Aryloxide Promoted Catalyst Turnover in Lewis Base Organocatalysis

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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, NHCl, tertiary amines

1. Introduction

Enantioselective Lewis base catalysis is a popular field of research, with tertiary amine and NHC catalysts 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, carboxylic acid derivatives, or α-functionalised aldehydes. The nucelophile reacts with an electrophilic reagent containing a latent nucelophile 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).

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 and Rovis 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, forming the azolium enol species. 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-bromoadehyde 7 with NHCl 8 and phenol led to the formation of phenyl ester 9 in 55% yield (Scheme 1b). 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. While HOAt achieved the
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.

**Scheme 2** Catalytic enantioselective generation of α-chloroaryl 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-fluorobenzenesulfonylimide (NFSI). Initial studies showed the difficulty of this transformation, with only trace product detected (Scheme 3). 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 alkyarylketene substrates.

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

<table>
<thead>
<tr>
<th>entry</th>
<th>Nu-M</th>
<th>yield (%)</th>
<th>er (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>MeO-H</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>PhNH-H</td>
<td>&lt;5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>t-BuO-Na</td>
<td>54</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5</td>
<td>PhO-Na</td>
<td>79</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>C₆F₅O-Na</td>
<td>98^b</td>
<td>99.5:0.5</td>
</tr>
<tr>
<td>7</td>
<td>C₆F₅O-K</td>
<td>98</td>
<td>99.5:0.5</td>
</tr>
</tbody>
</table>

^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.
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 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 C1-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).

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3.1.2 Enantioselective 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 aids 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-514 or NaHCO3/15-crown-515) 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 K2CO3 as a shuttle base and polybrominated quinone. Various secondary α-bromoesters 37 were prepared in up to 76% yield and excellent enantiocntrol (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 enantiocntrol (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 alkyarylketenes has been reported by Smith and co-workers (Scheme 6).\(^\text{22}\) Using chlorinating agent 32 with NHC precatalyst 41 at \(-40^\circ\text{C}\) proved optimal, providing \(\alpha\)-chloroester 42 in up to 97\% yield but with moderate enantioselectivity (up to 80:20 \(\text{er}\)). A single example also showed the viability of the corresponding bromination procedure, giving \(\alpha\)-bromoester 43 in 92\% yield and moderate 72:28 \(\text{er}\).

### 3.2.1 Aryloxide promoted catalyst turnover generated from an \(\alpha\)-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.\(^\text{23}\) Instead, an aryloxide acts as a leaving group from within an \(\alpha\)-aryloxyaldehyde (in NHC catalysis) or aryl ester (in tertiary amine catalysis) \(\text{en route}\) to the azolium or ammonium enolate precursor respectively. The aryloxide released is used to perform catalyst turnover through addition to the \(\alpha\)-functionalised acyl azolium (Figure 4a) or acyl ammonium (Figure 4b).

### 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 \(\alpha\)-aryloxyacetaldheydes.\(^\text{23}\) Coupling of \(N\)-tosylimines with these substrates in the presence of an NHC precatalyst and base afforded a range of \(\beta\)-amino acid derivatives 47 upon addition of a nucleophile (Scheme 7).

![Scheme 6](image)

**Scheme 6** NHC-promoted halogenation and aryloxide turnover.

![Figure 4](image)

**Figure 4** Generation of aryloxide \(\text{en route}\) to the azolium or ammonium enolate precursor. a) NHC catalysis. b) Tertiary amine catalysis.

![Scheme 7](image)

**Scheme 7** NHC-catalysed enantioselective Mannich reaction to generate \(\beta\)-amino acid derivatives.

Importantly, the electronic properties of the \(\alpha\)-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.

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.

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, 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).

It is proposed that N-acylation of BTM occurs to generate a dicaticonic acyl ammonium species 59 with release of p-nitrophenoxide (Figure 6). Deprotonation forms anylide 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 19F NMR to determine temporal concentration profiles of the reaction in situ. Isotopic labelling 13C (substrate) and 15N (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 enantiomeric purity, and cation-π interactions being responsible for high syn-diastereoselectivity (Figure 6).
Snaddon and co-workers recently reported an enantioselective allylation of pentafluorophenyl esters using a Xanthos-palladium catalyst and a Lewis base isothiourea in a proposed cooperative catalytic process (Scheme 9).\textsuperscript{34}

The proposed mechanism for this system involves two cooperative cycles: a nucleophile-generating cycle and an electrophile-generating cycle (Figure 7). The pentafluorophenyl ester substrate \textit{67} undergoes addition-elimination with the Lewis base isothiourea \textit{55} to release the aryl oxide, with subsequent deprotonation generating the ammonium enolate \textit{69}. In the electrophilic cycle, the allylic species \textit{70} coordinates to palladium(0) \textit{71}, generating the reactive \(\pi\)-allyl complex \textit{72} that is intercepted by the chiral ammonium enolate to give \textit{73}. The aryl oxide 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 \textit{74}.

Following this work, Hartwig and co-workers reported a similar process, coupling Lewis base and iridium catalytic cycles.\textsuperscript{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 metallaacyclic iridium complex \textit{75} allows for stereodivergent allylic substitution, in which two adjacent stereocentres can be formed in all four combinations \textit{76a-d} (Scheme 10). By pairing either enantiomer of the Lewis base and iridium catalysts, both the \textit{syn} and \textit{anti} diastereoisomers can be formed in high diastereoselectivity, with their respective enantiomers obtained with excellent enantioselectivity. Both enantiomers of the \textit{anti} diastereoisomer are obtained in slightly lower \textit{dr}, which may represent a mismatched catalyst-catalyst scenario.
This process relies on a related catalytic cycle to Figure 7, with the isothiourea benzotriazolium 55 acylated by the activated ester, followed by deprotonation to generate the ammonium enolate nucelophile (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.

4. Summary and Outlook

The use of aryl ether promoted catalyst release from an acyl ammonium or azolium intermediate has been utilised in a range of reaction processes. These include rebox-catalysed acylations using phenols as additives, enantioselective halogenations using in situ generated aryl oxide from an electrophilic starting material, as well as sigmatropic rearrangements and cooperative catalysis whereby the aryl oxide is catlytically generated from an α-arylalkylaldehyde 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 aryl oxide turnover leading to new avenues of catalysis research and a fundamental understanding of these reaction processes.

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References


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.