reissig, *Tetrahedron* **2000**, *56*, 4267.

[42] M. Sasaki, J. Collin, H. B. Kagan, *Tetrahedron Lett.* **1988**, *29*, 6105.

[43] R.S. Miller, J. M. Sealy, M. Shabangi, M. L. Kuhlman, J. R. Fuchs, R. A. Flowers II, *J. Am. Chem. Soc.* **2000**, *122*, 7718.

[44] K. A. Choquette, D. V. Sadasiwam, R. A. Flowers II, *J. Am. Chem. Soc.* **2010**, *132*, 17396.

[45] R. J. Enemaerke, T. Hertz, T. Skrydstrup, K. Daasbjerg, *Chem. Eur. J.* **2000**, *6*, 3747.

[46] J. T. Link, L. E. Overman, *J. Am. Chem. Soc.* **1996**, *118*, 8166.

[47] I. M. Rudkin, L. C. Miller, D. Procter, *J. Organomet. Chem.* **2008**, *34*, 19.

[48] E. Prasad, R. A. Flowers II, *J. Am. Chem. Soc.* **2005**, *127*, 18093.

[49] B. Giese, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969.

[50] D. Parmar, L. A. Duffy, D. V. Sadasivam, H. Matsubara, P. A. Bradley, R. A. Flowers II, D. J. Procter, *J. Am. Chem. Soc.* **2009**, *131*, 15467.

[51] D. Parmar, K. Price, M. Spain, H. Matsubara, P. A. Bradley, D. J. Procter, *J. Am. Chem. Soc.* **2011**, *133*, 2418.

[52] E. Prasad, B. W. Knettle, R. A. Flowers II, *J. Am. Chem. Soc.* **2002**, *124*, 14663.

[53] T. Ankner, M. Friedén-Saxin, N. Pemberton, T. Seifert, M. Grotli, K. Luthman, G. Hilmersson, *Org. Lett.* **2010**, *12*, 2210.

[54] S. Fukuzawa, K. Mutoh, T. Tsuchimoto, T. Hiyama, *J. Org. Chem.* **1996**, *61*, 5400.

[55] K. Mashima, T. Oshiki, K. Tani, *J. Org. Chem.* **1998**, *63*, 7114.

[56] S. Fukuzawa, Y. Yahara, A. Kamiyama, M. Hara, S. Kikuchi, *Org. Lett.* **2005**, *7*, 5809.

[57] W. J. Evans, S. L. Gonzales, J. W. Ziller, *J. Am. Chem. Soc.* **1994**, *116*, 2600.

[58] A. M. Bond, G. B. Deacon, R. H. Newnham, *Organometallics* **1986**, *5*, 2312.

[59] W. J. Evans, L. A. Hughes, T. P. Hanusa, *Organometallics* **1986**, *5*, 1285.

[60] W. J. Evans, T. A. Ulibarri, J. W. Ziller, *J. Am. Chem. Soc.* **1988**, *110*, 6877.

[61] W. J. Evans, N. T. Allen, J. W. Ziller, *J. Am. Chem. Soc.* **2000**, *122*, 11749.

[62] M. N. Bochkarev, I. L. Fedushkin, S. Dechert, A. A. Fagin, H. Schumann, *Angew. Chem. Int. Ed.* **2001**, *40*, 3176.

[63] M. N. Bochkarev, I. L. Fedushkin, A. A. Fagin, T. V. Petrovskaya, J. W. Ziller, R. N. R. Broomhall-Dillard, W. J. Evans, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 133.

[64] M. Szostak, B. Sautier, M. Spain, D. J. Procter, *Org. Lett.* **2014**, *16*, 1092.

[65] H.-M. Huang, D. J. Procter, *J. Am. Chem. Soc.* **2017**, *139*, 1661.

[66] F. Wudl, G. M. Smith, E. J. Hufnagel, *J. Chem. Soc.*, *Chem. Comm.*, **1970**, *21*, 1453.

[67] M. R. Bryce, *Aldrichimica Acta*, **1985**, *18*, 73.

[68] C. Lampard, J. A. Murphy, N. Lewis, *J. Chem. Soc.*, *Chem. Commun.*, **1993**, 295.

[69] J. A. Murphy, in *Radical in Organic Synthesis*, ed. P. Renaud, M. Sibi, Wiley-VCH, Weinheim, **2001**, vol. 1, p. 298.

[70] K. Takimiya, T. Jigami, M. Kawashima, M. Kodani, Y. Aso, T. Otsubo, *J. Org. Chem.*, **2002**, *67*, 4218.

[71] Y. Yamashita, Y. Kobayashi, T. Miyashi, *Angew. Chem.*, *Int. Ed. Engl.*, **1989**, *28*, 1052.

[72] M. Sato, M. V. Lakshmikantham, M. P. Cava, A. F. Garito, *J. Org. Chem.*, **1978**, *43*, 2084.

[73] P. Renaud, in *Radicals in Organic Synthesis*, ed. P. Renaud, M. Sibi, Wiley-VCH, Weinheim, **2001**, vol. 1, p. 153 *et seq*.

[74] C. Burkholder, W. R. Dolbier, M. Médebielle, *J. Org. Chem.*, **1998**, *63*, 5385.

[75] S. Aït-Mohand, N. Takechi, M. Médebielle, W. R. Dolbier, *Org. Lett.*, **2001**, *3*, 4271.

[76] M. Since, T. Terme, P. Vanelle, *Tetrahedron*, **2009**, *65*, 6128.

[77] J. A. Murphy, M. Mahesh, F. LeStrat, H. P. Wessel, *Beilstein J. Org. Chem.*, **2009**, *5*, 1.

[78] Z. Shi, R. P. Thummel, *J. Org. Chem.* **1995**, *60*, 5935.

[79] J. R. Ames, M. A. Houghtaling, D. L. Terrian, T. A. Mitchell, *Can. J. Chem.*, **1997**, *75*, 28.

[80] J. A. Murphy, T. A. Khan, S. Z. Zhou, D. W. Thomson, M. Mahesh, *Angew. Chem.*, *Int. Ed.*, **2005**, *44*, 1356.

[81] D. W. Thomson, PhD thesis, University of Strathclyde, Glasgow, **2005**, ch. 2.

[82] J. A. Murphy, S. Z. Zhou, D. W. Thomson, F. Schoenebeck, M. Mahesh, S. R. Park, T. Tuttle and L. E. A. Berlouis, *Angew. Chem.*, *Int. Ed.*, **2007**, *46*, 5178.

[83] R. P. Thummel, V. Goulle, B. Chen, *J. Org. Chem.*, **1989**, *54*, 3057.

[84] F. Schoenebeck, J. A. Murphy, S. Z. Zhou, Y. Uenoyama, Y. Miclo, T. Tuttle, *J. Am. Chem. Soc.* **2007**, *129*, 13368.

[85] C. Najera, M. Yus, *Tetrahedron*, **1999**, *55*, 10547.

[86] Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

[87] J. A. Murphy, F. Schoenebeck, N. J. Findlay, D. W. Thomson, S. Z. Zhou, J. Garnier, *J. Am. Chem. Soc.* **2009**, *131*, 6475.

[88] R. McKie, J. A. Murphy, S. R. Park, M. D. Spicer, S. Z. Zhou, *Angew. Chem.*, *Int. Ed.*, **2007**, *46*, 6525.

[89] J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S. Z. Zhou, A. T. Turner, *Org. Lett.*, **2008**, *10*, 1227.

[90] A. R. Kennedy, J. Garnier, L. E. A. Berlouis, A. T. Turner, J. A. Murphy, *Beilstein J. Org. Chem.*, **2010**, *6*, 73.

[91] R. Sword, L. A. Baldwin, J. A. Murphy, *Org. Biomol. Chem.* **2011**, *9*, 3560-3570.

[92] S. P. Y. Cutulic, J. A. Murphy, H. Farwaha, S. Z. Zhou, E. Chrystal, *Synlett* **2008**, 2132.

[93] S. P. Y. Cutulic, N. J. Findlay, S. Z. Zhou, E. J. T. Chrystal, J. A. Murphy, *J. Org. Chem* **2009**, *74*, 8713.

[94] P. I. Jolly, N. Fleary-Roberts, S. O'Sullivan, E. Doni, S. Z. Zhou, J. A. Murphy, *Org. Biomol. Chem.* **2012**, *10*, 5807.

[95] E. Cahard, F. Schoenebeck, F. J. Garnier, S. P. Y. Cutulic, S. Z. Zhou, J. A. Murphy, *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 3673.

[96] E. Doni, S. O'Sullivan, J. A. Murphy, *Angew. Chem.*, *Int. Ed.* **2013**, *52*, 2239.

[97] S. O'Sullivan, E. Doni, T. Tuttle, J. A. Murphy, *Angew. Chem.*, *Int. Ed.* **2014**, *53*, 474.

[98] E. Doni, B. Mondal, S. O'Sullivan, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 10934.

[99] F. Krollpfeiffer, A. Rosenberg, *A. Ber. Dtsch. Chem. Ges.***1936**, *69*, 465.

[100] H.-Y. Kang, W. S. Hong, Y. S. Cho, H. Y. Koh, *Tetrahedron Lett.* **1995**, *36*, 7661.

[101] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn*. **1971**, *44*, 581.

[102] R. F. Heck, J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*, 2320.

[103] N. Miyaura, A. Suzuki, *J. Chem. Soc.*, *Chem. Comm.*, **1979**, 866.

[104] Y. Hatanaka, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 918.

[105] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1979**, *101*, 4992.

[106] A. O. King, N. Okukado, E. Negishi, *J. Chem. Soc.*, *Chem. Comm.*, **1977**, 683.

[107] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.

[108] S. Yanagisawa, K. Ueda, T. Taniguchi, K. Itami, *Org. Lett.* **2008**, *10*, 4673.

[109] K. Fujita, M. Nonogawa, R. Yamaguchi, *Chem. Commun.* **2004**, 1926.

[110] C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li, Z.-J. Shi, *Nat. Chem.* **2010**, *2*, 1044.

[111] E. Shirakawa, K. Itoh, T. Higashino, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 15537.

[112] W. R. Bowman, J. M. D. Storey, *Chem. Soc. Rev.* **2007**, *36*, 1803.

[113] E. C. Ashby, J. N. Argyropoulos, *J. Org. Chem.* **1986**, *51*, 3593.

[114] J. F. Bunnett, *Acc. Chem. Res.* **1978**, *11*, 413.

[115] W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 16737.

[116] C.-L. Sun, Y.-F. Gu, B. Wang, Z.-J. Shi, *Chem.-Eur. J.* **2011**, *17*, 10844.

[117] C.-L. Sun, Y.-F. Gu, W.-P. Huang, Z.-J. Shi, *Chem. Commun.* **2011**, *47*, 9813.

[118] A. Studer, D. P. Curran, *Angew. Chem.*, *Int. Ed.* **2011**, *50*, 5018.

[119] Z. V. Todres, *Organic Ion Radicals: Principles and Applications*, CRC, Boca Raton, **2009**.

[120] G.-P. Yong, W.-L. She, Y.-M. Zhang, Y.-Z. Li, *Chem. Commun.* **2011**, *47*, 11766.

[121] M. Rueping, M. Leiendecker, A. Das, T. Poisson, L. Bui, *Chem. Commun.* **2011**, *47*, 10629.

[122] Y. Qiu, Y. Liu, K. Yang, W. Hong, Z. Li, Z. Wang, Z. Yao, S. Jiang, *Org. Lett.* **2011**, *13*, 3556.

[123] W.-C. Chen, Y.-C. Hsu, W.-C. shih, C.-Y. Lee, W.-H. Chuang, Y.-F. Tsai, P. P.-Y. Chen, T.-G. Ong, *Chem. Commun.* **2012**, *48*, 6702.

[124] H. Zhang, R. Shi, A. Ding, L. Lu, B. Chen, A. Lei, *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 12542.

[125] B. Pieber, D. Cantillo, C. O. Kappe, *Chem. Eur. J.* **2012**, *18*, 5047.

[126] B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar, S. Kumar, *Org. Lett.* **2012**, *14*, 2838.

[127] S. De, S. Ghosh, S. Bhunia, J. A. Sheikh, A. Bisai, *Org. Lett.* **2012**, *14*, 4466.

[128] K. Tanimoro, M. Ueno, K. Takeda, M. Kirihata, S. Tanimori, *J. Org. Chem.* **2012**, *77*, 7844.

[129] Y. Wu, S. M. Wong, F. Mao, T. L. Chan, F. Y. Kwong, *Synlett* **2012**, *23*, 2714.

[130] D. S. Roman, Y. Takahashi, A. B. Charette, *Org. Lett.* **2011**, *13*, 3242.

[131] I. Thomé, C. Bolm, *Org. Lett.* **2012**, *14*, 1892.

[132] H. Zhao, J. Shen, J. Guo, R. Ye, H. Zeng, *Chem. Commun.* **2013**, *49*, 2323.

[133] M. E. Budén, J. F. Guastavino, R. A. Rossi, *Org. Lett.* **2013**, *15*, 1174.

[134] W. Liu, F. Tian, X. Wang, H. Yu, Y. Bi, *Chem. Commun.* **2013**, *49*, 2983.

[135] S. Z. Zhou, G. M. Anderson, B. Mondal, E. Doni, V. Ironmonger, M. Kranz, T. Tuttle, J. A. Murphy, *Chem. Sci.* **2014**, *5*, 476.

[136] G. B. Bajracharya, O. Daugulis, *Org. Lett.* **2008**, *10*, 4625.

[137] M. D. Gheorghiu, R. Hoffmann, *Revue Roumaine de Chimie* **1969**, *14*, 947.

[138] R. G. Miller, M. Stiles, *J. Am. Chem. Soc.* **1963**, *85*, 1798.

[139] P. G. Gassman, H. P. Benecke, *Tetrahedron Lett.* **1969**, *10*, 1089.

[140] A. T. Bowne, T. A. Christopher, R. H. Levin, *Tetrahedron Lett.* **1976**, *14*, 4111.

[141] S. Yamabe, T. Minato, A. Ishiwata, O. Irinamihira, T. Machiguchi, *J. Org. Chem.* **2007**, *72*, 2832.

[142] K. Okuma, S. Sonoda, Y. Koga, K. Shioji, *J. Chem. Soc.*, *Perkin Trans*. *1* **1999**, 2997.

[143] S. Z. Zou, E. Doni, G. M. Anderson, R. G. Kane, S. W. MacDougall, V. M. Ironmonger, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2014**, *136*, 17818.

[144] Nonappa, K. Ahonen, M. Lahtinen, E. Kolehmainen, *Green Chem.* **2011**, *13*, 1203.

[145] R. B. Woodward, L. Wendler, F. J. Brutschy, *J. Am. Chem. Soc.* **1945**, *67*, 1425.

[146] P. C. Andrikopoulos, D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, R. B. Rowlings, *Eur. J. Inorg. Chem.* **2003**, 3354.

[147] R. Campbell, D. Cannon, P. Garcia-Alvarez, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, J. Saβmannshausen, T. Tuttle, *J. Am. Chem. Soc.* **2011**, *13*, 13706.

[148] J. H. Wotiz, R. D. Kleopfer, P. M. Barelski, C. C. Hinckley, D. F. Koster, *J. Org. Chem.* **1972**, *37*, 1758.

[149] J. Cuthbertson, V. J. Gray, J. D. Wilden, *Chem. Commun.* **2014**, *50*, 2575.

[150] N. S. Poonia, M. R. Truter, *J. Chem. Soc.*, *Dalton Trans.*, **1973**, 2062.

[151] M. P. Drapeau, I. Fabre, L. Grimaud, I. Ciofini, T. Ollevier, M. Taillefer, *Angew. Chem.*, *Int. Ed.* **2015**, *54*, 10587.

[152] W.-T. Wei, X.-J. Dong, S.-Z. Nie, Y.-Y. Chen, X.-J. Zhang, M. Yan, *Org. Lett.* **2013**, *15*, 6018.

[153] Y.-Y. Chen, X.-J. Zhang, H.-M. Yuan, W.-T. Wei, M. Yan, *Chem. Commun.* **2013**, *49*, 10974.

[154] G. Oksdath-Mansilla, J. E. Arguello, A. B. Penénory, *Tetrahedron Lett.* **2013**, *54*, 1515.

[155] H. Yi, A. Jutand, A. Lei, *Chem. Commun.* **2015**, *51*, 545.

[156] J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2016**, *138*, 7402.

[157] W. von E. Doering, A. K. Hoffmann, *J. Am. Chem. Soc.* **1954**, *76*, 6162.

[158] D. A. Di Rocco, K. Dykstra, S. Krska, P. Vachal, D. V. Conway, M. Tudge, *Angew. Chem.*, *Int. Ed.* **2014**, *53*, 4802.

[159] J. T. Reeves, Z. Tan, M. A. Herbage, Z. S. Han, M. A. Marsini, Z. Li, G. Li, Y. Xu, K. R. Fandrick, N. C. Gonnella, S. Campbell, S. Ma, N. Grinberg, H. Lee, B. Z. Lu, C. H. Senanayake, *J. Am. Chem. Soc.* **2013**, *135*, 5565.

[160] J. T. Reeves, C. Lorenc, K. Camara, Z. Li, H. Lee, C. A. Bussaca, C. H. Senanayake, *J. Org. Chem.* **2014**, *79*, 5895.

[161] Y. Wu, P. Y. Choy, F. Y. Kwong, *Org. Biomol. Chem.* **2014**, *12*, 6820.

[162] J. P. Barham, G. Coulthard, R. G. Kane, N. Delgado, M. P. John, J. A. Murphy, *Angew. Chem.*, *Int. Ed.* **2016**, *55*, 4492.

[163] L. Zhang, H. Yang, L. Jiao, *J. Am. Chem. Soc.* **2016**, *138*, 7151.

[164] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V.Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford, CT, USA, **2009**.

[165] Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157.

[166] T. H. Dunning, *J. Chem. Phys.* **1989**, *90*, 1007.

[167] V. Barone, M. Cossi, *J. Phys. Chem. A*. **1998**, *102*, 1995.

[168] M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003,** *24*, 669.

[169] E. Ceppi, W. Eckhardt, C. A. Grob, *Tetrahedron Lett.* **1973**, *14*, 3627.

[170] J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, D. A. Semenow, *J. Am. Chem. Soc.* **1956**, *78*, 611.

[171] J. H. Wotiz, F. Huba, *J. Org. Chem.* **1959**, *24*, 595.

[172] Y. Dong, M. I. Lipschutz, T. D. Tilley, *Org. Chem. Lett.* **2016**, *18*, 1530.

[173] E. Picazo, K. N. Houk, N. K. Garg, *Tetrahedron Lett.* **2015**, *56*, 3511.

[174] R. A. Marcus, *J. Chem. Phys.* **1965**, *43*, 679.

[175] S. F. Nelsen, S. C. Blackstock, Y. Kim, *J. Am. Chem. Soc.* **1987**, *109*, 677.

[176] L. Pause, M. Robert, J.-M. Savéant, *J. Am. Chem. Soc.* **1999**, *121*, 7158.

[177] M. Mailhe, A. Murat, *Bulletin de la Société Chimique de France*, **1912**, *4*, 123.

[178] A. J. Birch, *J. Chem. Soc.* **1947**, *69*, 102.

[179] R. Beugelmans, S. Bourdet, A. Bigot, J. Zhu, *Tetrahedron Lett.***1994**, *35*, 4349.

[180] M. Dessolin, M.-G. Guillerez, N. Thieriet, F. Guibe, A. Loffet, *Tetrahedron Lett.* **1995**, *36*, 5741.

[181] P. Four, F. Guibe, *Tetrahedron Lett.* **1982**, *23*, 1825.

[182] P. R. Brooks, M. C. Wirtz, M. G. Vetelino, D. M. Rescek, G. F. Woodworth, B. P. Morgan, J. W. Coe, *J. Org. Chem.* **1999**, *64*, 9719.

[183] W.-C. Sun, K. R. Gee, D. H. Klaubert, R. P. Haugland, *J. Org. Chem.* **1997**, *62*, 6469.

[184] G. Driver, K. E. Johnson, *Green Chem.* **2003**, *5*, 163.

[185] G. J. Kemperman, T. A. Roeters, P. W. Hilberink, *Eur. J. Org. Chem.* **2003**, *9*, 1681.

[186] J. R. Hwu, F. F. Wong, J.-J. Huang, S.-C. Tsay, *J. Org. Chem.* **1997**, *62*, 4097.

[187] A. Fedorov, A. A. Toutov, N. A. Swisher, R. H. Grubbs, *Chem. Sci.* **2013**, *4*, 1640.

[188] M.-X. Zhang, X.-H. Hu, Y.-H. Xu, T.-P. Loh, *Asian. J. Org. Chem.* **2015**, *4*, 1047.

[189] Y.-X. Chen, L.-F. Qian, W. Zhang, B. Han, *Angew. Chem.*, *Int. Ed.* **2008**, *47*, 9330.

[190] H. A. Pacevitz, H. Gilman, *J. Am. Chem. Soc.* **1939**, *61*, 1603.

[191] D. Siegel, J. Brubaker, F. Liu, *Organometallics in Organic Synthesis*, Schlosser, M., Wiley: New York, **1994**, 172.

[192] E. Spath, *Monatsh. Chem.* **1914**, *35*, 322.

[193] M. A. Sobrero, *C. R.* **1847**, *24*, 247.

[194] J. Wilbrand, *Ann. Chem. Phar.* **1863**, *128*, 178.

[195] A. Laurent, *Ann. Chem. Phys.* **1841**, *3*, 195.

[196] C. Yu, B. Liu, L. Hu, *J. Org. Chem.* **2001**, *66*, 919.

[197] F. A. Khan, J. Dash, C. Sudheer, R. K. Gupta, *Tetrahedron Lett.* **2003**, *44*, 7783.

[198] R. M. Deshpande, A. N. Mahajan, M. M. Diwakar, P. S. Ozarde, R. V. Chaudhari, *J. Org. Chem.* **2004**, *69*, 4835.

[199] P. M. G. Bavin, *Org. Synth.* **1960**, *40*, 5.

[200] A. S. Kende, J. S. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699.

[201] J. Souppe, L. Danon, J. L. Namy, H. B. Kagan, *J. Org. Chem.* **1983**, *250*, 227.

[202] N. Sakai, K. Fujii, S. Nabeshima, R. Ikeda, T. Konakahara, *Chem. Commun.* **2010**, *46*, 3173.

[203] N. Sakai, S. Asama, S. Anai, T. Konakahara, *Tetrahedron* **2014**, *70*, 2027.

[204] L. Hu, X. Cao, L. Chen, J. Zheng, J. Lu, X. Sun, H. Gu, *Chem. Commun.* **2012**, *48*, 3445.

[205] M. L. Di Gioia, A. Leggio, I. F. Guarino, V. Leotta, E. Romio, A. Liguori, *Tetrahedron Lett.* **2015**, *56*, 5341.

[206] R. Porta, A. Puglisi, G. Colombo, S. Rossi, M. Benaglia, *Beilstein J. Org. Chem.* **2016**, *12*, 2614.

[207] Experiments were carried out using two Blak Ray B-100 Series high intensity inspection lamps, with 100 W, 365 nm spot bulbs.

[208] I. Biljan, G. Cvjetojevic, V. Smrecki, P. Novak, G. Mali, J. Plavec, D. Babic, Z. Mihalic, H. Vancik, *J. Mol. Struct*. **2010**, *979*, 22.

[209] F. D. Greene, K. E. Gilbert, *J. Org. Chem.* **1975**, *40*, 1409.

[210] B. G. Gowenlock, G. B. Richter-Addo, *Chem. Soc. Rev.* **2005**, *34*, 797.

[211] T. Kajimoto, H. Takahashi, J. Tsuji, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3673.

[212] J. Fotie, J. L. Rhodus, H. A. Taha, C. S. Reid, *Heteroat. Chem.* **2012**, *23*, 598.

[213] F. Haber, *Thermodynamik technischer Gasreaktionen* **2012**, 1st ed.

[214] M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45.

[215] F. Pfrengle, H.-U. Reissig, *Chem. Soc. Rev.* **2010**, *39*, 549.

[216] S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.

[217] S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.

[218] M. Helms, W. Schade, R. Pulz, T. Watanabe, A. Al-Harrasi, L. Fisera, L. Hlobilova, G. Zhan, H.-U. Reissig, *Eur. J. Org. Chem.* **2005**, 1003.

[219] V. M. Schmiedel, S. Stefani, H.-U. Reissig, *Beilstein J. Org. Chem.* **2013**, *9*, 2564.

[220] G. M. Okala Amombo, O. Flogel, S. Kord Daoruun Kalai, S. Schoder, U. Warzok, H.-U. Reissig, *Eur. J. Org. Chem.* **2017**, 1965.

[221] P. Magnus, P. Albaugh-Robertson, *J. Chem. Soc.*, *Chem. Commun.* **1984**, 804.

[222] J. E. Baldwin, *J. Chem. Soc.*, *Chem. Commun.* **1976**, 734.

[223] K. Gilmore, I. V. Alabugin, *Chem. Rev.* **2011***, 111*, 6513.

[224] C. A. Dyker, V. Lavallo, B. Donnadieu, G. Bertrand, *Angew. Chem.*, *Int. Ed.* **2008**, *47*, 3206.

[225] D. S. Patel, P. V. Bharatam, *J. Org. Chem.* **2011**, *76*, 2558.

[226] V. A. Rassolov, M. A. Ratner, J. A. Pople, P. C. Redfern, L. A. Curtiss, *J. Comput. Chem.* **2001**, *22*, 1007.

[227] B. Alcaide, P. Almendros, C. Aragoncillo, G. Gomez-Campillos, M. T. Quiros, E. Soriano, *J. Org. Chem.* **2016**, *81*, 7362.

[228] S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron Lett*. **2007**, *63*, 1191.

[229] Y. Wen, X. Chen, H. Wen, X. Tang, *Lett. Org. Chem.* **2011**, *8*, 732.

[230] A. L. Cardoso, C. Sousa, M. S. C. Henriques, J. A. Paixo, T. M. V. D. Pinho E Melo, K. Banert, *Molecules* **2015**, *20*, 22351.

[231] H. Morimoto, R. Fujiwara, Y. Shimizu, K. Morisaki, T. Ohshima, *Org. Lett.* **2014**, *16*, 2018.

[232] V. Vecchietti, G. D. Clarke, R. Colle, G. Giardina, G. Petrone and M. Sbacchi, *J. Med. Chem.* **1991**, *34*, 2624.

[233] Murnen, A. M. Rosales, J. N. Jaworski, R. A. Segalman and R. N. Zuckermann, *J. Am. Chem. Soc.* **2010**, *132*, 16112.

[234] F. Cumine, S.-Z. Zhou, T. Tuttle, J. A. Murphy, *Org. Biomol. Chem.* **2017**, *15*, 3324.

[235] J. Zhou, S. Yu, K. Cheng and C. Qi, *J. Chem. Res.* **2012**, *36*, 672.

[236] M.-J. Jin, D.-H. Lee, *Angew. Chem., Int. Ed.* **2010**, *49*, 1119.

[237] A. Devanji, S. Murorka, D. Curran, A. Studer, *Org. Lett.* **2013**, *15*, 6102.

[238] J. Zeng, K. M. Liu, X. F. Duan, *Org. Lett.* **2013**, *15*, 5342.

[239] S. Zhou, M. Johuson, J. G. C. Veinot, *Chem. Commun.* **2010**, *46*, 2411.

[240] M. J. Iglesias, A. Priesta, M. Nicasio, *Org. Lett.* **2012**, *14*, 4318.

[241] C. A. Parrish, S. L. Buchwald, *J. Org. Chem*. **2001**, *66*, 2498.

[242] B. DeCosta, S. Pincock, *J. Org. Chem.* **2000**, *65*, 4162.

[243] J.-P. Pittelond, Z.-T. Zhang, Y. Liang, L. Cabrera, S. F. Wnuk, *J. Org. Chem.* **2010**, *75*, 8199.

[244] T. A. Ramirez, B. Zhao, Y. Shi, *Tetrahedron Lett.* **2010**, *51*, 1822.

[245] K. Cheng, S. Hu, B. Zhao, X.-M. Zhang, C. Qi, *J. Org. Chem.* **2013**, *78*, 5022.

[246] C. Pedroli, D. Ravelli, S. Protti, A. Albini, M. Fagnoni, *J. Org. Chem.* **2017**, *82*, 6592.

[247] C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656.

[248] J. Terao, M. Nakamura, N. Kambe, *Chem. Commun.* **2009**, *40*, 6011.

[249] T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353.

[250] R. G. Cooks, I. Howe, S. W. Tam, D. H. Williams, *J. Am. Chem. Soc.* **1968**, *90*, 4064.

[251] R. Akawie, *J. Org. Chem.* **1961**, *26*, 243.

[252] J. Xu, X. Wang, C. Shao, D. Su, G. Cheng, Y. Hu, *Org. Lett.* **2010**, *12*, 1964.

[253] L. Vargha, J. Ramonczai, P. Bite, *J. Am. Chem. Soc.* **1948**, *70*, 371.

[254] E. T. Ecik, A. Atilgan, R. Guliyev, T. B. Uyan, A. Gunns, E. U. Ahkaya, *Dalton. Trans.* **2014**, *43*, 67.

[255] M. Xu, J. Zhang, X. Wu, J. Sun, Z. Shi, *Synth. Commun.* **2010**, *40*, 992.

[256] J. W. Emsley, S. Hadenfeldt, T. J. Horne, G. Celebre, M. Longeri, *J. Chem. Soc., Perkin Trans. 2*, **1991**, 583.

[257] M. Begala, *J. Mass. Spec.* **2015**, *50*, 693.

[258] M. Jiang, H. Yang, H. Fu, *Org. Lett.* **2016**, *18*, 5248.

[259] J. Gatenyo, I. Vints, S. Rozen, *Chem. Commun.* **2013**, *49*, 7379.

[260] G. H. Posner, K. A. Canella, *J. Am. Chem. Soc.* **1985**, *107*, 2571.

[261] B. Schmidt, M. Riemer, M. Karras, *J. Org. Chem.* **2013**, *78*, 8680.

[262] J. W. Gathirwa, T. Maki, *Tetrahedron* **2012**, *68*, 370.

[263] Y. Nishimoto, Y. Kita, H. Ueda, H. Imaoka, K. Chiba, M. Yasuda, A. Baba, *Chem. Eur. J.* **2016**, *22*, 11837.

[264] Y. Kaneko, Y. Kiyotsuka, H. P. Acharya, Y. Kabayashi, *Chem. Commun.* **2010**, *46*, 5482.

[265] No high-resolution mass spectrometry was made for this compound.

[266] Y. Zhang, Q. Tang, M. Luo, *Org. Biomol. Chem.* **2011**, *9*, 4977.

[267] N. Sakai, S. Asama, S. Anai, T. Konakahara, *Tetrahedron* **2014**, *70*, 2027.

[268] P. Shauna, R.-S. Liu, *Org. Lett.* **2016**, *18*, 412.

[269] U. Svanholm, V. D. Parker, *J. Am. Chem. Soc.* **1972**, *94*, 5507.

[270] Q. Tang, C. Zhang, M. Luo, *J. Am. Chem. Soc.* **2008**, *130*, 5840.

[271] J. Fotie, J. L. Rhodus, H. A. Taha, C. S. Reid, Heteroatom Chem. ***2012,*** 33*, 598.*

[272] Y. Sheng, Q. Chen, J. Yao, Y. Lu, H. Liu, S. Dai, *Angew. Chem. Int. Ed.* **2016**, *55*, 3378.

[273] G. Wang, H. Zhang, J. Zhao, W. Li, J. Cao, C. Zhu, S. Li, *Angew. Chem. Int. Ed.* **2016**, *55*, 5985.

[274] S. Chiba, L. Zhang, J.-Y. Lee, *J. Am. Chem. Soc.* **2010**, *132*, 7266.

Author's publications

- F. Cumine, S.-Z. Zhou, T. Tuttle, J. A. Murphy, *Org. Biomol. Chem.* **2017**, *15*, 3324.
- F. Cumine, A. Young, H.-U. Reissig, T. Tuttle, J. A. Murphy, *Eur. J. Org. Chem.* **2017**, 6867.