Aryloxide Promoted Catalyst Turnover in Lewis Base Organocatalysis

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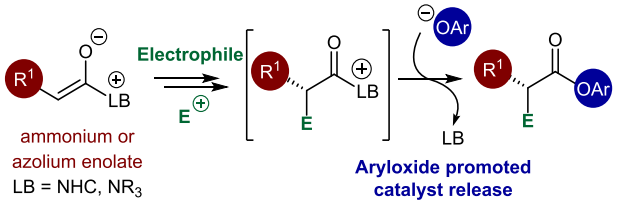
Dedicated to Prof. Herbert Mayr on the occasion of his 70th birthday.



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Abstract: This short review highlights select examples of enantioselective Lewis base promoted reactions that use tertiary amine (cinchona alkaloids, isothioureas and DMAP/PPY derivatives) or NHC catalysts and employ aryloxide promoted catalyst turnover from an acyl ammonium or azolium intermediate. This review focuses on the range of strategies that have been developed within this area, and discusses their evolution and context.

Key words Lewis base catalysis, catalyst turnover and release, aryloxide, isothiourea, NHC, tertiary amines

1. Introduction

Enantioselective Lewis base catalysis[1] is a popular field of research, with tertiary amine[2] and NHC catalysts[3] commonly employed to effect stereocontrol in numerous reaction processes. One of the most popular applications of these strategies is in formal cycloaddition reactions that utilise the *in situ* formation of ammonium or azolium enolates generated from ketenes,[4,5] carboxylic acid derivatives,[6] or α-functionalised aldehydes.[7] The nucleophilic enolate reacts with an electrophilic reagent containing a latent nucleophile that promotes catalyst turnover in an intramolecular event (Figure 1, eq 1). While this approach is tremendously successful and powerful, it highlights a key fundamental limitation in this branch of catalysis, with this strategy typically applied in formal [2+2], [3+2] or [4+2] cycloaddition processes. An alternative area within these fields requires an external nucleophile to promote catalyst turnover from an acyl ammonium or acyl azolium intermediate generated in the Lewis base catalytic cycle. In this context, this review offers a selective summary of enantioselective Lewis base promoted reactions that use tertiary amine (cinchona alkaloids, isothioureas and DMAP/PPY derivatives) or NHC catalysts and employ aryloxide promoted catalyst turnover from an acyl ammonium or azolium intermediate (Figure 1, eq 2). This review highlights the range of strategies that have been developed within this area. The aryloxide necessary for catalyst turnover can be generated through either (i) stoichiometric inclusion of a phenol as an additive (Section 2) or (ii) *in situ* catalytic generation of aryloxide (Section 3).

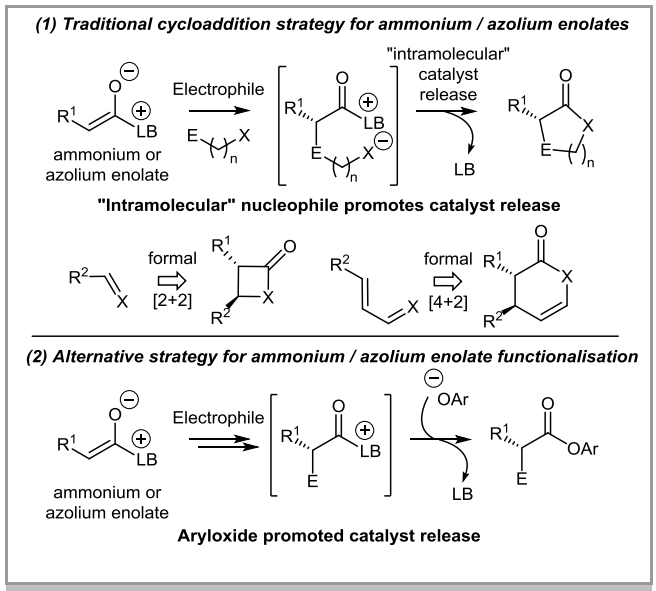
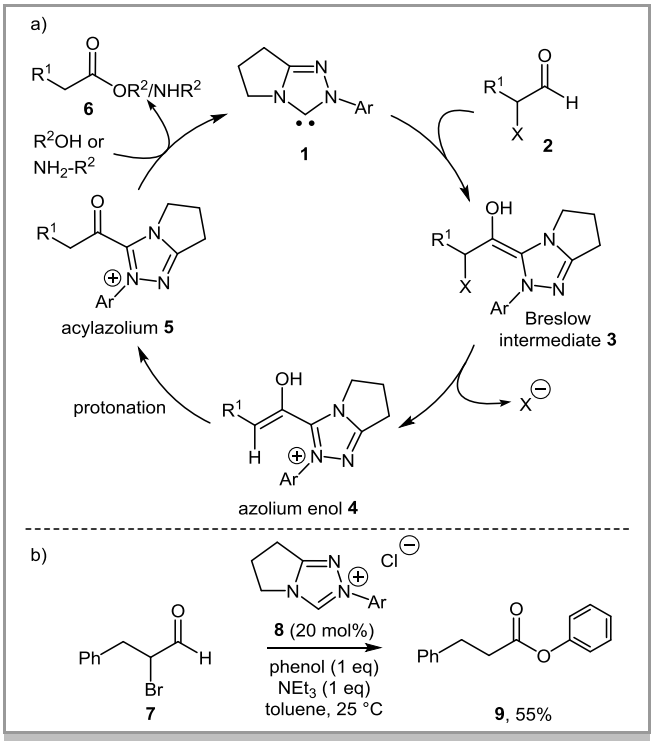


Figure 1 (1) Established "intramolecular" turnover strategies in Lewis base catalysed *C*1-ammonium/azolium enolate chemistry. (2) Aryloxide promoted catalyst turnover strategy.

2. Phenols as additives to promote catalyst turnover

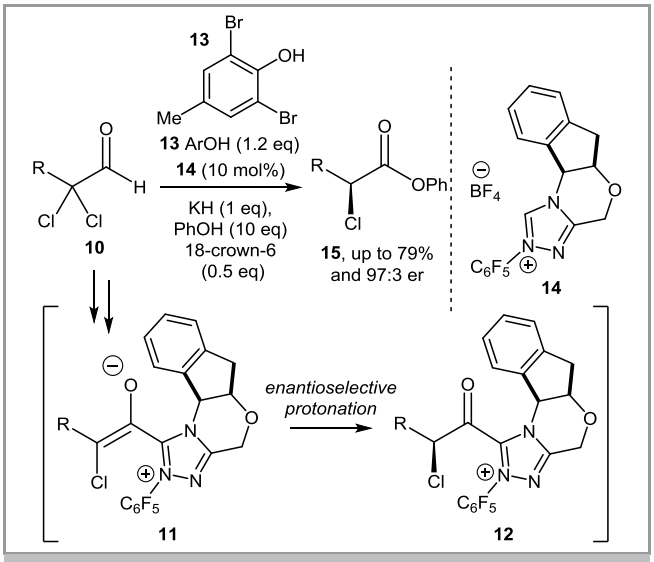
2.1 NHC catalysis with α-functionalised aldehydes and phenols. The formation of a "Breslow intermediate" in NHC catalysis is one of the basic principles on which significant advances have been based within the last 15 years. Pioneering work from Bode[8] and Rovis[9] extended this methodology to α-functionalised aldehydes bearing an α-leaving group. This allowed for sequential elimination of the leaving group from the Breslow intermediate **3**, forming the azolium enol species **4**. Subsequent tautomerisation forms acylazolium **5**, with catalyst turnover by an alcohol or amine leading to redox esterification or amidation processes (Scheme 1a). For example, using α-bromoaldehyde **7** with NHC **8** and phenol led to the formation of phenyl ester **9** in 55% yield (Scheme 1b).[10] Subsequent work revealed that addition of co-catalytic nucleophiles greatly increased yield of amide products in this process, promoting catalyst release from **5** to reform **1**.[11] While HOAt achieved the

greatest increase in yield, an electron-deficient pentafluorophenol also proved an excellent co-catalyst, presumably due to facile aryloxide promoted catalyst turnover.



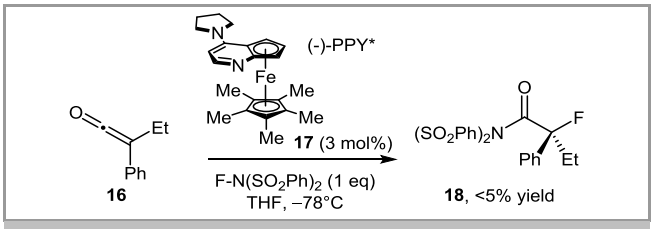
Scheme 1 Redox esterification with NHCs employing aryloxide turnover.

Rovis applied this methodology to generate enantioenriched aryl esters from α,α-dichloroaldehydes through enantioselective protonation of an *in situ* generated α-chloroenolate **11** (Scheme 2).[9] In this case, using a bulky acidic phenol **13** as a buffer negated background product epimerisation, while addition of an excess of another phenol for reaction turnover gave α-chloroesters **15** in good yield and excellent enantioselectivity (up to 97:3 er).[9]



Scheme 2 Catalytic enantioselective generation of α-chloro aryl esters.

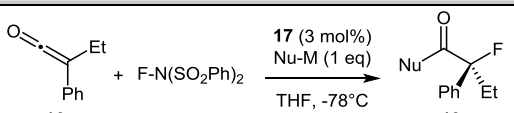
2.2 Enantioselective fluorination with aryloxide promoted catalyst turnover. In another strategy, Fu investigated the enantioselective synthesis of tertiary alkyl fluorides from disubstituted ketenes using planar chiral PPY* catalyst **17** and *N*-fluorobenzenesulfonimide (NFSI). Initial studies showed the difficulty of this transformation, with only trace product detected (Scheme 3).[12]



Scheme 3 Reaction of ketenes with NFSI in the presence of Lewis base catalyst (-)-PPY*.

It was hypothesised that this poor reactivity was due to poor catalyst turnover between the desired acyl ammonium intermediate and the *in situ* generated sulfonimide anion. To aid catalyst release the addition of an alternative nucleophile to promote turnover was investigated. Screening of stoichiometric nucleophilic additives showed that alkoxides were largely poor turnover promoters. However, aryloxides, in particular sodium pentafluorophenoxide, provided excellent reactivity and enantioselectivity (Table 1). This example provides an intriguing example of carefully tuning the co-nucleophile to ensure it only participates in a specific step of a given catalytic cycle. These optimised conditions provided a robust reaction protocol that tolerates a wide range of alkylarylketene substrates.

Table 1 Effect of nucleophile on the catalytic enantioselective synthesis of tertiary alkyl fluorides.



entry	Nu-M	yield (%)[a]	er (%)
1	-	<5	-
2	MeO-H	<5	-
3	PhNH-H	<5	-
4	*t*-BuO-Na	54	<2
5	PhO-Na	79	94:6
6	**C_6F_5O-Na**	**98**[b]	**99.5:0.5**
7	C_6F_5O-K	98	99.5:0.5

[a] Determined by GC analysis with an internal standard. [b] Yield of purified product.

The most plausible mechanism involves a chiral ammonium enolate intermediate **21**, which preferentially attacks the electrophilic source of fluorine, followed by aryloxide promoted catalyst turnover (Figure 2). Another possible mechanism, involving initial addition of the Lewis base **17** to NFSI to generate a chiral electrophilic source of fluorine, was ruled out based upon kinetic analysis. To support the role of aryloxide in promoting catalyst turnover, isolation of an acyl ammonium salt, followed by addition of sodium pentafluorophenoxide, gave product in excellent yield and ee.

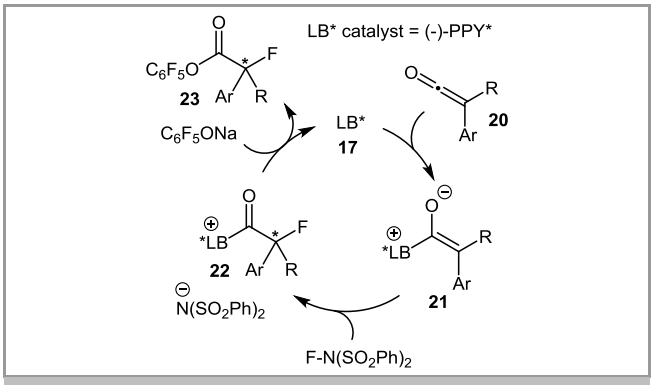


Figure 2 Postulated mechanism for Fu's enantioselective α-fluorination

3. *In situ* catalytic generation of aryloxide

The *in situ* catalytic generation of aryloxide can be achieved through using either (i) an electrophilic polyhalogenated quinone as an aryloxide precursor, or alternatively (ii) an α-functionalised aldehyde / activated aryl ester as an azolium or ammonium enolate precursor respectively.

3.1.1 Aryloxide promoted turnover generated from an electrophilic polyhalogenated quinone: overview. Lectka has employed a conceptually different system involving aryloxide promoted catalyst turnover for the catalytic enantioselective α-chlorination and α-bromination of acid chlorides. Key to this process is α-halogenation of an intermediate *C*1-ammonium enolate **26** with an electrophilic halogen source **27** (such as a polyhalogenated quinone) to generate an acyl ammonium aryloxide salt **28**. Catalyst turnover is promoted by acylation of the *in situ* generated aryloxide **29** (Figure 3).

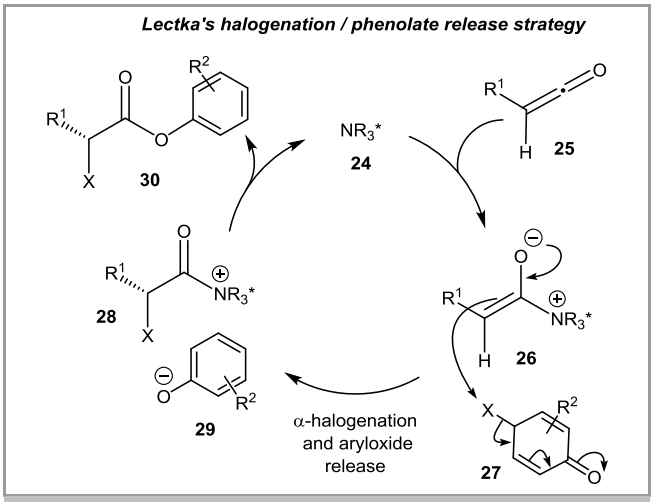
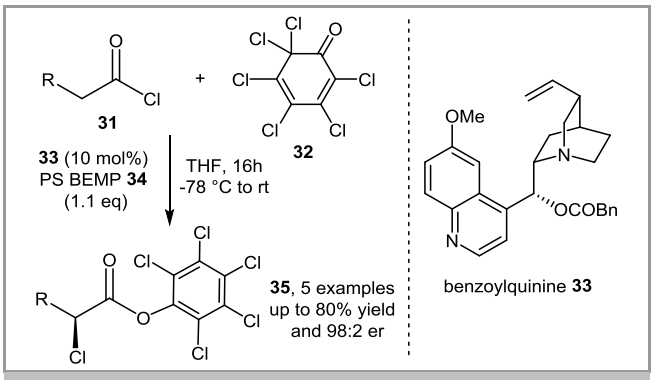


Figure 3 Lectka's halogenation and aryloxide release strategy.

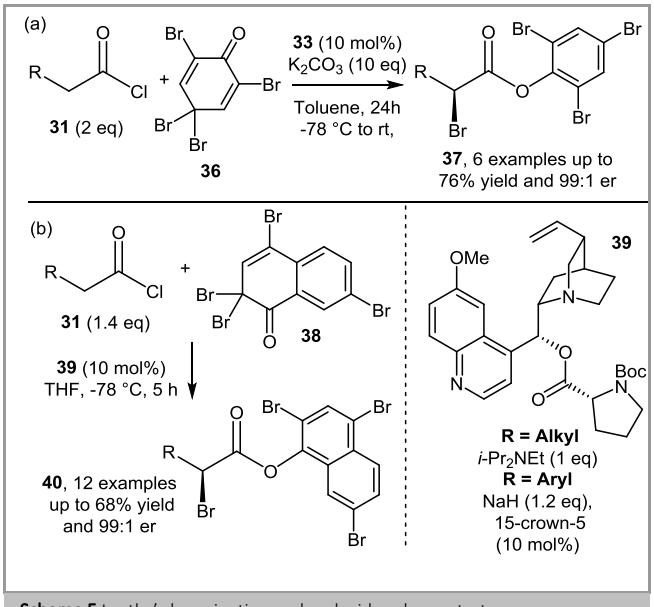
3.1.2 Enantioselecive α-chlorination.

Benzoylquinine **33** promotes the α-chlorination of various *in situ* generated monosubstituted ketenes with perchlorinated quinone **32** in the presence of PS BEMP **34** (a solid-phase base which aides ketene formation), giving a range of α-chloroesters **35** in up to 80% yield and excellent enantiocontrol (typically ≥97.5:2.5 er) (Scheme 4).[13] Alternatives bases (NaH/15-crown-5[14] or $NaHCO_3$/15-crown-5[15]) can be used to generate α-chloro esters with comparable yields and enantioselectivities, while a polymer-supported catalyst can be used in "column asymmetric synthesis" without compromising enantiocontrol.[16]



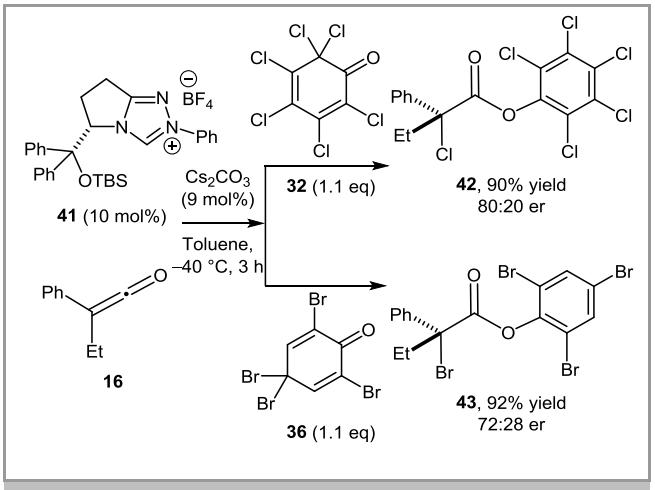
Scheme 4 Lectka's chlorination and aryloxide release strategy.

3.1.3 Enantioselective α-bromination. Further work demonstrated that benzoylquinine **33** catalyses the α-bromination of monosubstituted ketenes (formed *in situ* by dehydrohalogenation) using super stoichiometric K_2CO_3 as a shuttle base and polybrominated quinone. Various secondary α-bromoesters **37** were prepared in up to 76% yield and excellent enantiocontrol (up to 99:1 er) (Scheme 5a).[17] Although effective, this catalytic α-bromination methodology often resulted in low yields and diminished enantioselectivities on increased scale. This was addressed though the use of *N*-Boc-proline derived quinine derivative **39**, using either NaH or Hünig's base as a stoichiometric and electrophilic polybrominated **38** as a brominating agent. Under optimised conditions, a range of secondary α-bromoesters **40** were accessed in up to 68% yield and excellent enantiocontrol (typically ≥99:1 er) (Scheme 5b).[18] Notably, these processes could be carried out on gram-scale without loss in yield or enantioselectivity. Lectka has extended this methodology to enantioselective α-fluorination, although as this methodology does not employ catalyst turnover by aryloxide addition within the catalytic cycle, this is beyond the scope of this review.[19–21]



Scheme 5 Lectka's bromination and aryloxide release strategy.

Using this aryloxide-promoted catalyst turnover strategy, the NHC-catalysed halogenation of disubstituted alkylarylketenes has been reported by Smith and co-workers (Scheme 6).[22] Using chlorinating agent **32** with NHC precatalyst **41** at –40 °C proved optimal, providing α-chloroester **42** in up to 97% yield but with moderate enantioselectivity (up to 80:20 er). A single example also showed the viability of the corresponding bromination procedure, giving α-bromoester **43** in 92% yield and moderate 72:28 er.



Scheme 6 NHC-promoted halogenation and aryloxide turnover.

3.2.1 Aryloxide promoted catalyst turnover generated from an α-aryloxyaldehyde or aryl ester starting material: overview. Recently, an alternative approach has been introduced in this area that bypasses the need for either stoichiometric addition of a phenol as a turnover reagent, or catalytic generation of the aryloxide from the reaction of the azolium or ammonium enolate with the electrophilic partner.[23] Instead, an aryloxide acts as a leaving group from within an α-aryloxyaldehyde (in NHC catalysis) or aryl ester (in tertiary amine catalysis) *en route* to the azolium or ammonium enolate precursor respectively. The aryloxide released is used to perform catalyst turnover through addition to the α-functionalised acyl azolium (Figure 4a) or acyl ammonium (Figure 4b).

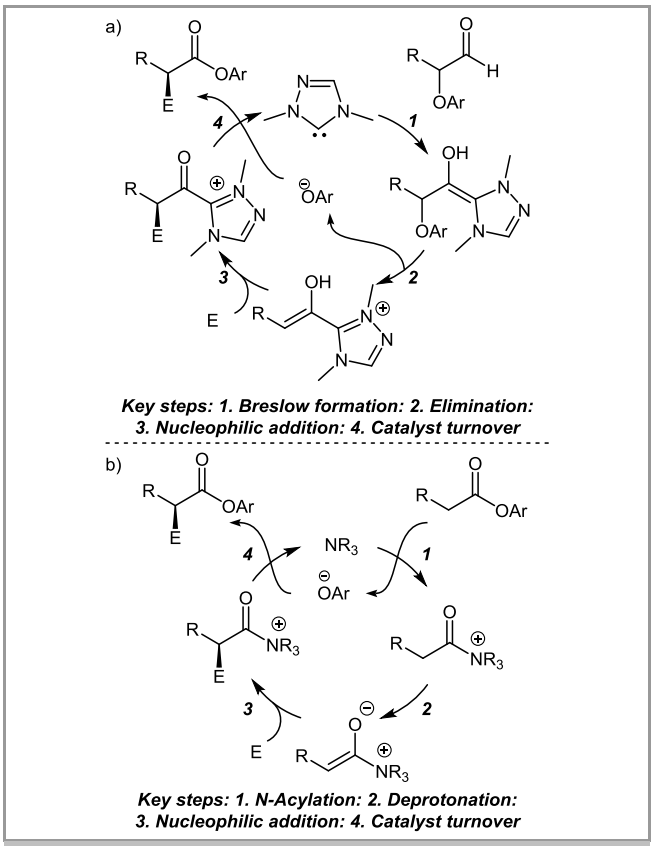
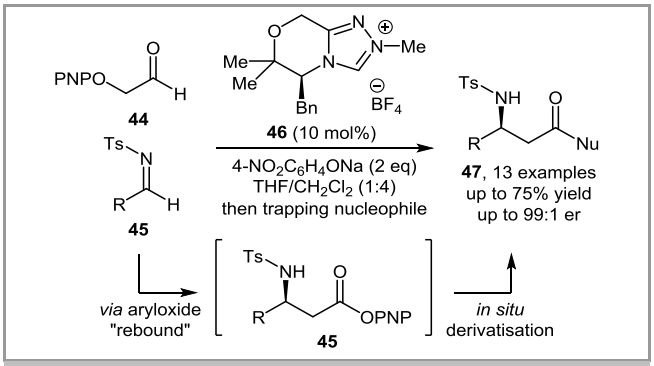


Figure 4 Generation of aryloxide en route to the azolium or ammonium enolate precursor. a) NHC catalysis. b) Tertiary amine catalysis.

3.2.2 NHC "rebound" catalysis. The first example of this approach was reported by Scheidt in 2009 while carrying out NHC-catalysed enantioselective Mannich reactions with α-aryloxyacetaldehydes.[23] Coupling of *N*-tosylimines with these substrates in the presence of an NHC precatalyst **46** and base afforded a range of β-amino acid derivatives **47** upon addition of a nucleophile (Scheme 7).



Scheme 7 NHC-catalysed enantioselective Mannich reaction to generate β-amino acid derivatives.

Importantly, the electronic properties of the α-aryloxy-substituent are crucial, with only the electron-deficient *p*-nitrophenoxide leaving group tolerated. Screening a range of bases showed that sodium *p*-nitrophenoxide substantially increased product yield compared to triethylamine or sodium hydride. In this case, two equivalents of sodium *p*-nitrophenoxide allows for both deprotonation of the NHC precatalyst and increases the concentration of the aryloxide required for catalyst turnover. The proposed catalytic cycle is

shown in Figure 5. To be successful, the nature of the aryloxide leaving group must be carefully balanced with respect to nucleophilicity and nucleofugality. The free species must be stable enough in its anionic form to act as a leaving group for the formation of the enol **51**, which will undergo a Mannich reaction with imine **45**. This aryloxide leaving group must, however, be nucleophilic enough to "rebound" after the imine-aldehyde *C-C* bond forming event, releasing the catalyst **48** and forming the ester product **53**.

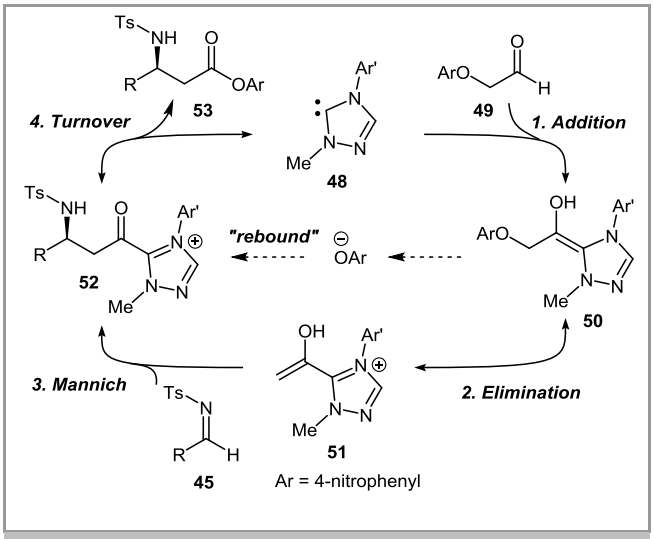
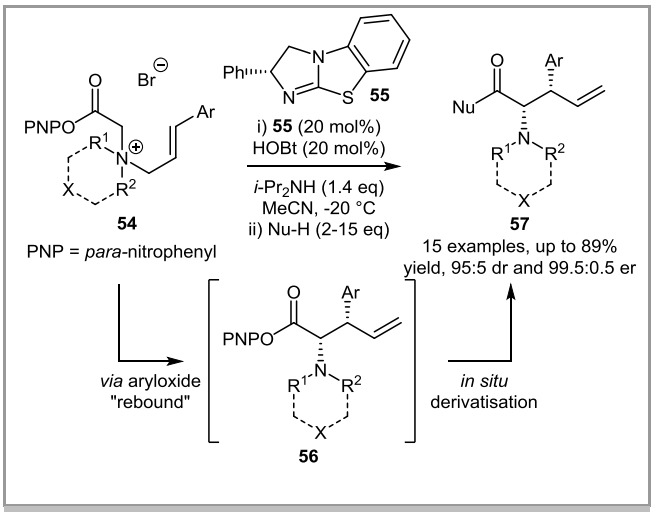


Figure 5 "Rebound" catalytic cycle using aryloxide elimination and catalyst turnover.

A feature of this process is the capability for *in situ* derivatisation of the aryl ester with a nucleophile. Benzylamine was used to furnish a range of β-amino acid derivatives from aryl imines. In a similar manner, the incorporation of an α-phenoxy substituent within an aldehyde allows for aryloxide turnover in NHC redox catalysis.[24]

3.2.3 Aryl esters as precursors. As an alternative strategy, aryloxide can be released by initial *N*-acylation of an aryl ester with a tertiary amine. Building upon work by Chi and co-workers using aryl esters as azolium enolate precursors using NHC catalysis,[25–31] the Smith group considered *p*-nitrophenoxide as a bifunctional anion in an enantioselective [2,3]-rearrangement of allylic ammonium ylides **54** promoted by the isothiourea benzotetramisole (BTM, **55**) with co-catalytic HOBt (Scheme 8).[32]



Scheme 8 Isothiourea-catalysed enantioselective [2,3]-rearrangement of allylic ammonium ylides.

It is proposed that *N*-acylation of BTM occurs to generate a dicationic acyl ammonium species **59** with release of *p*-nitrophenoxide (Figure 6). Deprotonation forms an ylide **60** that undergoes enantioselective [2,3]-rearrangement to give **61**. Esterification with HOBt to form intermediate **63** followed by transesterification with *p*-nitrophenoxide generates the desired product. The mechanism of this process has been investigated both with and without the HOBt co-catalyst, and using ^{19}F NMR to determine temporal concentration profiles of the reaction *in situ*.[33] Isotopic labelling ^{13}C (substrate) and ^{15}N (catalyst) was used to unambiguously identify post-rearrangement **61** as a reaction intermediate, with isotopic entrainment studies showing this intermediate to be formed irreversibly. In the absence of HOBt, the turnover-rate limiting step is proposed to be product-release by *p*-nitrophenoxide as ascertained through computational analysis. Addition of excess HOBt shifts the turnover-rate limiting step to be at, or prior to, the stage of [2,3]-rearrangement. Key interactions for stereochemical control have been identified (see **66**), with a 1,5 S•••O interaction providing transition state rigidity, resulting in high enantiocontrol, and cation-π interactions being responsible for high *syn*-diastereoselectivity (Figure 6).

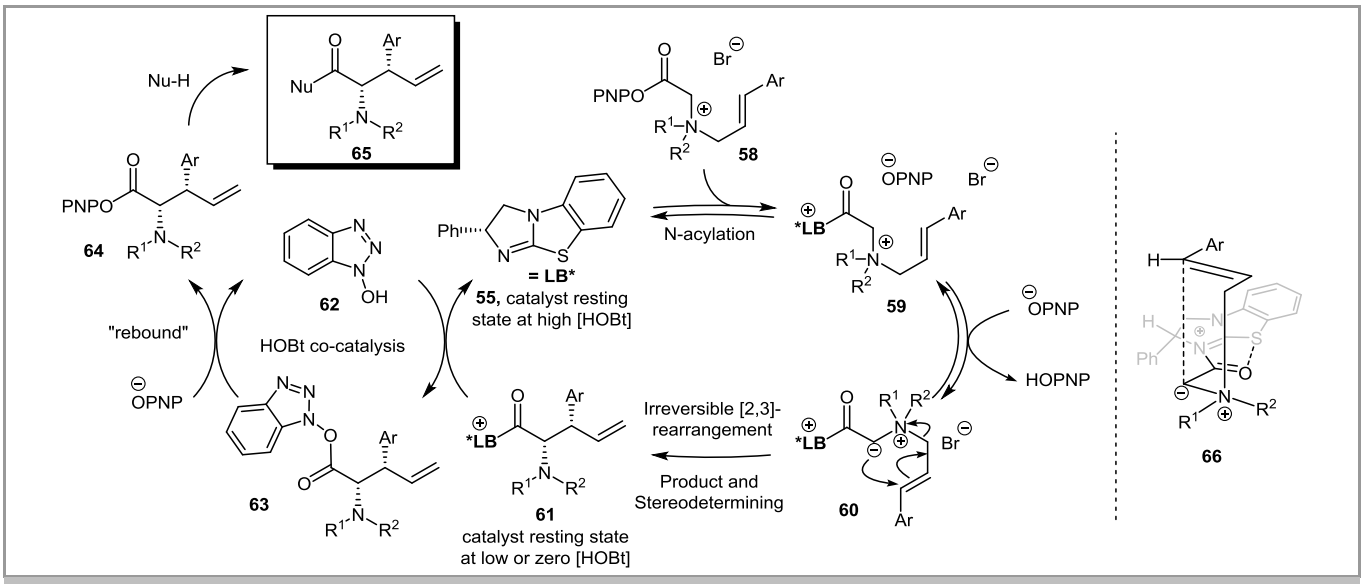
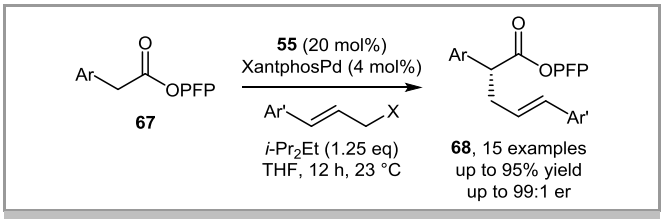


Figure 6 Mechanism of the enantioselective [2,3]-rearrangement of allylic ammonium ylides using catalytic benzotetramisole and 1-hydroxybenzotriazole.

Snaddon and co-workers recently reported an enantioselective allylation of pentafluorophenyl esters using a Xantphos-palladium catalyst and a Lewis base isothiourea in a proposed co-operative catalytic process (Scheme 9).[34]



Scheme 9 Snaddon's α-allylation of aryl esters using (+)-BTM with XantphosPd and allylic pseudo-halides.

The proposed mechanism for this system involves two co-operative cycles: a nucleophile-generating cycle and an electrophile-generating cycle (Figure 7). The pentafluorophenyl ester substrate **67** undergoes addition-elimination with the Lewis base isothiourea **55** to release the aryloxide, with subsequent deprotonation generating the ammonium enolate **69**. In the electrophilic cycle, the allylic species **70** coordinates to palladium(0) **71**, generating the reactive π-allyl complex **72** that is intercepted by the chiral ammonium enolate to give **73**. The aryloxide released from the aryl ester substrate may then "rebound" with the allylated species to release the Lewis base catalyst and reform the aryl ester functionality as **74**.

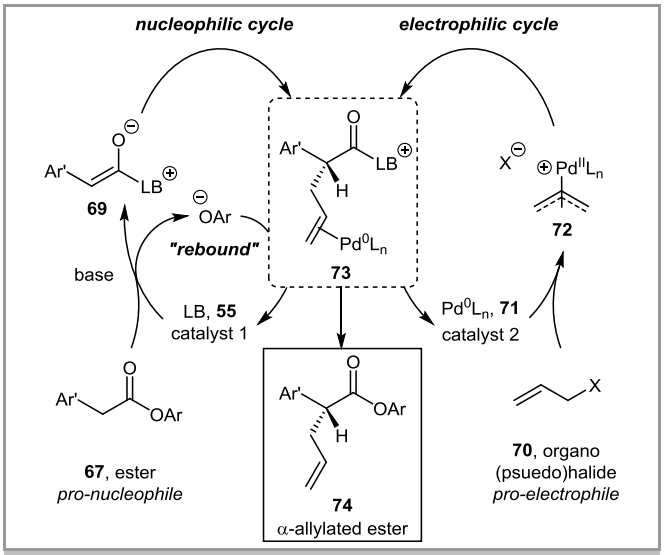
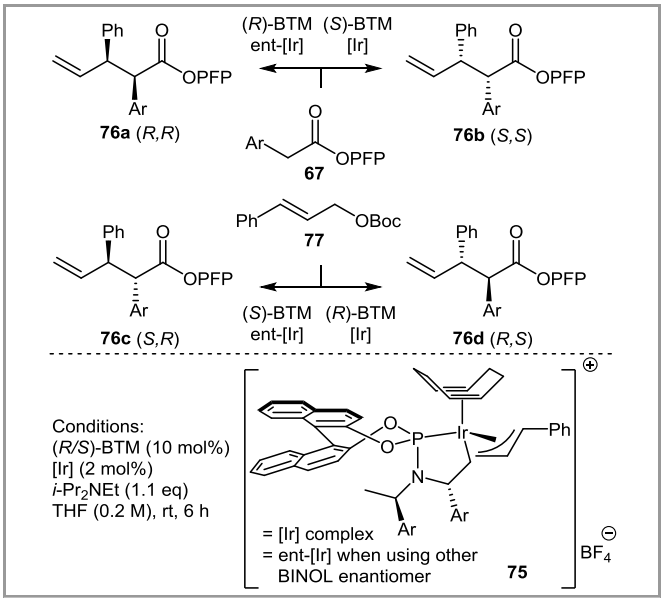


Figure 7 Proposed mechanism of Snaddon's α-allylation of aryl esters *via* co-operative palladium catalysis.

Following this work, Hartwig and co-workers reported a similar process, coupling Lewis base and iridium catalytic cycles.[35] In this case, BINOL (1,1'-bi-2-naphthol) is used as a chiral bidentate ligand. Combined with Lewis base catalysis to generate the enolate nucleophile, the chiral metallacyclic iridium complex **75** allows for stereodivergent allylic substitution, in which two adjacent stereocentres can be formed in all four combinations **76a-d** (Scheme 10). By pairing either enantiomer of the Lewis base and iridium catalysts, both the *syn* and *anti* diastereoisomers can be formed in high diastereoselectivity, with their respective enantiomers obtained with excellent enantioselectivity. Both enantiomers of the *anti* diastereoisomer are obtained in slightly lower dr, which may represent a mismatched catalyst-catalyst scenario.



Scheme 10 Synthesis of all four possible stereoisomeric products, each obtained in up to 99% yield and >99% ee. For (*R,R*) and (*S,S*) >20:1 dr observed, (*S,R*) and (*R,S*) >11:1 dr.

This process relies on a related catalytic cycle to Figure 7, with the isothiourea benzotetramisole **55** acylated by the activated ester, followed by deprotonation to generate the ammonium-enolate nucleophile (Figure 8). The crucial carbon-carbon bond-forming event takes place by addition of the enolate **79** to a chiral iridium coordinated allyl electrophile **82**, with the isothiourea controlling the configuration of the α-stereocentre, and the ligand bound iridium species controlling the configuration of the β-stereocentre.

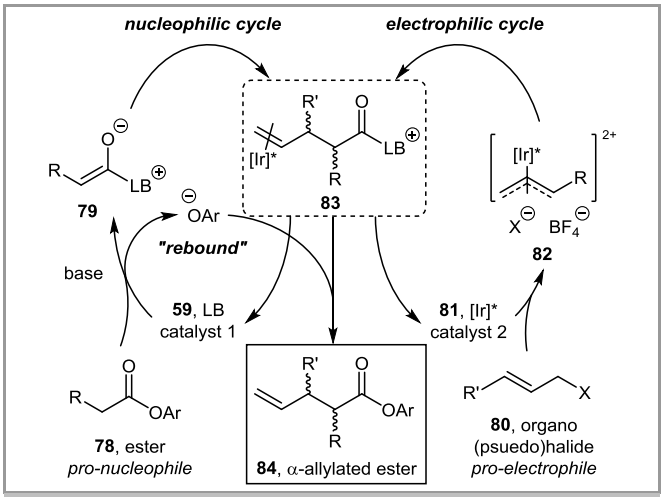


Figure 8 Proposed mechanism of Hartwig's stereodivergent α-allylation of aryl esters *via* co-operative isothiourea/Iridium catalysis.

4. Summary and Outlook

The use of aryloxide promoted catalyst release from an acyl ammonium or azolium intermediate has been utilised in a range of reaction processes. These include redox-catalysed acylations using phenols as additives, enantioselective halogenations using *in situ* generated aryloxide from an electrophilic starting material, as well as sigmatropic rearrangements and co-operative catalysis whereby the aryloxide is catalytically generated from an α-aryloxyaldehyde or activated ester starting material. It is clear that many new applications that utilise this latter strategy remain to be discovered in the coming years, with mechanistic aspects of the importance of aryloxide turnover leading to new avenues of catalysis research and a fundamental understanding of these reaction processes.

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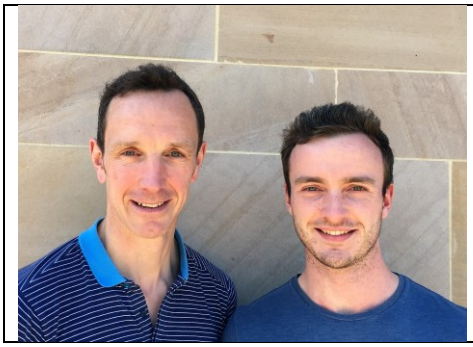

Andy Smith (left) was appointed as a Royal Society URF within the School of Chemistry at St Andrews in October 2005, being promoted to Professor in 2012. He was awarded the RSC Merck Award in 2014 and is Director of the EPSRC CDT in Critical Resource Catalysis (CRITICAT), a joint initiative by St Andrews, Edinburgh and Heriot-Watt Universities. His research programme is focused on catalytic enantioselective reaction processes using Lewis base catalysts and developing a comprehensive mechanistic understanding of these transformations. Will Hartley (right) received his MChem degree from the University of Sheffield in 2016. He is currently carrying out his PhD studies under the supervision of Andy Smith funded through the CRITICAT CDT, with his project focused upon enantioselective Lewis base catalysed reaction processes.