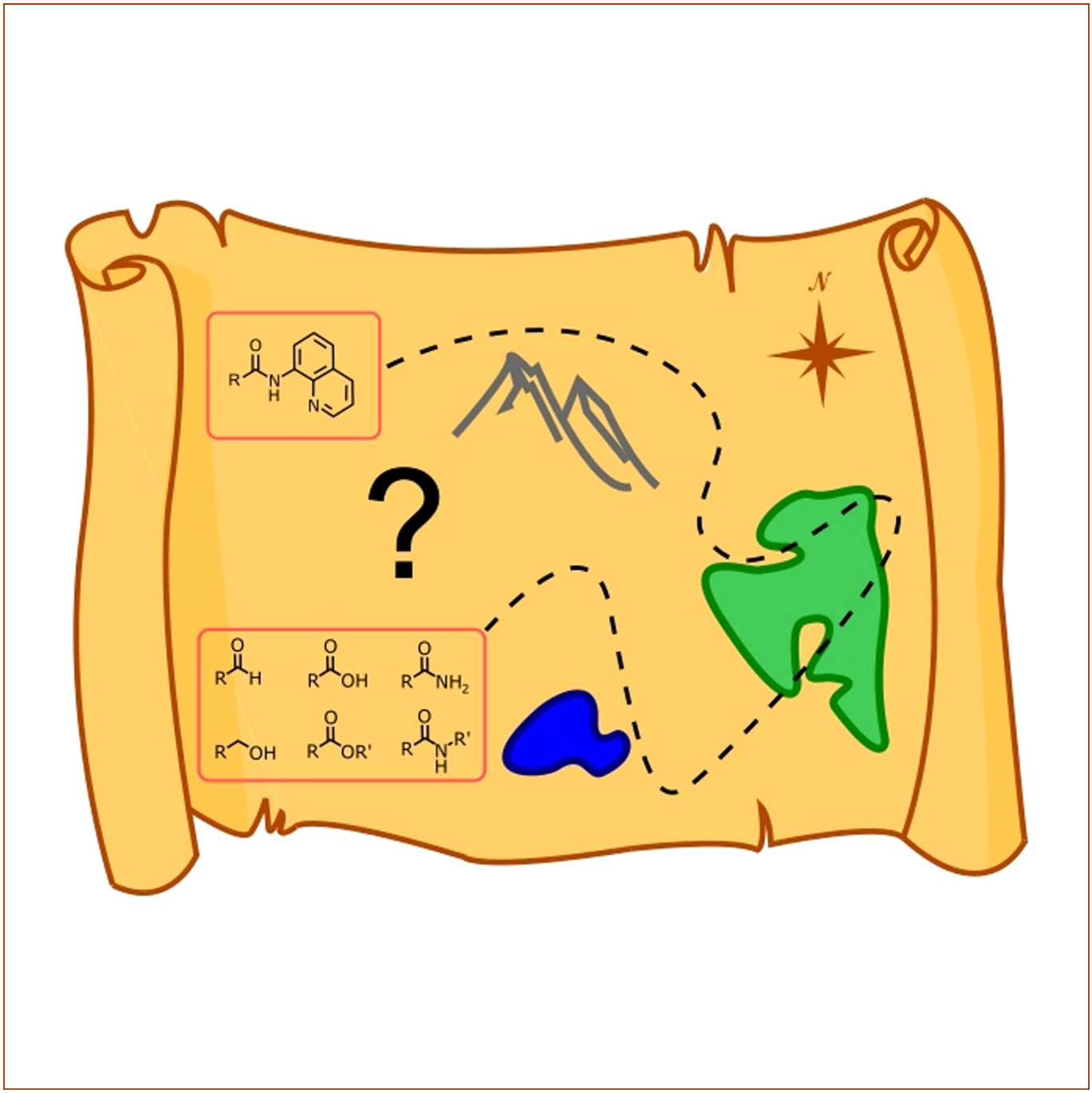
Synthetic Methods

A Guide to Directing Group Removal: 8-Aminoquinoline

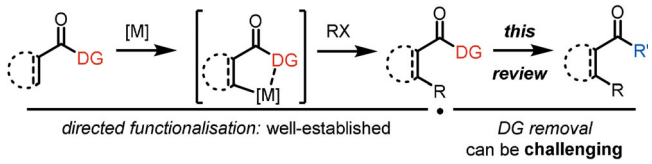
Liam S. Fitzgerald[a] and Miriam L. O'Duill*[b]



Abstract: The use of directing groups allows high levels of selectivity to be achieved in transition metal-catalyzed transformations. Efficient removal of these auxiliaries after successful functionalization, however, can be very challenging. This review provides a critical overview of strategies used for removal of Daugulis' 8-aminoquinoline (2005–2020), one of the most widely used *N*,*N*-bidentate directing groups. The limitations of these strategies are discussed and alternative approaches are suggested for challenging substrates. Our aim is to provide a comprehensive end-users' guide for chemists in academia and industry who want to harness the synthetic power of directing groups—and be able to remove them from their final products.

Introduction

The field of transition metal-catalyzed C–H activation and alkene functionalization has been rapidly expanding in the last few decades, finding application in methodology development, total synthesis and medicinal chemistry. Achieving high levels of selectivity in these transformations can be challenging and is often governed by the innate reactivity of the substrates. High degrees of regio-, stereo- and in some cases enantioselectivity—that can overrule this innate reactivity—are achieved with directing groups (DGs). These auxiliaries, which are covalently attached to the substrate, coordinate to the metal catalyst and direct it to the vicinity of the desired reactive center. The selectivity of the subsequent transformation is controlled by the formation of the kinetically and thermodynamically favored metallacycle intermediate (Scheme 1).[1–3] Both mono- and bidentate directing groups have been developed; the latter often show stronger coordination to the metal catalyst and thus fewer side reactions.[4]



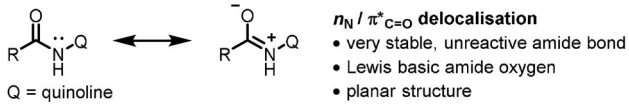
Scheme 1. Directing groups in synthesis and methodology. (In this review, DG = 8-aminoquinoline.)

Since its introduction by Daugulis in 2005,[5] 8-aminoquinoline (AQ) (Scheme 3) has evolved into one of the most versatile and widely used *N*,*N*-bidentate directing groups. (For a recent review on other bidentate directing groups, see reference [4]).[4] It coordinates strongly but reversibly to transition metal catalysts, selectively forming stable 5- or 6-membered chelates and stabilizing the high oxidation states required for C–H activation and alkene functionalization.[2] AQ's wide applicability could also be explained by its ease of use: the directing group is commercially available (Sigma Aldrich catalogue, September 2020: 9.04 €/g) and easily attached to most carboxylic acid substrates by straightforward amide coupling. The full range and utility of synthetic transformations facilitated by the AQ directing group has been the topic of excellent recent reviews and will not be covered here.[6–8]

A critical aspect in auxiliary chemistry, however, is the removal of the directing group after successful functionalization (Scheme 1). Clearly, this step needs to be highly efficient to justify the use of a directing group strategy in any synthetic route. 8-Aminoquinoline is often advertised as "easily removable" and "reusable", however its cleavage can in fact be very challenging and there exist numerous examples in the literature where all attempts to remove the auxiliary were unsuccessful (see Section 1.1.1.2), due to the high resonance stability of the amide bond. This review gives a critical overview of the current strategies used for 8-aminoquinoline removal (as of October 2020), their limitations, and suggestions for as-of-yet unused approaches. It is intended as a guide to synthetic chemists planning to use 8-aminoquinoline or similar amide directing groups to access their target molecules.

The discussion will focus on the reactivity of the AQ amide bond. While its high stability and geometric rigidity make it compatible with a wide variety of catalytic conditions, they also explain why AQ removal can require forcing conditions. This low reactivity is due to delocalization of the nitrogen lone pair (n_N) into the carbonyl group ($\pi^*_{C=O}$) which reduces the electrophilic character of the amide bond, while making the carbonyl oxygen Lewis basic (Scheme 2).[9–12] In the context of directing group removal, three main conclusions can be drawn from this:

(1) Amides are relatively unreactive towards nucleophilic attack, especially compared to other carbonyl derivatives. This may lead to selectivity issues and/or functional group incompatibility in the DG cleavage step. The review will start with a discussion of classic hydrolysis/solvolysis of the amide bond under strongly acidic or basic conditions to



Scheme 2. Resonance stabilization of the AQ amide bond.

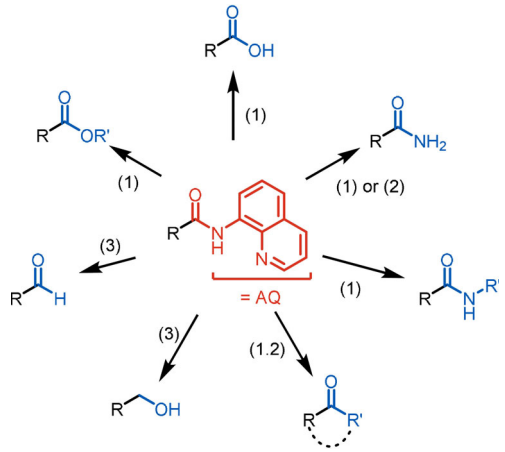
[a] *L. S. Fitzgerald*
School of Chemistry, National University of Ireland Galway
University Road, Galway, H91 TK33 (Ireland)
[b] *Dr. M. L. O'Duill*
School of Chemistry, University of Nottingham
University Park, Nottingham, NG7 2RD (UK)
E-mail: miriam.oduill@nottingham.ac.uk
The ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202100093.

afford carboxylic acids, esters and amide products, and highlight substrates for which this approach is inappropriate or unsuccessful (Section 1.1) (Scheme 3).

(2) The electrophilicity of the AQ-amide can be increased by coordination to Lewis acidic metals, leading to AQ-cleavage with concomitant inter- or intramolecular C–O, C–N and C–C bond formation. This strategy is described in Section 1.2.

(3) Disrupting or reducing $n_N/\pi^*_{C=O}$ delocalization destabilizes the amide bond and increases its reactivity. This can be achieved by substituting the nitrogen with bulky, electron-withdrawing groups and is discussed in Section 1.3.

Similar reactivity principles will be considered in the description of oxidative (Section 2) and reductive (Section 3) methods for amide bond cleavage that furnish amide and aldehyde/alcohol products, respectively.



Scheme 3. Scope of the review (with reference to the sections of the review that the relevant transformations are discussed in): Strategies for 8-aminoquinoline removal and their limitations.

1. Nucleophilic Cleavage of the Amide Bond

1.1. Brønsted acid/base mediated solvolysis

1.1.1. Hydrolysis and alcoholysis

By far the most common method for AQ removal from unhindered amide substrates is solvolysis of the amide bond under strongly acidic or basic conditions (often conc. HCl or NaOH) in water[13] or alcoholic solvents[14] to afford the carboxylic acid or ester products with recovery of the 8-aminoquinoline directing group (Scheme 4). Due to the stability of the amide bond and its resulting low reactivity (see Introduction), harsh reaction conditions are required (concentrated acid/base, 100–130 °C, reaction times ranging from several hours to several days) which limit the functional group compatibility of this method. Steric bulk around the amide bond in particular, can lead to very low or no reactivity.

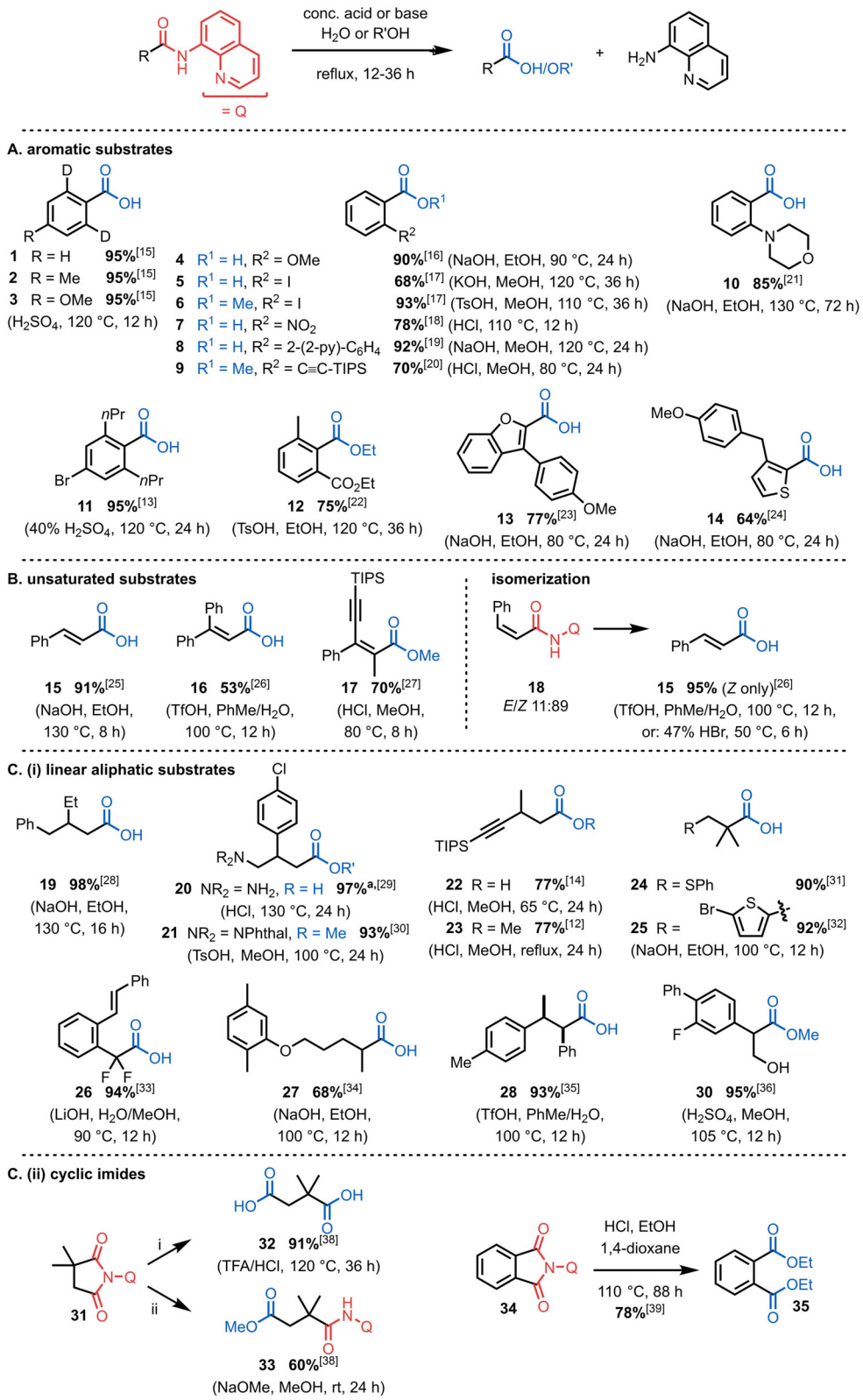
This method generally gives high yields for aromatic (**1**–**12**)[13,15–22] and heteroaromatic AQ-amides (**13**–**14**)[23,24] (Scheme 4 A). Electronics have a largely negligible effect on hydrolysis yield (**1**–**7**), while sterics are very important. One bulky substituent *ortho* to the amide can often be tolerated (**4**–**10**)—though in some cases reaction times may increase substantially (**10**)—but the yields drop considerably for *ortho*,*ortho*-disubstituted aromatics (**11**–**12**) which require the use of very strong acids and long reaction times for successful hydrolysis and are often conspicuous in their absence from successful substrates scopes.

Olefinic, including α,β-unsaturated amides can be converted to the corresponding carboxylic acids and esters in moderate to good yields (**15**–**18**, Scheme 4 B),[25–27] however the conditions unsurprisingly favor the formation of the thermodynamic *E*-alkene products. Removal of AQ from *Z*-cinnamic acid derivative **18**, for example, required highly acidic conditions (TfOH, PhMe/H_2O, 100 °C, 12 h; or 47% HBr, 50 °C, 6 h) under which *Z*-to-*E* isomerization of the double bond could not be avoided. Attempts to hydrolyze the amide bond under milder conditions in an effort to obtain *Z*-cinnamic acid failed.[26]

Unhindered, linear, aliphatic substrates with alkyl, (hetero)aryl, amine, alcohol and (thio)ether substituents generally afford good hydrolysis/alcoholysis yields (**19**–**30**, Scheme 4 Ci),[14,28–36] however certain functional groups are incompatible with strongly Brønsted acidic/basic conditions (see also Scheme 7). For instance, phthaloyl protecting groups are hydrolyzed concomitantly with the AQ directing group (**20**).[29] Alcoholysis conditions can be slightly more compatible (**21**),[30] and Lewis acidic (see Section 1.2.1) or oxidative CAN conditions (see Section 2.2) can offer a milder alternative to preserve some of these functionalities.

Liam Fitzgerald received his BSc from Maynooth University in 2014. He is currently pursuing his PhD at the National University of Ireland, Galway under the supervision of Dr. Miriam O'Duill and Prof. Paul Murphy. His research currently focuses on the deuteration of bioactive molecules using C–H activation.

Miriam O'Duill received her DPhil in Organic Chemistry from the University of Oxford in 2016, where she carried out research on late-stage fluorination with Prof. V. Gouverneur. She spent two years as a postdoctoral fellow at the Scripps Research Institute, investigating selective catalytic alkene functionalization with Prof. K. M. Engle. In 2018, Miriam began her independent career at NUI Galway, before accepting a position as Assistant Professor at the University of Nottingham in 2020. Her research interests include transition metal-catalyzed late-stage functionalization.



Scheme 4. Solvolysis of AQ-amides under acidic or basic conditions. [a] Concomitant hydrolysis of *N*-Phth protecting group ($NR_2 = NH_2$).

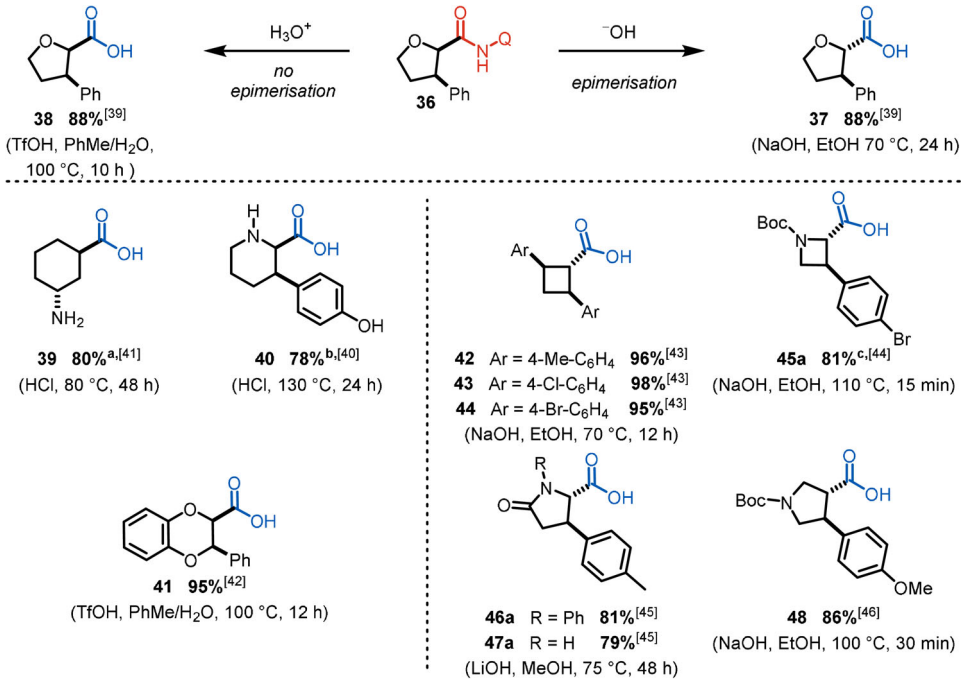
Small substituents *alpha* to the AQ-amide bond pose no challenge (**24**–**27**),[31–34] but harsher conditions are required for substrates with bulky *alpha*-substituents. Hydrolysis of a substrate bearing a bulky phenyl substituent *alpha* to the reactive AQ-amide center to give carboxylic acid **28** was unsuccessful under standard acidic or basic conditions (conc. HCl, 100 °C, 12 h; or NaOH/EtOH, 80 °C, 12 h), but use of a superacid (TfOH, $PhMe/H_2O$, 100 °C, 12 h) furnished the desired carboxylic acid

product in high yields.[35] If possible, sterically bulky *alpha*-substituents can also be derivatized to smaller groups before AQ removal to make this step more efficient (*e.g.* **78**, Scheme 10).[37]

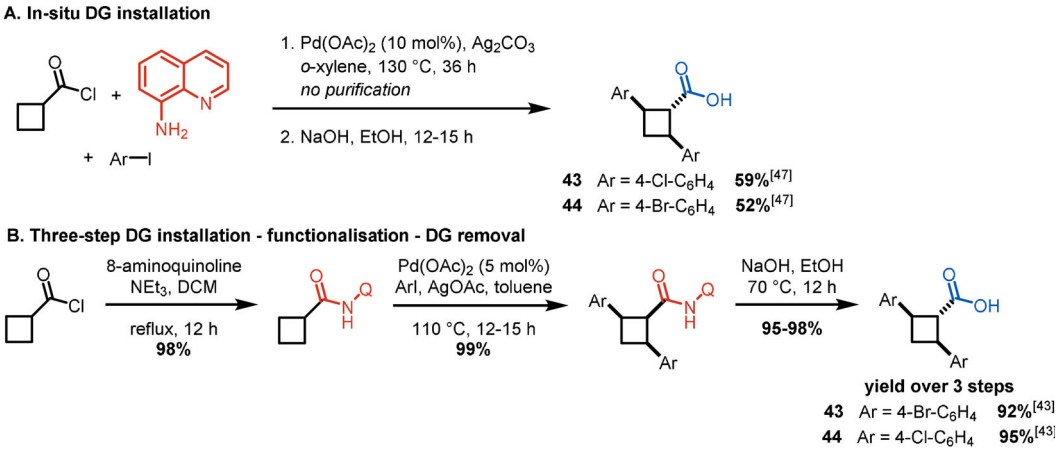
Conversely, even though imides are generally more electrophilic than amides (see Section 1.1.2)—and indeed phthalimide AQ-derivatives undergo straightforward acid/base-catalyzed transamidation at room temperature (see Scheme 18)—succinimide **31** and phthalimide **34** require forcing hydrolysis conditions (Scheme 4Cii).[38,39]

Care must be taken to consider the stereochemical outcome of the reaction when hydrolyzing substrates with chiral information *alpha* to the AQ-amide (Scheme 5).[40–46] As illustrated for cycloalkane AQ-derivative **36**, basic hydrolysis causes epimerization at the reactive carbonyl center (**37**), while hydrolysis under acidic conditions occurs with retention at this stereocenter (**38**).[40] However, cycloalkyl amides are often unreactive under standard acid hydrolysis conditions using HCl (see Section 1.1.1.2 for more information on the reduced reactivity of cycloalkyl amides), and stronger acids (*e.g.* TfOH or TsOH) can be required for a successful transformation (**41**).[42] Alternatively, epimerization can also be avoided by pre-activating the AQ-amide by *N*-Boc substitution (see Section 1.3.1)[46] or ozonolysis (Section 2.1)[45] prior to basic hydrolysis.

An obvious limitation of auxiliary chemistry is the requirement for their addition and removal, adding two steps to the



Scheme 5. Stereochemical outcome of acidic/basic hydrolysis of cycloalkyl AQ-amides. [a] Concomitant hydrolysis of *N*-succinimide protecting group. [b] Concomitant hydrolysis of *N*-Boc protecting group and *para*-methoxy benzyl ether. Yield based on AQ recovery. [c] Yield over two steps: 1. *N*-Boc protection, 2. hydrolysis.



Scheme 6. *In situ* installation of AQ and removal from crude functionalization product without prior purification (**A**) compared to 3-step DG installation—functionalization—DG removal protocol (**B**).

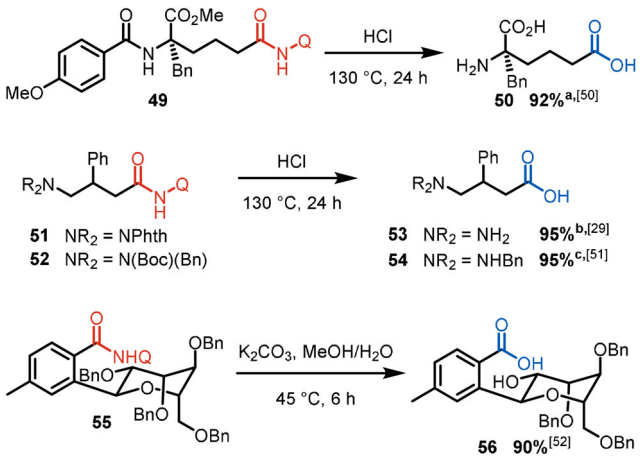
synthetic sequence. The Babu group have had some success with *in situ* installation of the AQ directing group and functionalization in one pot, followed by AQ removal from the crude product prior to purification (Scheme 6 A).[47–49] While this strategy may be more time-efficient since it only requires one purification step, yields are not yet comparable to the traditional three-step DG installation—functionalization—DG removal protocol with purification after each step (Scheme 6 B).

1.1.1.1. Limitations: Side-reactions

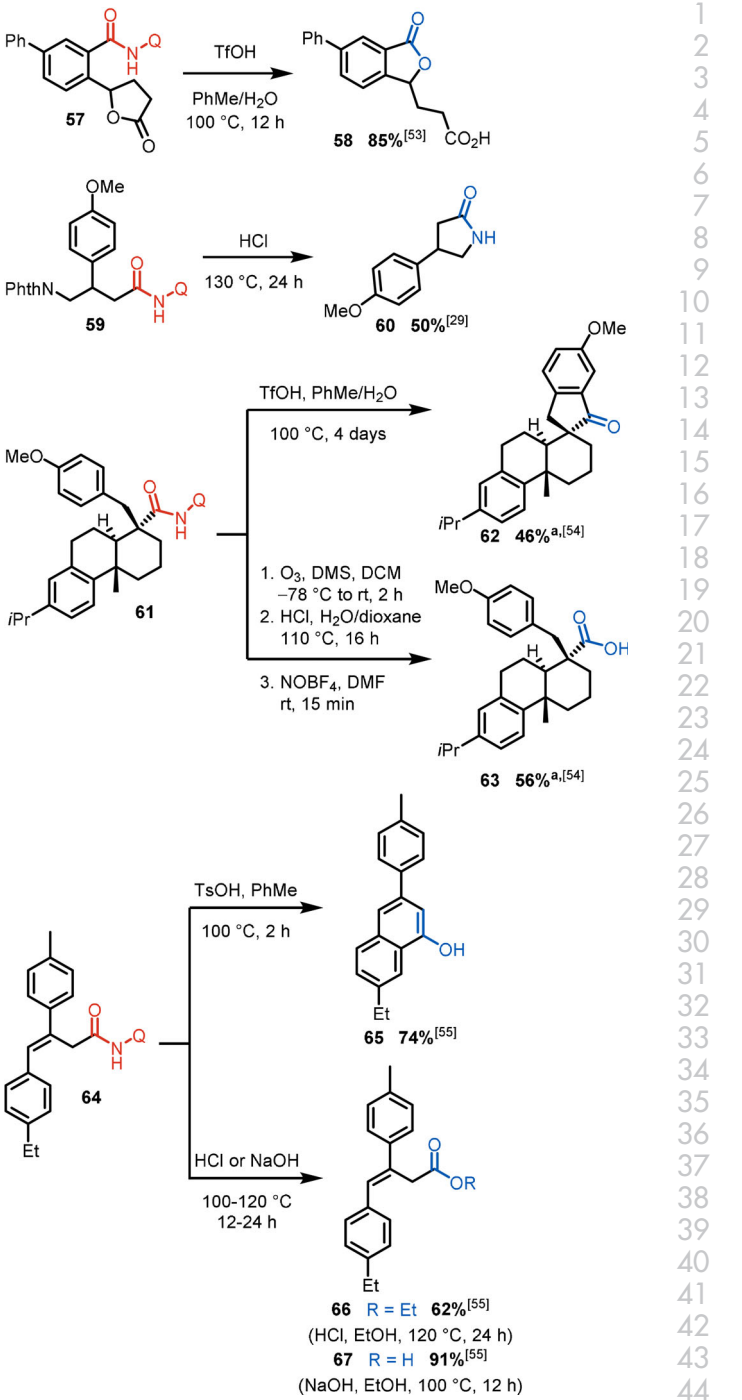
As shown above, acid or base-mediated solvolysis of the amide bond requires harsh reaction conditions (concentrated acid/base, reaction temperatures of 100–130 °C, reaction times ranging from several hours to several days) which not only limits its functional group compatibility, but can also lead to side-reactions.

Isomerization to the thermodynamic *E*-alkene (**15**, Scheme 4) and the hydrolysis of acid- or base-labile functional groups have already been touched upon (**20**, **39**–**40**, **45 a**, Scheme 4 & Scheme 5), and further examples of the latter are given in Scheme 7 below. Due to the stability of the amide bond, it is extremely challenging to achieve chemoselectivity in the presence of more reactive functional groups, as demonstrated by global deprotection of all acid-sensitive groups in **49** (Scheme 7).[50] As expected, *N*-Phth (**51**)[29] and *N*-Boc (**52**)[51] protecting groups are hydrolyzed during AQ-removal. While benzyl protecting groups are generally inert under the conditions used for acid/base hydrolysis of AQ-amides (**54**), this is not always the case, as can be seen in the base-mediated AQ-cleavage of **55**, during which the equatorial O-Bn group also underwent deprotection.[52]

Deprotection of nucleophilic functional groups can cause intramolecular cyclisation (**58**–**60**, Scheme 8).[29,53–55] These side-reactions can be both a limitation (if unexpected), or an opportunity to access new product classes or methodology (if predictable). Due to the forcing reaction conditions, nucleophilic functional groups are not always necessary to trigger intramolecular cyclisation—cases of Friedel–Crafts-like reactivity have also been reported: Compound **61** proved extremely resistant to hydrolysis due to high steric hindrance around the AQ-amide. Under forcing acidic conditions, *spiro*-compound **62** was isolated instead of the desired carboxylic acid. However, the target carboxylic acid **63** was eventually accessed by activation of the AQ-amide through ozonolysis prior to transamidation and hydrolysis (see Section 2.1).[54] Lv and co-workers exploited this reactivity for the synthesis of different pharma-



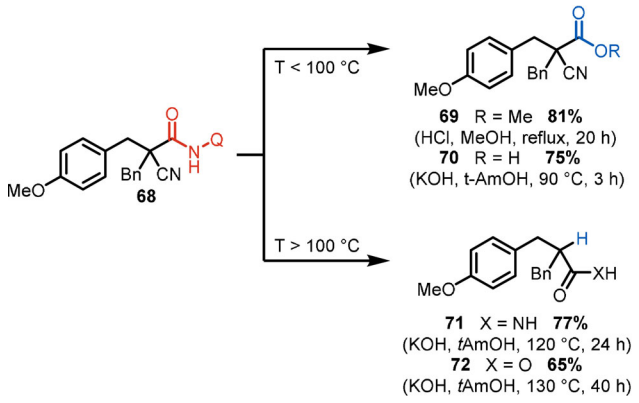
Scheme 7. Limitations: functional group compatibility in acid/base mediated AQ-hydrolysis. [a] *ee* not reported. [b] Hydrolysis of *N*-Phth protecting group. [c] Hydrolysis of *N*-Boc protecting group.



Scheme 8. Limitations: intramolecular cyclisation side-reactions during acid/base-mediated AQ-hydrolysis. [a] *ee* not reported.

ceutically interesting derivatives of alkene **64**. While alcoholysis in the presence of HCl afforded the corresponding ethyl ester in moderate yields (**66**), TsOH was required for hydrolysis which caused intramolecular cyclisation to produce naphthalen-1-ol **65**. Carboxylic acid **67** was finally accessed under basic conditions.[55]

Watkins *et al.* investigated the basic hydrolysis of *alpha*-cyano AQ-amide **68** and found that conditions had to be kept relatively mild (KOH, *t*-AmOH, 90 °C, 3 h) to obtain the desired carboxylic acid **70** (Scheme 9). At higher reaction temperatures of 120–130 °C, the α-cyano group was hydrolyzed to the amide or carboxylic acid, respectively, which caused decarboxylation of the AQ-carbonyl (**71**–**72**).[56] This transformation is interesting as it hints at the possibility of using 8-aminoquinoline as a traceless directing group (*i.e.* a directing group that can be transformed into a simple C–H bond)[57,58] that can undergo decarboxylative cleavage after successful functionalization—albeit only in the presence of electron-withdrawing *alpha*-substituents.

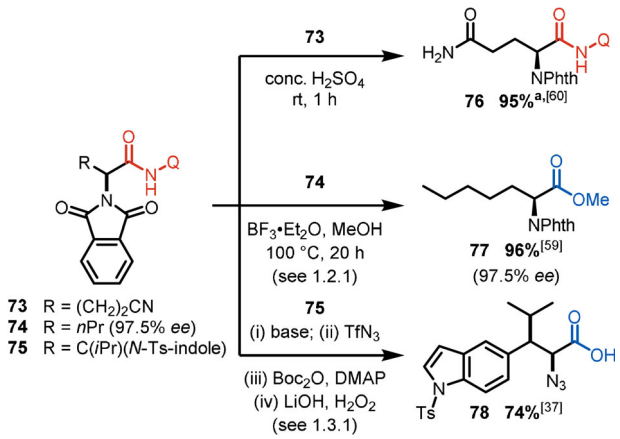


Scheme 9. Basic AQ-hydrolysis/decarboxylation for traceless directing groups.[56]

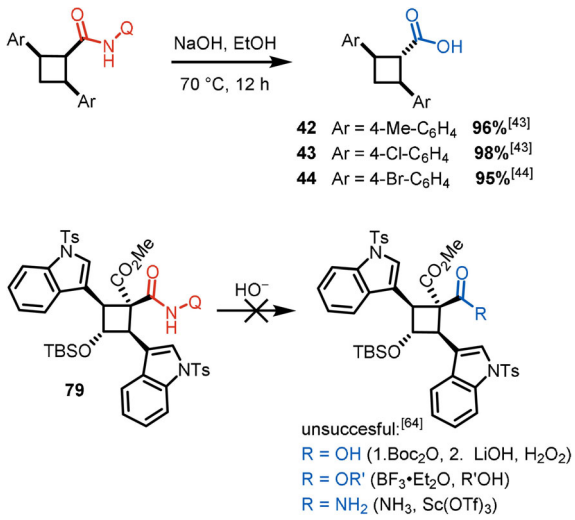
1.1.1.2. Limitations: Challenging substrates

There have been several reports in the literature where removal of the AQ-directing group after successful functionalization has failed (Scheme 10, Scheme 11, Scheme 12, Scheme 13, Scheme 14, Scheme 15). The main structural motifs that make AQ removal difficult are sterically shielding groups around the amide bond, sterically encumbered cycloalkyl amides, and lactams in which the AQ-group is part of the ring system.

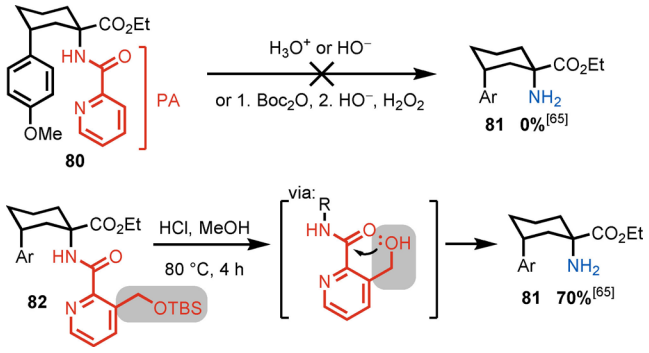
Some substrates with bulky *ortho*- or *alpha*-substituents can be successfully hydrolyzed in the presence of a strong acid such as TsOH (**7**, **12**) or TfOH (**28**–**29**, Scheme 4), but in other cases the bulky *alpha*-substituent has to be transformed into a smaller group prior to AQ-removal. Amino acid derivatives are commonly protected with phthaloyl groups during transition metal-catalyzed functionalization. However, the bulkiness of this group can be problematic when trying to remove the AQ directing group, as it can act as a steric shield blocking hydrolysis of the amide bond (Scheme 10). For instance, methyl ester **77** was accessed in high yields under Lewis acidic conditions (see Section 1.2.1),[59] however attempts to hydrolyze *alpha*-phthaloyl amide **73** under relatively mild Brønsted acidic conditions only succeeded in hydrolyzing the nitrile and not the AQ-amide (**76**).[60] A possible solution to this problem is



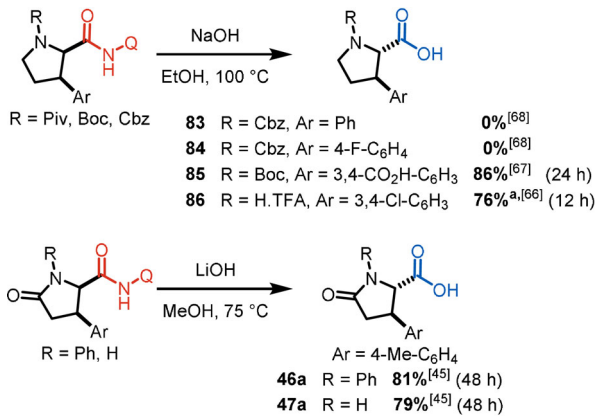
Scheme 10. Unsuccessful acid-mediated AQ-hydrolysis: *alpha*-substituted substrates. [a] Hydrolysis of nitrile. *ee* not reported.



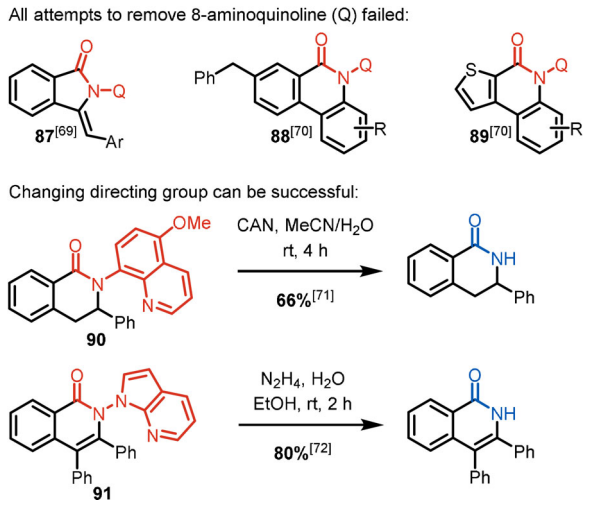
Scheme 11. Base mediated AQ-cleavage in hindered cycloalkane substrates.



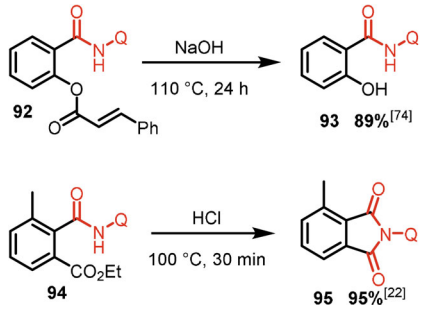
Scheme 12. Neighboring group participation accelerates hydrolysis of modified picolinamide (PA) directing group.



Scheme 13. Effect of *alpha*-N-substituent size on AQ hydrolysis. [a] Yield over two steps: 1. NaOH: AQ- and *N*-Piv hydrolysis, 2. TFA/H_2O: salt formation.



Scheme 14. Unsuccessful cleavage of AQ-amides incorporated into lactam rings.



Scheme 15. Unsuccessful acid/base mediated AQ-hydrolysis in the presence of more reactive functional groups.

conversion of the phthaloyl group to a smaller azide and preactivation of the AQ-amide prior to hydrolysis (see Section 1.3.1) to afford the desired carboxylic acid (**78**) in good yields.[37]

It has previously been proposed that nucleophilic addition to amides is accelerated by the presence of *alpha*-hydrogens on the amide substrate that can stabilize the transition state by hydrogen-bonding to the carbonyl oxygen. Due to geometric constraints, this effect is decreased in substrates bearing bulky or cyclic *alpha*-substituents.[61–63] Therefore, AQ-removal can be particularly challenging from cycloalkyl amides, in particular cyclobutyl amides and β-/γ-lactams (Scheme 11). 2,4-Substitution on cyclobutanes does not impede successful hydrolysis (**42**–**44**),[43] but highly substituted cyclobutane **79** with a quaternary center next to the AQ-amide was completely unreactive to all AQ-cleavage conditions it was submitted to.[64] Baran and co-workers ultimately had to switch to a more easily removable picolinimide directing group for this synthesis. Chen *et al.* have shown that removal of the picolinamide (PA) directing group from hindered quaternary centers can be improved by installation of a masked *ortho*-hydroxymethylene substituent on the directing group (**82**) that can aid amide bond cleavage by neighboring group participation (Scheme 12).[65] For AQ, a similar approach is described in Section 1.3.4 (amide *N*-β-hydroxyethylation), but we do not believe that this strategy has been thoroughly investigated for AQ-cleavage from hindered quaternary substrates and may improve results in these systems.

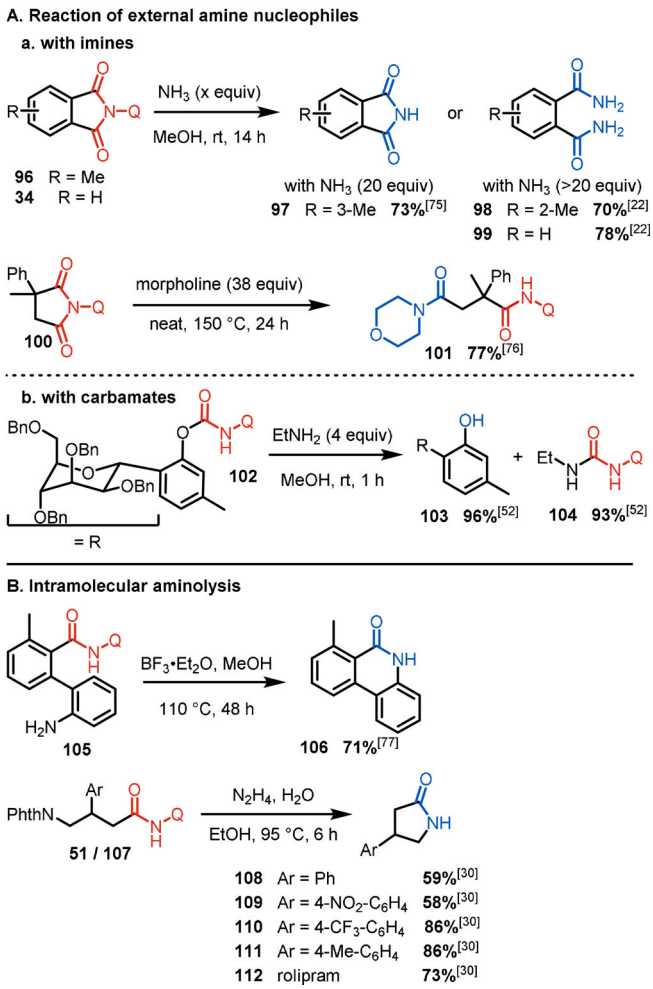
Scheme 5 includes a range of lactam and pyrrolidine AQ-derivatives that are successfully hydrolyzed under acidic/basic conditions. Ease of AQ removal in these cases once again depends on the accessibility of the amide bond which can be strongly influenced by the size of substituents on the ring nitrogen (Scheme 13). While a direct comparison of substituent size on AQ-hydrolysis has not been published in the literature, the following trends can be deduced from selected examples: While Boc- and Piv-protection did not impede AQ removal (**85**–**86**),[66,67] Cbz-protection adjacent to the AQ-amide made it highly resistant to hydrolysis (**83**–**84**).[68] In this case, the directing group had to be modified to the more reactive 5-methoxy-8-amino-quinoline (MQ) derivative for successful removal (see Section 2.2). The difference between an unprotected (**46 a**) and phenylated (**47 a**) nitrogen adjacent to the reactive center was negligible.[45]

Unlike substrates with cycloalkyl substituents (all previous examples), lactams in which the aminoquinoline amide is incorporated into the ring (**87**–**89**, Scheme 14) are a special case that require cleavage of the N–Q bond (as opposed to the (O)C–N bond discussed so far). These molecules are particularly resistant to AQ cleavage and all attempts to remove the directing group from compounds **87**–**89** were unsuccessful.[69,70] Some success has been reported by changing to the more labile MQ (Section 2.2)[71] or *N*-amino-7-azaindole (Section 3.2)[72] directing groups which could be removed from **90** and **91** to give the desired lactam in 66% yield and 80% yield, respectively, however this strategy is not always successful. The MQ directing group, in particular, is popular since it can usually be removed under mild oxidative conditions (see Section 2.2), however in the case of these AQ-lactams, unusually forcing conditions can be required[73] and sometimes the MQ directing group is also completely unremovable.[69] In recent years, interesting one-pot C–H annulation/AQ-removal strategies have been developed that can circumvent this problem (see Section 1.2.2).

Finally, due to the forcing conditions required for lactam deprotection, chemoselectivity in the presence of more reactive functional groups is an issue that has already been flagged (**93**, **95**, Scheme 15).[22,74]

1.1.2. Transamidation

Section 1.1.1 describes hydrolysis and alcoholysis of the amide bond under acidic/basic conditions. Despite the higher nucleophilicity of amines compared to water or alcohols, transamidation is a challenging transformation for both kinetic and thermodynamic reasons (for a more detailed discussion, see Section 1.3.1), and AQ aminolysis under similar conditions has only been demonstrated on activated substrates (Scheme 16). Imides are more electrophilic than amides (see Section 1.3). Phthalimide AQ-derivatives thus react with amines under relatively mild conditions to afford either the free phthalimide (**97**)[75] or the ring-opened 1,2-bis-amide (**98**–**99**),[22] depending on the amount of nucleophile used (Scheme 16 A). Transamidation of AQ-succinimide derivatives requires higher reaction temperatures and has only been reported to afford non-cyclic amides (**101**) which still contain the AQ-moiety.[76] Carbamates benefit from a similar weakening of the amide bond to imides. Carbamate **102** reacts with ethylamine to give a free phenol (**103**) after cleavage of the auxiliary.[52] The proximity effect of intramolecular nucleophilic functional groups discussed above can also be exploited to facilitate AQ transamidation to yield β- and γ-lactams, albeit under relatively forcing conditions (**106**, **108**–**112**).[30,77] Notably, AQ-amide **105** is activated towards nucleophilic attack of the pendant amine by addition of a Lewis acid—further examples of this type of reactivity are discussed in the next section.



Scheme 16. Direct aminolysis of activated AQ-amides: **A**. Reaction of external nucleophiles with **a**. imines and **b**. carbamates. **B**. Intramolecular aminolysis.

1.2. Pre-activation of the amide bond with Lewis acids

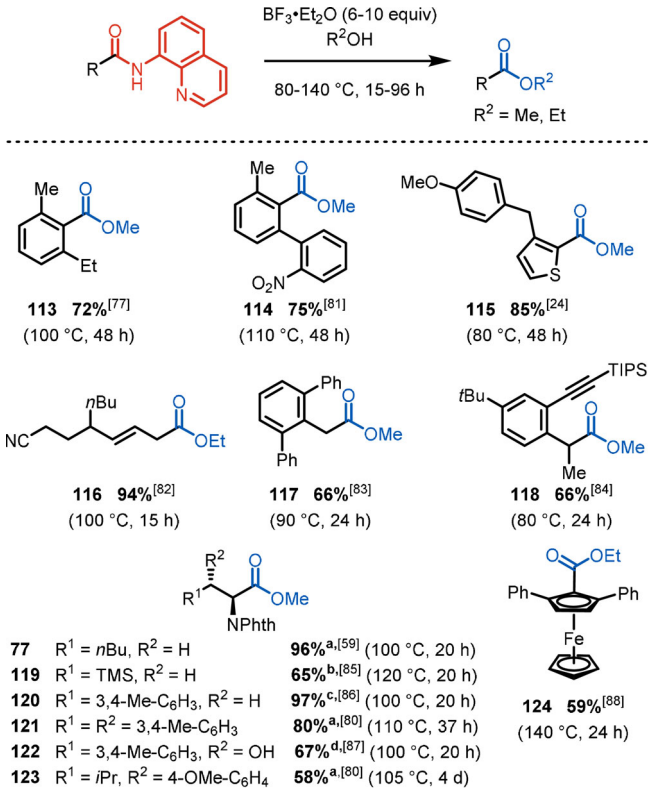
Section 1.1 has shown that solvolysis of the amide bond under acidic or basic conditions can be a straightforward, powerful way to remove the 8-aminoquinoline directing group. However, the harsh conditions used (conc. acid/base, high temperatures, long reaction times) limit the functional group compatibility of this method and can even fail to remove the auxiliary in some cases. Due to the Lewis basic nature of amides (Scheme 2), their reactivity towards nucleophiles can be increased by complexation with Lewis acids, which may allow for milder reaction conditions and therefore a wider functional group tolerance than in Brønsted acidic/basic approaches.

1.2.1. Lewis acid mediated alcoholysis

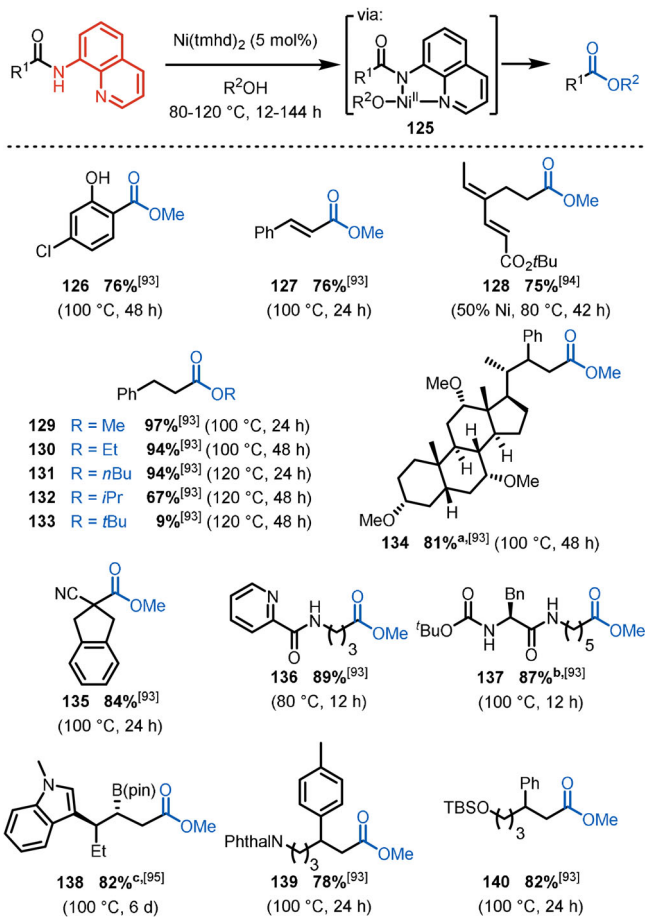
Based on reports by Hanessian and Keck,[78,79] Daugulis developed a protocol for Lewis acid mediated alcoholysis of AQ-amides to access the corresponding esters (Scheme 17).[80] Yields are high for (hetero)aromatic AQ-amides (**113**–**115**),[24,77,81] including *ortho*–*ortho* disubstituted aromatics **113** and **114** (if one of the substituents is small), and unhindered aliphatic AQ-amides (**116**),[82] but—as with Brønsted acid catalysis (Section 1.1)—a decrease in yield is observed for sterically hindered substrates (**77**, **119**–**123**).[59,80,83–87] Nitrile (**116**), *N*-phthalimide (**77**, **119**–**123**) and ferrocene groups (**124**)[88] are tolerated well, though a slight erosion of *ee* is commonly observed in enantioenriched substrates (from 99% *ee* to 97% *ee*) and certain functional groups (*e.g.* acetate, **122**) remain labile. The products accessed through this methodology are most commonly limited to methyl and ethyl esters. A strategy often used in the literature to pre-activate amides is the generation of an imidate or iminium ether, for example, by reaction with triflic anhydride.[9] To the best of our knowledge, this approach has not yet been applied to AQ removal and may offer a route towards more diverse ester products.

1.2.2 .Transition metal-mediated C–O, C–N and C–C bond formation

AQ-amide activation with Lewis acidic transition metals offers a different method to vastly expand product diversity, enabling inter- and intramolecular esterification, transamidation and C–C bond forming reactions with concomitant removal of the AQ directing group.



Scheme 17. Lewis acid catalyzed alcoholysis of AQ. [a] *ee* not reported. [b] 99% *ee* (starting material: 98% *ee*). [c] 96.5% *ee* (starting material: 99% *ee*). [d] Concomitant hydrolysis of -OAc (R^2). 98.5% *ee* (starting material: 99% *ee*).



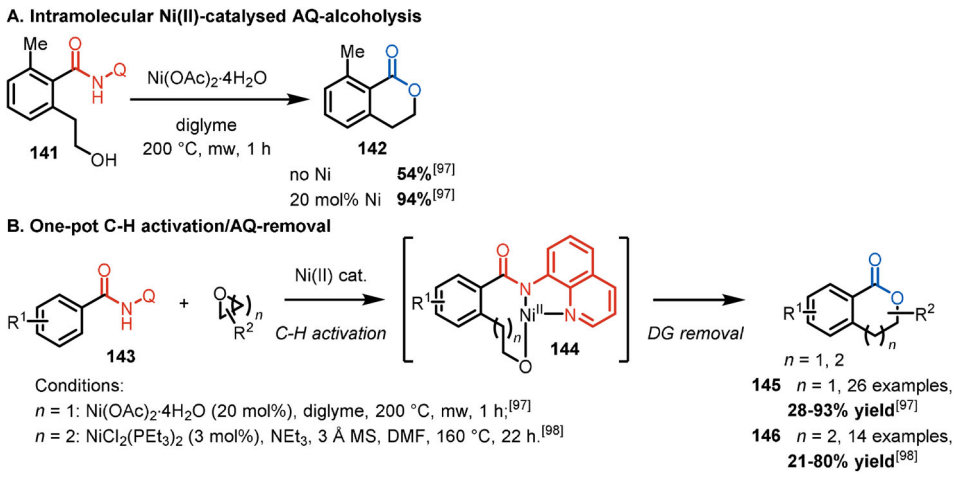
Scheme 18. Ni^{II}-catalyzed AQ-alcoholysis. [a] *ee* not reported. [b] 97% *ee* (starting material: 97% *ee*). [c] 92% *ee* (starting material: 90% *ee*).

Based on precedent by Mashima[89] and Garg,[90–92] Ohshima *et al.* proposed the use of a Ni catalyst to transform AQ-amides into esters by (1) activating the amide bond and (2) increasing the nucleophilicity of alcohols by coordination to the Lewis acidic metal (Scheme 18).[93] Using commercially available, air-stable $Ni(tmhd)_2$ as the catalyst, a variety of different esters (**126**–**140**) can be accessed from the corresponding AQ-amides.[93–95] No erosion of *ee* is observed in enantiopure substrates (**134**, **137**–**138**) and *Z*-alkenes undergo negligible isomerization (**128** was isolated as a 12:1 *Z*:*E* mixture, starting from a 14:1 ratio). The method is highly selective for the alcoholysis of AQ-amides over other amides (including the picolinamide directing group: **136**) and tolerates a variety of acid/base-labile functional groups such as nitriles (**135**), carbamates (**137**), boronic esters (**138**), *N*-phthalimides (**139**) and silyl ethers (**140**). However, it is largely limited to unhindered aliphatic AQ-amides. We were only able to find one aromatic example (**126**) and one example of a substrate with a bulky *alpha*-substituent (**135**), though in both cases yields were high. Good yields are obtained with linear, unbranched alcohols (**129**–**131**), but yields drop off rapidly as the alcohol's steric bulk increases (**132**–**133**).

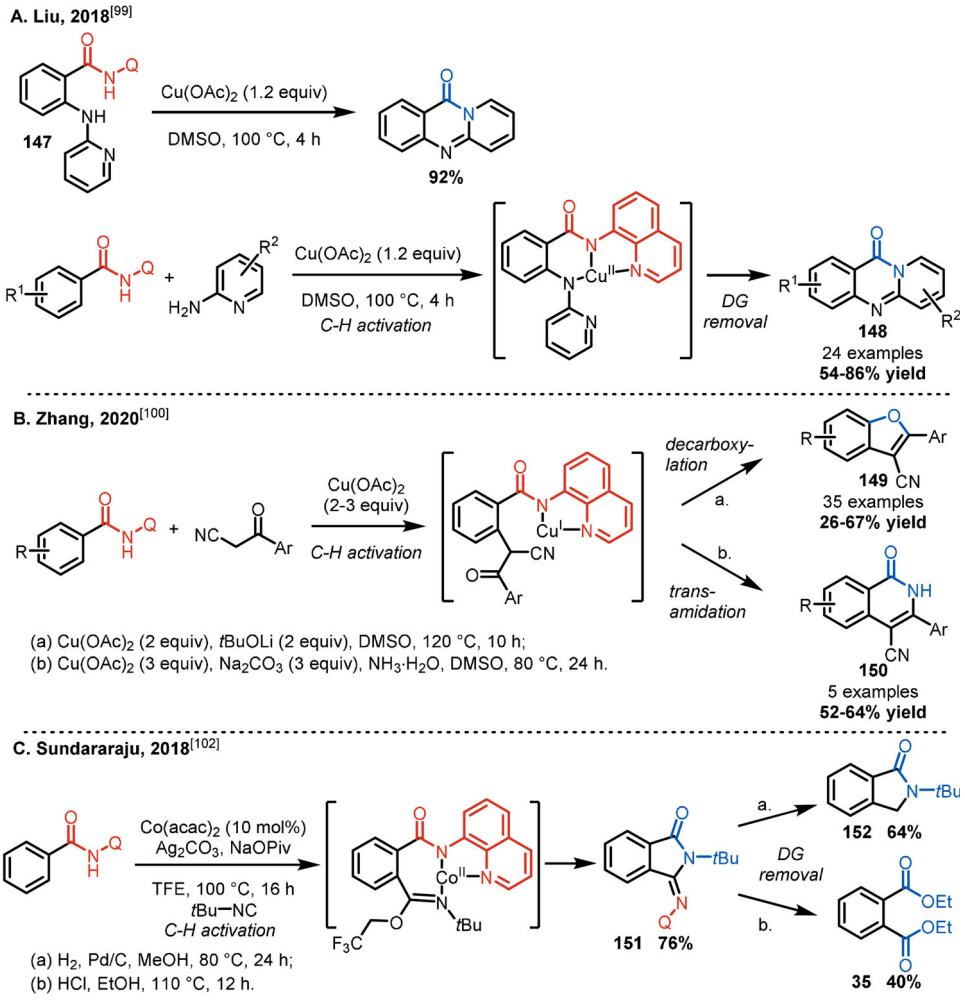
Mechanistically, this esterification is thought to proceed through Ni^{II} intermediate **125** (Scheme 18) in which the catalyst is coordinated to the AQ directing group and the alcohol nucleophile, which is thus brought into close proximity to the activated amide bond and attacks it via an inner sphere mechanism.[93,96] It is conceivable that instead of an external alcohol, a tethered nucleophile could be used to afford a similar esterification with concomitant cyclisation and loss of the directing group. Indeed, Hirano and Miura showed that aromatic AQ-amides with a pendant *ortho*-hydroxyethyl or -butyl substituent undergo cyclisation with simultaneous loss of the AQ directing group under Ni^{II} catalysis in high yields (Scheme 19A).[97] In fact, these compounds can be accessed by Ni^{II} catalyzed C–H activation of AQ-benzamides with epoxides or oxetanes, enabling the development of a one-pot C–H activation/AQ removal strategy to afford six- and seven-membered benzolactones (**145**, **146**) respectively (Scheme 19B).[97,98]

This is just one example of a range of one-pot C–H activation/AQ removal strategies that have been developed in the last four years to access cyclized products through intramolecular C-heteroatom and C–C bond forming reactions. Currently, these transformations still require high temperatures (80–200 °C), but they offer access to an interesting range of products.

Liu and co-workers demonstrated that stoichiometric amounts of $Cu(OAc)_2$ enabled a similar cyclisation with spontaneous loss of AQ on *ortho*-aminopyridine-AQ-benzamides (**147**, Scheme 20A). These compounds could be accessed via



Scheme 19. Intramolecular Ni^{II}-catalyzed AQ-alcoholysis.



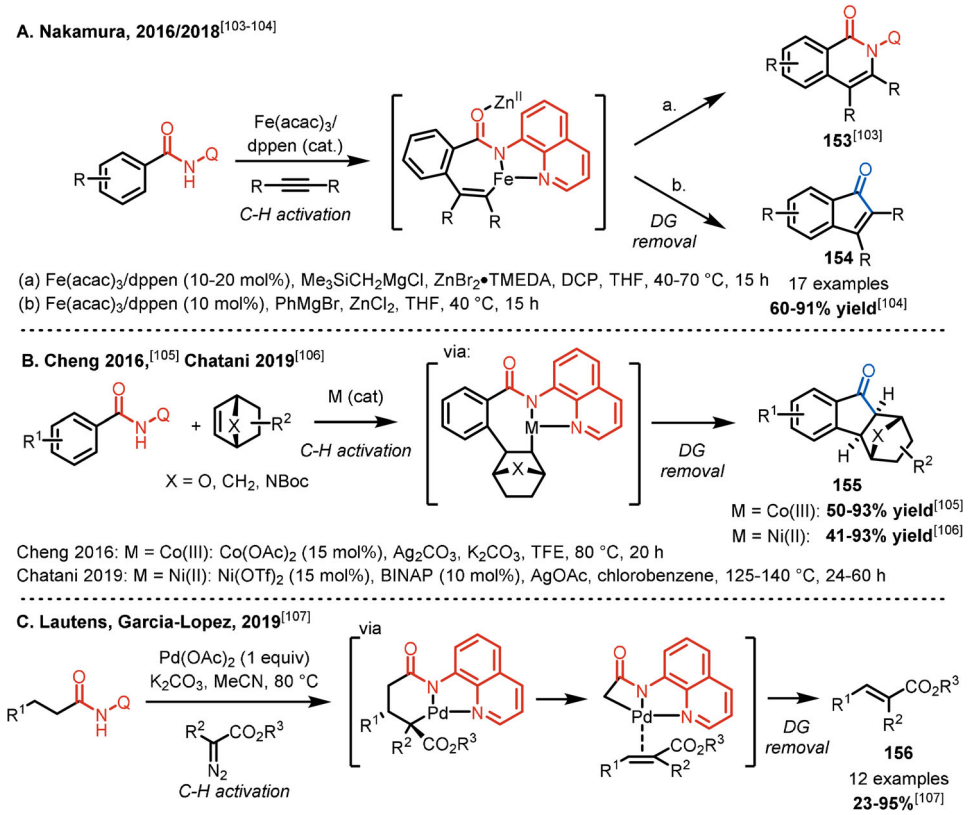
Scheme 20. Intramolecular transition metal-catalyzed AQ-transamidation.

copper-mediated C–H functionalization of AQ-benzamides with 2-aminopyridines, giving access to pyrido-fused quinazolinone derivatives **148** in one pot.[99] A similar C–H functionalization of AQ-benzamides with benzoylacetonitriles can afford two different products depending on the reaction conditions: In the presence of ammonia and sodium carbonate, transamidation occurs to yield isoquinolinones (**150**, Scheme 20 B),[100] a useful transformation with regard to directing group removal, since AQ-isoquinolinones are very resistant to hydrolysis (as discussed in Section 1.1.1.2, Scheme 15) and oxidative removal

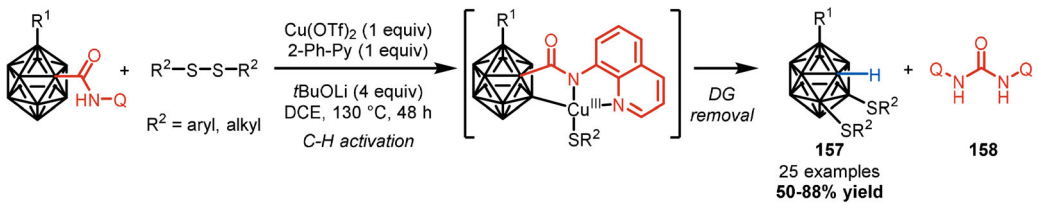
of the MQ directing group (see Section 2.2) causes concomitant oxidation of the desired product to the lactone.[101] When a stronger base (LiO*t*Bu) was used in the absence of ammonia, decarboxylation occurred instead, leading to the formation of benzofurans (**149**, Scheme 20B).[100] Catalytic intramolecular transamidation has been demonstrated by Sundararaju and co-workers who developed a cobalt-catalyzed method to access 3-(imino)isoindolinones **151** through a key *N*-AQ/*N*-*t*Bu acyl swap (Scheme 20C).[102] However, in this method the AQ group remains on the product molecule and requires cleavage through a subsequent hydrolysis or reduction step.

Nakamura *et al.* developed an oxidative, iron-catalyzed annulation of alkynes and benzamides to afford pyridones and isoquinolones **153** (Scheme 21A).[103] However, as discussed above (Section 1.1.1.2, Scheme 14), the AQ directing group is extremely resistant to cleavage from these products. The authors found that in the absence of an oxidant, C–C bond formation with concomitant loss of AQ was favored over C–N bond formation, giving indenones **154** in good to excellent yields.[104] *Ortho*-substituents on the benzamide moiety shut down the reaction almost completely. Cheng and Chatani demonstrated similar Co^{III}[105] and Ni^{II}[106] catalyzed annulations of benzamides with cycloalkenes, respectively (**155**, Scheme 21B). In these systems, AgOAc was found to prevent the cleaved AQ directing group from poisoning the catalyst. Lautens and Garcia-Lopez have developed an interesting AQ-directed strategy for the formation of alkenes **156** that involves remote C–H activation, carbene insertion and a key β-carbon elimination step that furnishes the desired products along with a palladacycle still bearing the AQ directing group (Scheme 21C).[107]

Quan and Xie recently described a copper-mediated C–H sulfenylation and selenylation of *o*-carboranes using 8-aminoquinoline as a traceless directing group (Scheme 22).[108] The authors invoke a decarboxylative removal of the directing group *in situ* to afford functionalized products **157** along with *N*,*N*′-di-8-quinolinyl-urea **158**, though the exact mechanism still requires elucidation.



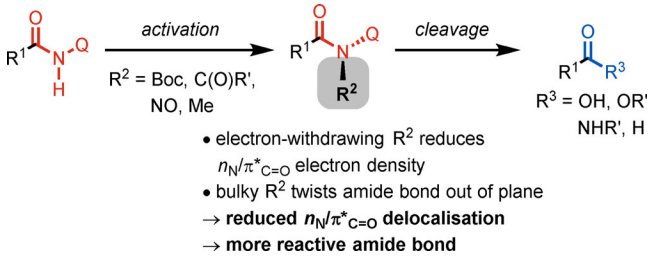
Scheme 21. Intramolecular transition metal-mediated C–C bond formation with loss of AQ.



Scheme 22. Copper-mediated decarboxylative AQ-cleavage.[108]

1.3. Pre-activation of the amide bond by *N*-substitution

An alternative strategy to increase the reactivity of amides towards nucleophilic cleavage that is particularly popular for sterically encumbered AQ-substrates is activation by *N*-substitution with bulky, electron-withdrawing groups (Scheme 23).[11] In this case, the observed increase in reactivity is mainly due to two effects: (1) electron-withdrawing substituents reduce electron density in the $n_N/\pi^*_{C=O}$ system, and (2) the substituent's steric bulk twists the amide bond out of planarity. Szostak and co-workers showed that *N*-Boc substitution of benzamide resulted in an almost perpendicular amide bond that twisted 87° out of planarity.[109] While the barrier to rotation around the C–N bond in planar amides is high (ca. 15–20 kcal mol^{-1}),[110] it can drop to ca. 7 kcal mol^{-1} in twisted, *N*-Boc substituted amides,[111] allowing for full rotation around this bond.[109] Both effects reduce delocalization, making the amide less stable and thus more reactive.



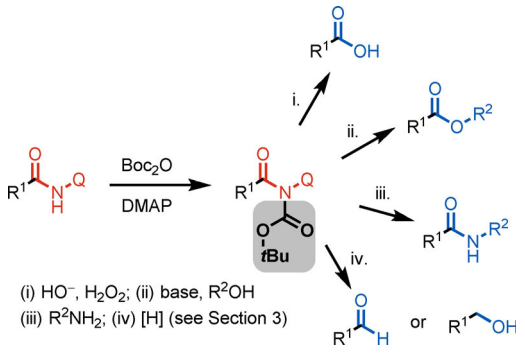
Scheme 23. Activation of AQ-amides by *N*-substitution to reduce resonance stabilization prior to cleavage.

1.3.1. *N*-Boc activation

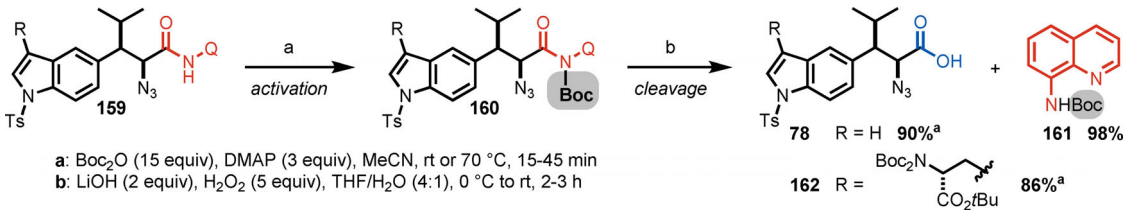
This effect was first exploited by Grieco *et al.* in 1983 who showed that *N*-Boc derivatization of secondary amides activated them towards hydrolysis with LiOH and solvolysis with MeOH or NaOMe.[112] In addition, solvolysis selectively occurred on the amide carbonyl of interest (not the Boc carbonyl) due to the Boc *tert*-butyl group acting as a steric shield. Evans *et al.* improved Grieco's method by using a combination of LiOH with H_2O_2 for hydrolysis, which is known to give a stronger, less basic nucleophile than hydroxide due to the *alpha* effect of the second oxygen.[113] The main limitation in both these studies was the poor reactivity of bulky *alpha*-substituted amides with Boc anhydride.

Chen *et al.* were the first to apply this strategy to the hydrolysis of an AQ-amide in their total synthesis of Celogentin C in 2010 (Scheme 24).[37] Since then, *N*-Boc activation has become one of the go-to methods for removing the 8-aminoquinoline auxiliary from sterically hindered substrates that are unreactive under traditional acid/base hydrolysis or that contain acid/base sensitive functional groups, allowing access to carboxylic acid, ester, amide (this section), aldehyde and alcohol products (Section 3) (Scheme 25). The *N*-Boc imide is generally purified by column chromatography and then subjected to a nucleophile for cleavage (all yields for *N*-Boc activation/cleavage discussed in this review are given over two steps). The *tert*-butyl quinolin-8-ylcarbamate by-product **161** can be easily deprotected under acidic conditions to recover the AQ auxiliary in near quantitative yields.[114]

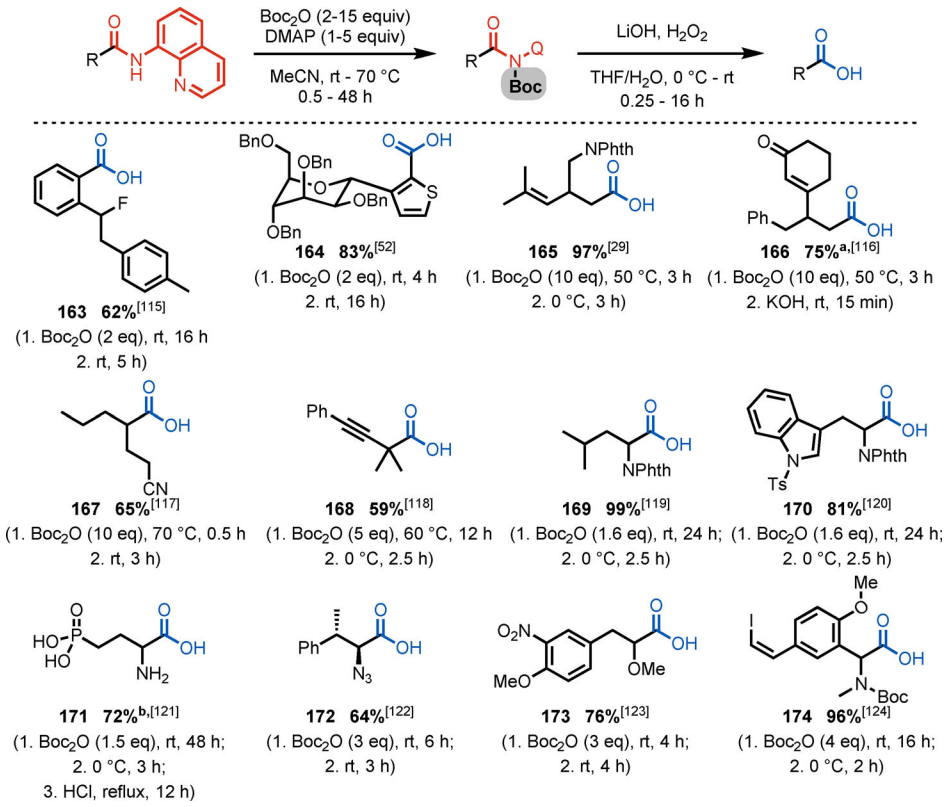
Not many examples exist of *N*-Boc activation and hydrolysis of simple aromatic AQ-amides as acid/base hydrolysis or oxidative removal of the MQ directing group (Section 2.2) usually afford similar yields. The method's strength lies in its transformation of sterically hindered substrates such as *ortho*-substituted (hetero)aromatics (**163**–**164**, Scheme 26)[52,115] (though no examples have been found of *ortho*,*ortho*-substituted aromatic AQ-amides) and *alpha*-substituted aliphatic AQ-amides (**167**–**174**),[29,116–124] though increased bulk around the amide bond decreases the efficiency of the *N*-Boc activation step which may require a large excess of Boc anhydride (**165**–**167**), high reaction temperatures (**165**–**168**) and long reaction times (**169**–**171**, **174**). Bulky *alpha*-phthaloyl groups are tolerated in some cases (**169**–**171**) but can require transformation to a smaller azide if a *beta*-substituent is also present (**78**, **172**). A wider variety of functional groups are tolerated compared to acid/base hydrolysis conditions, such as phthalimides (**165**, **169**–**170**), nitriles (**167**), alkynes (**168**) and alkenes, including Michael acceptors (**166**) and *Z*-vinyliodide **174** that did not undergo alkene isomerization or deiodination during AQ removal.



Scheme 25. Removal of AQ by *N*-Boc activation.



Scheme 24. Hydrolysis of AQ-amide **159** (Celogentin C precursor).[37] [a] Yields are given over two steps (1. *N*-Boc activation, 2. cleavage).



Scheme 26. *N*-Boc activation of AQ-amides prior to hydrolysis. (Yields are given over two steps: 1. *N*-Boc activation, 2. cleavage.) [a] No H_2O_2. [b] Concomitant hydrolysis of P-OEt/Me phosphate ester. Yield over 3 steps (3. *N*-Phth hydrolysis).

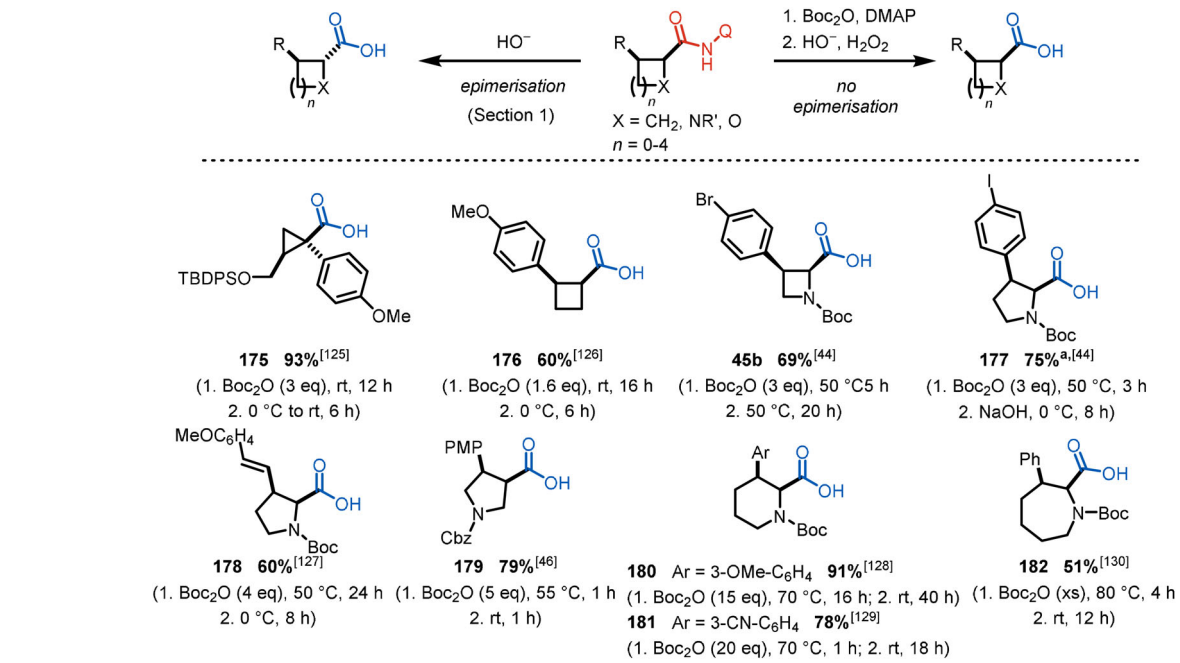
However, other groups are still prone to hydrolysis under these conditions, such as phosphate esters (**171**). In the presence of oxidizable functional groups (**166**), H_2O_2 can be omitted from the hydrolysis step.

As discussed in Section 1.1, basic hydrolysis of AQ-amides can cause epimerization at the carbonyl substituent (Scheme 5). This can be prevented by *N*-Boc activation prior to hydrolysis. A wide variety of lactams and cycloalkyl AQ-amides can be deprotected in good to excellent yields using this approach, including hindered quaternary cyclopropyl amides (**175**),[125] cyclobutyl amides (**176**),[126] as well as 4- to 7-membered cyclic secondary amides with bulky electron-withdrawing and -donating *alpha* substituents (**45b**, **177**–**182**)[44,46,127–130] (Scheme 27).

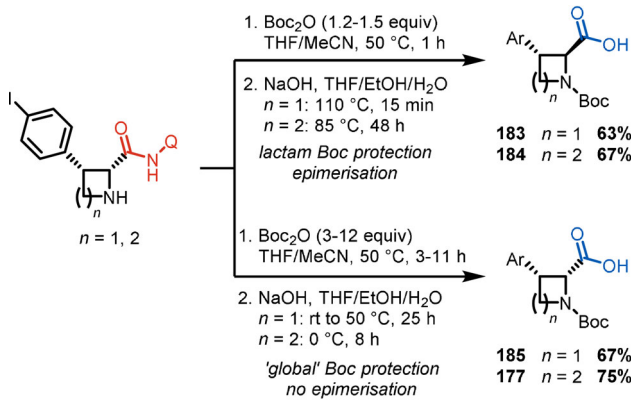
Schreiber,[44,45,131] Bull,[46] Verho[127] and others have exploited regiodivergent AQ deprotection approaches for the divergent synthesis of cyclic amide compound libraries for small molecule screening (Scheme 28). Protection of the lactam nitrogen only with near-stoichiometric amounts of Boc_2O results in epimerization upon hydrolysis (**183**, **184**); when both the lactam nitrogen and the AQ-amide nitrogen are Boc-protected, milder hydrolysis conditions can be used that furnish the opposite diastereoisomer with retention of stereochemistry at the carbonyl center (**185**, **177**).[131]

If an alcoholic (or thiol) solvent is used in combination with a base, the corresponding esters (or thioesters) can be accessed after *N*-Boc activation (Scheme 29).[46,132–135] As with previous examples, steric bulk around the amide bond decreases the efficiency of the activation and AQ-cleavage steps (**186**–**188**). However, while hydrolysis of the *N*-Boc amide generally occurs with clean retention of stereochemistry, some epimerization can occur under the more basic solvolysis conditions (**191**).

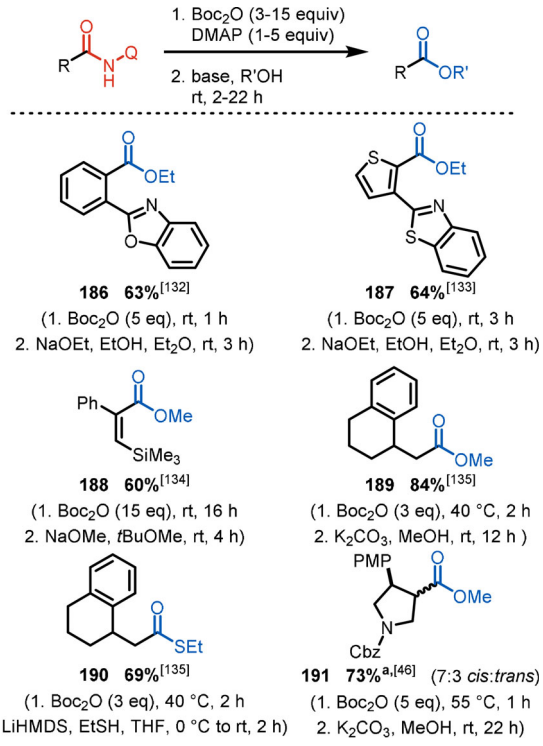
Transamidation of secondary amides is notoriously difficult for both kinetic and thermodynamic reasons: the resonance stabilization of the amide bond (discussed above) presents a high kinetic activation barrier, and there is often no thermodynamic driving force for the transformation of a secondary amide substrate to a different secondary amide product. However, Garg[90] and Szostak[136] have shown that twisted amides such as the *N*-Boc activated amides discussed in this section readily undergo oxidative addition with Ni- and Pd-catalysts, making them susceptible to further transformations such as transamidation reactions. The Szostak group have also developed metal-free transamidation conditions for twisted amides.[137,138] Inspired by this research, Verho *et al.* exploited destabilization of the amide bond by *N*-Boc activation to develop the first transamidation of AQ-amides under relatively mild conditions (Scheme 30).[111] The method works excellently for unhindered amide substrates and primary amine nucleophiles (including hydrazine), but yields drop for more sterically hindered secondary amines (**202**) and less nucleophilic anilines (**201**). *Ortho*-substituted heteroaromatics are tolerated (**196**–**198**), but *ortho*-substituted aromatics are essentially unreactive (**193**–**194**), though Kanai and Kuninobu were able to improve their reactivity by using an excess of Boc anhydride and higher



Scheme 27. Stereoretentive hydrolysis of *N*-Boc activated AQ-amides. (PMP = *para*-methoxyphenyl). [a] No H_2O_2.



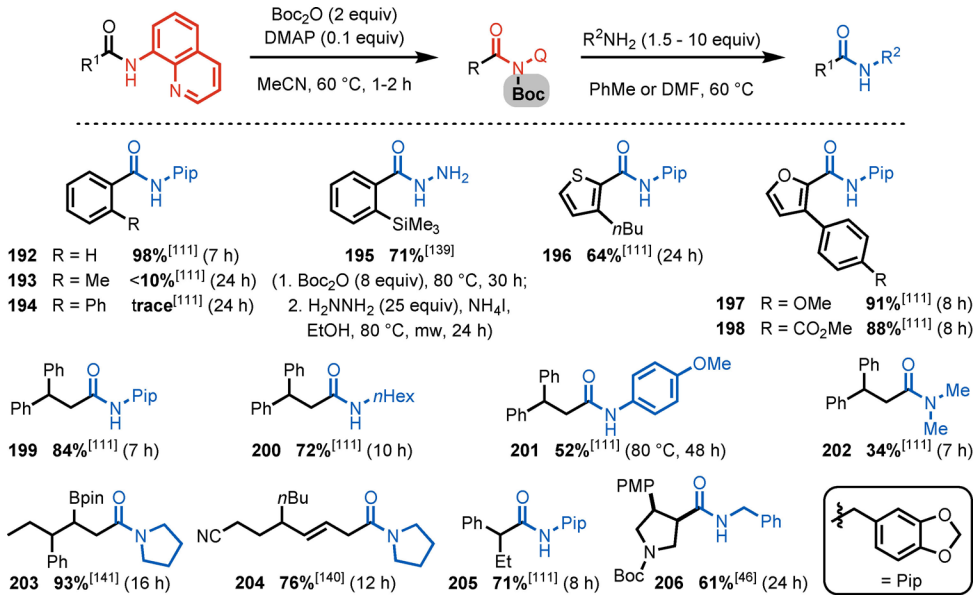
Scheme 28. Divergent AQ-removal for the synthesis of compound libraries (*ee* values not reported).[131]



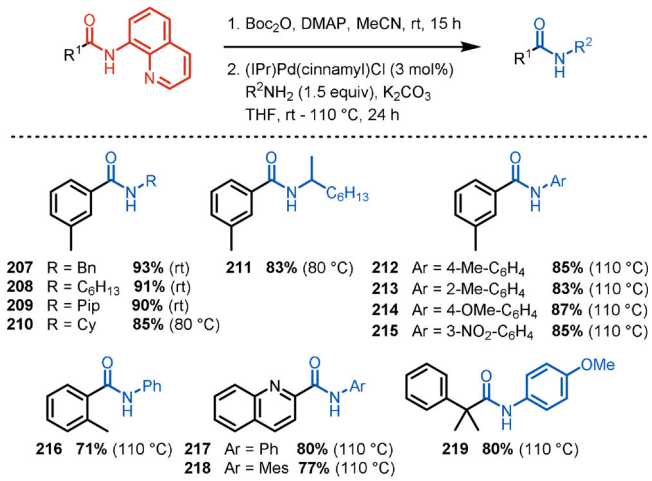
Scheme 29. *N*-Boc activation of AQ-amides prior to solvolysis. [a] Some epimerization of pure *cis* starting material.

reaction temperatures for the *N*-Boc protection step and microwave assisted transamidation (**195**).[139] A one-pot *N*-Boc protection/hydrolysis protocol of Verho's method was developed, but yields are considerably lower than fort the two-step workflow (**199** was obtained in 53% yield in the one-step protocol, compared to 81% in two steps).[111]

The low reactivity of secondary amines and anilines in metal-free transamidation reactions was addressed by Yuan *et al.* who showed that Szostak's palladium-catalyzed transamidation methodology can also be applied to AQ-amides (Scheme 31):[114] (IPr)Pd(cinnamyl)Cl was successfully used for the transamidation of *N*-Boc activated AQ-amides with primary amines (at room temperature) (**207**–**209**), secondary amines (at 80° C) (**210**–**211**) and aromatic amines (at 110° C) (**212**–**219**). While the scope of amine nucleophiles was investigated in detail, information on the compatibility of *ortho*-substituted aromatic AQ-amides (**216**) and *alpha*-substituted aliphatic AQ-amides (**219**) is limited, though the two examples given are high yielding.



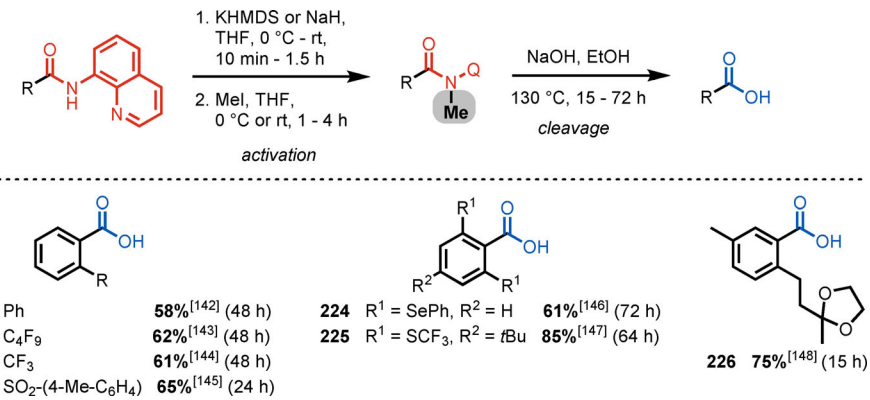
Scheme 30. Metal-free transamidation of *N*-Boc activated AQ-amides.[46, 111, 139, 147, 148]



Scheme 31. Pd-catalyzed transamidation of *N*-Boc activated AQ-amides. (Cy = cyclohexyl, Pip = see Scheme 30).[114]

1.3.2. N-Methylation

The yields given in the discussion above are after two steps: (1) *N*-Boc activation, followed by (2) cleavage of the amide bond. For sterically encumbered substrates, *N*-Boc protection can require a large excess of reagents, high temperatures and long reaction times, and can still be very low yielding, impacting the efficiency of this AQ-removal protocol. In this case, *N*-methylation can offer an alternate approach, since a methyl group is much smaller and therefore more likely to react with a sterically shielded amide (Scheme 32).[140] For the same reason, however, and because it is not electron-withdrawing, a methyl group is not a strong amide activator. Because of this, forcing conditions are necessary for the hydrolysis of *N*-methyl activated AQ-amides (130 °C, 15–72 h) and yields are generally moderate (**220**–**226**).[140–146] Furthermore, base-labile functional groups may not be tolerated or may require protection (**226**).



Scheme 32. Activation of AQ-amides by *N*-methylation prior to hydrolysis.

1.3.3. N-Nitrosylation

Evans *et al.* found in their original amide activation paper that nitrosamide was a stronger amide activating agent than the corresponding *N*-Boc imide.[113] *N*-Nitrosylation is commonly used for removal of Shi's 2-(pyridin-2-yl)isopropyl amine (PIP) directing group,[149,150] and has recently also been applied to AQ-removal. The use of $NOBF_4$ as a mild nitrosylating reagent in combination with pyridine allowed for the hydrolysis of AQ-amide **227** at low temperatures without significant racemization of its acid/base sensitive stereocenter (Scheme 33).[151]

1.3.4. Peptide chemistry-inspired N-activation

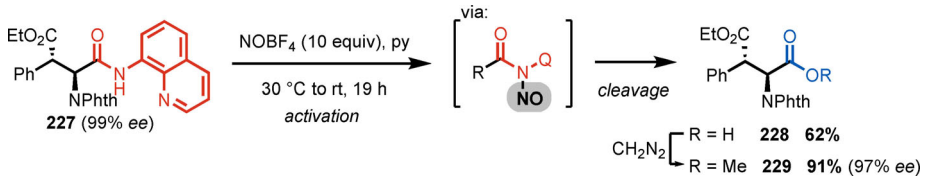
In peptide chemistry, reversible, intramolecular esterification of amide bonds (*N*,*O*-acyl shift) is often observed in peptide chains containing amino acids with β-hydroxyethyl groups (serine and threonine).[152–154] Since esters are more reactive towards hydrolysis than amides, this can lead to spontaneous cleavage of the peptide bond at these residues, which can be exploited, for example in automated peptide synthesis or for the development of prodrugs.[155–157] Mashima and co-workers took inspiration from this strategy to develop an interesting zinc-catalyzed protocol for the *N*-β-hydroxyethylation of amides, which pre-activated them for facile intramolecular esterification followed by alcoholysis in the presence of diethyl carbonate (Scheme 34 A).[158] Their substrate scope included various common amide directing groups such as triazole amine (TAM), 2-(pyridin-2-yl)isopropyl amine (PIP), and 8-aminoquinoline (AQ). In general, good yields were observed for electron-poor substrates, with moderate yields for electron-rich and sterically hindered substrates such as *ortho*-substituted aromatic amides.

With the aim of developing an AQ-removal strategy for sterically encumbered α-amino acid substrates, Geyer *et al.* looked towards the easily cleavable Dawson linker used in solid phase peptide synthesis for inspiration. Reduction of the AQ pyridyl moiety with Hantzsch ester, followed by urea formation with phosgene afforded an AQ-urea derivative that was highly reactive towards nucleophiles (Scheme 34B).[197] The authors were able to cleave the AQ directing group from this intermediate in high yields, accessing the corresponding carboxylic acid, primary amide and alcohol products. This method is particularly useful for substrates containing oxidizable functional groups (*e.g.* indoles) as it avoids the oxidative conditions (discussed in the next section) that are often used for the cleavage of sterically hindered AQ-amides.

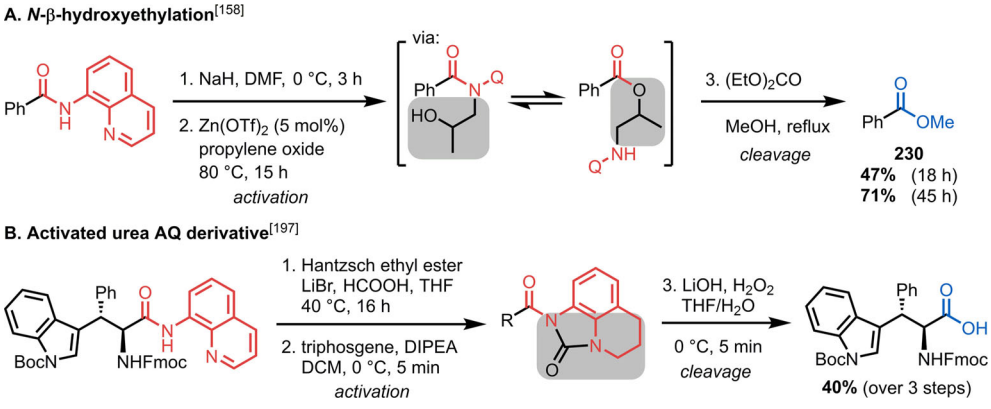
2. Oxidative Cleavage of the Amide Bond

2.1. Ozonolysis

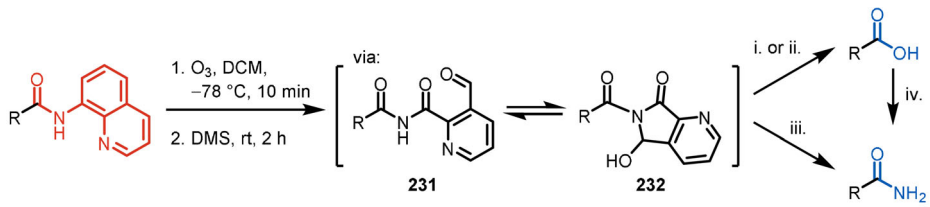
While activation of AQ-amides by substitution on nitrogen can achieve good solvolysis yields, the substitution step can be very inefficient on sterically hindered amides (as seen in Section 1.3). For these cases, Maulide *et al.* developed an elegant activation strategy that relies on oxidative fragmentation of the directing group and does not require the amide bond to be as sterically accessible (Scheme 35).[159] Reaction of 8-aminoquinoline with ozone at −78 °C followed by DMS affords imide **231** which is in equilibrium with hydroxyazaisoindolinone **232**. This undergoes rapid reaction with peroxide to give carboxylic acids (Scheme 36)[159] or ammonia to give primary amides



Scheme 33. Activation of AQ-amide by *N*-nitrosylation prior to hydrolysis.[151]

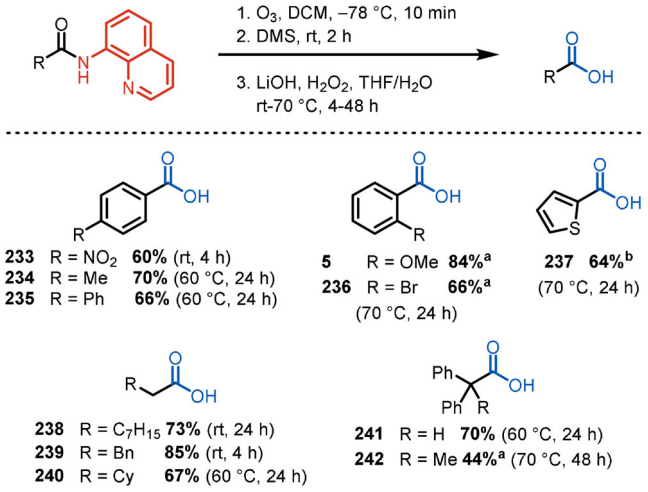


Scheme 34. Peptide chemistry-inspired activation of AQ-amides.



(i) LiOH (6 equiv), H_2O_2 (10 equiv), THF/H_2O, rt-70 °C, 24-48 h; (ii) $CuCl_2$ (1 equiv), H_2O, dioxane, 100 °C (mw), 1 h; (iii) NH_4OH, THF, rt, 4-24 h; (iv) $NOBF_4$, DMF, rt, 15 min.

Scheme 35. Activation of AQ-amide by ozonolysis.[159]

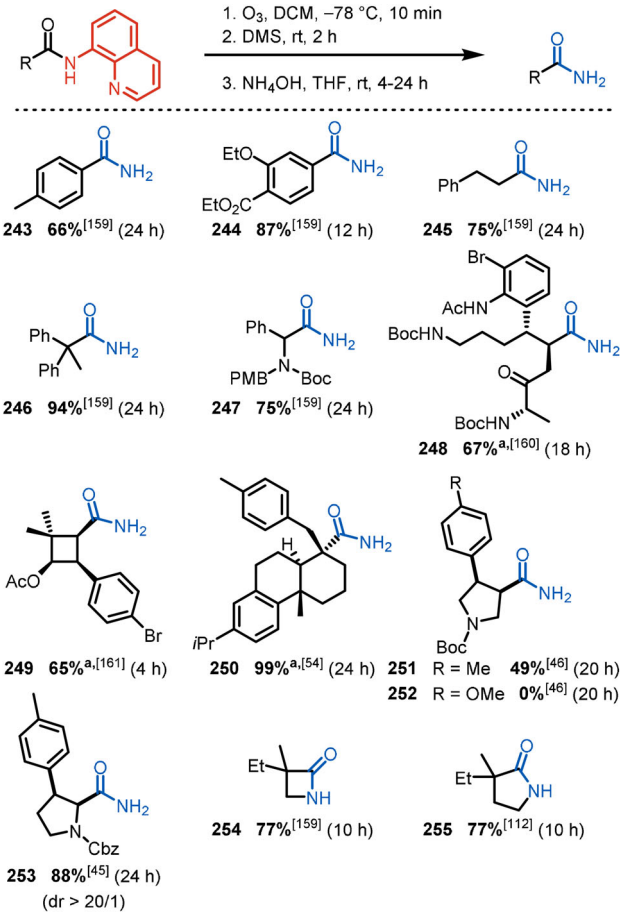


Scheme 36. Ozonolysis and basic hydrolysis of AQ-amides[159] (Cy = cyclohexyl). [a] Excess LiOH/H_2O_2. [b] No H_2O_2.

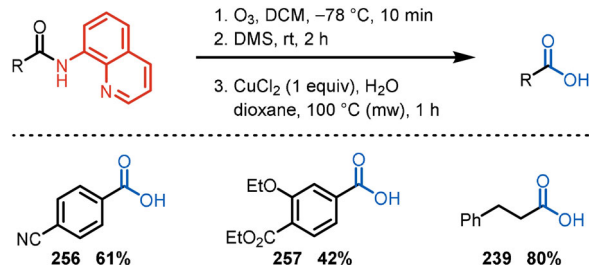
(Scheme 37)[45,46,54,159–162] without epimerization of the reactive center. In fact, the imide intermediate is so labile that it can also be hydrolyzed under pH-neutral microwave-assisted conditions (Scheme 38),[159] making it attractive for molecules containing base-labile functional groups-although the use of ozone comes with its own limitations in terms of functional group compatibility.

(Hetero)aromatic and aliphatic AQ-amides are readily converted to the corresponding carboxylic acids and primary amides in good to excellent yields (Scheme 36 and Scheme 37).[45,46,54,159–162] Sterically encumbered substrates (**5**, **236**, **242**) afford good yields when an excess of LiOH/H_2O_2 is used in the hydrolysis step. Some oxidizable heteroaromatics (*e.g.* thiophene **237**) are tolerated in the ozonolysis step but require the omission of H_2O_2 in the hydrolysis step. Cleavage of the AQ group from cycloalkyl amides and lactams occurs in very good yields (**249**–**255**), though an electron-rich *para*-methoxyphenyl group *alpha* to the reactive amide center in pyrrolidine **252** was not tolerated and led to decomposition.[46]

This strategy has been successfully applied to the total synthesis of highly hindered amide natural products and drug targets that are unreactive to all other AQ cleavage conditions (**248**–**250**, Scheme 36).[54,160,161] For instance, it was discussed in Section 1 that the precursor for compound **250**, AQ-amide **62**, was resistant to AQ hydrolysis and underwent Friedel–Crafts cyclisation instead when forcing conditions were used

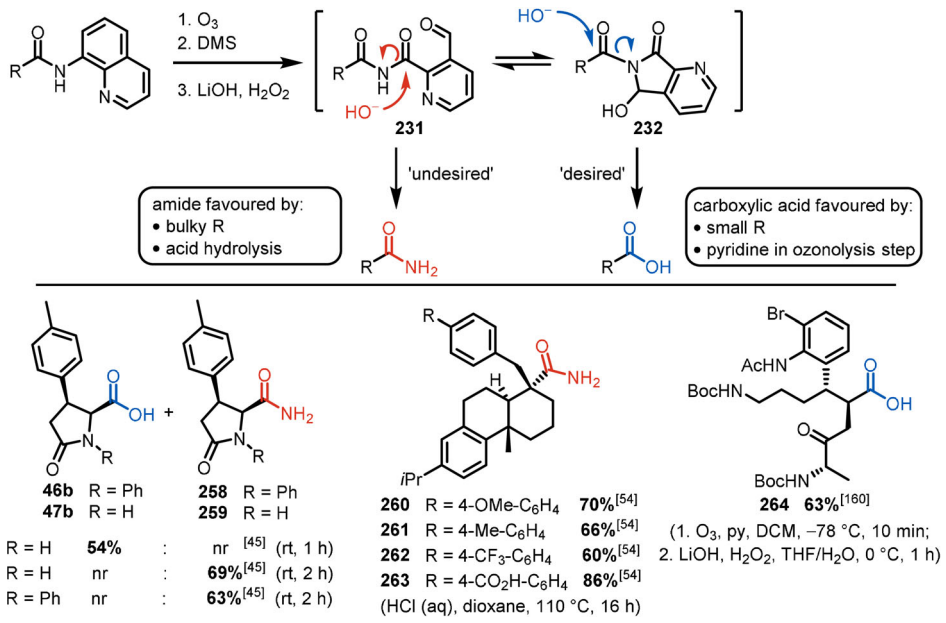


Scheme 37. Ozonolysis and aminolysis of AQ-amides. [a] *ee* not reported.



Scheme 38. Ozonolysis and pH-neutral hydrolysis of AQ-amides.[159]

(Scheme 8). Ozonolysis, on the other hand, cleanly afforded amide **250** in quantitative yields, which was transformed into



Scheme 39. Selectivity in AQ ozonolysis/hydrolysis (nr = not reported) (*ee* values not reported).

the corresponding carboxylic acid **63** by treatment with $NOBF_4$.[54]

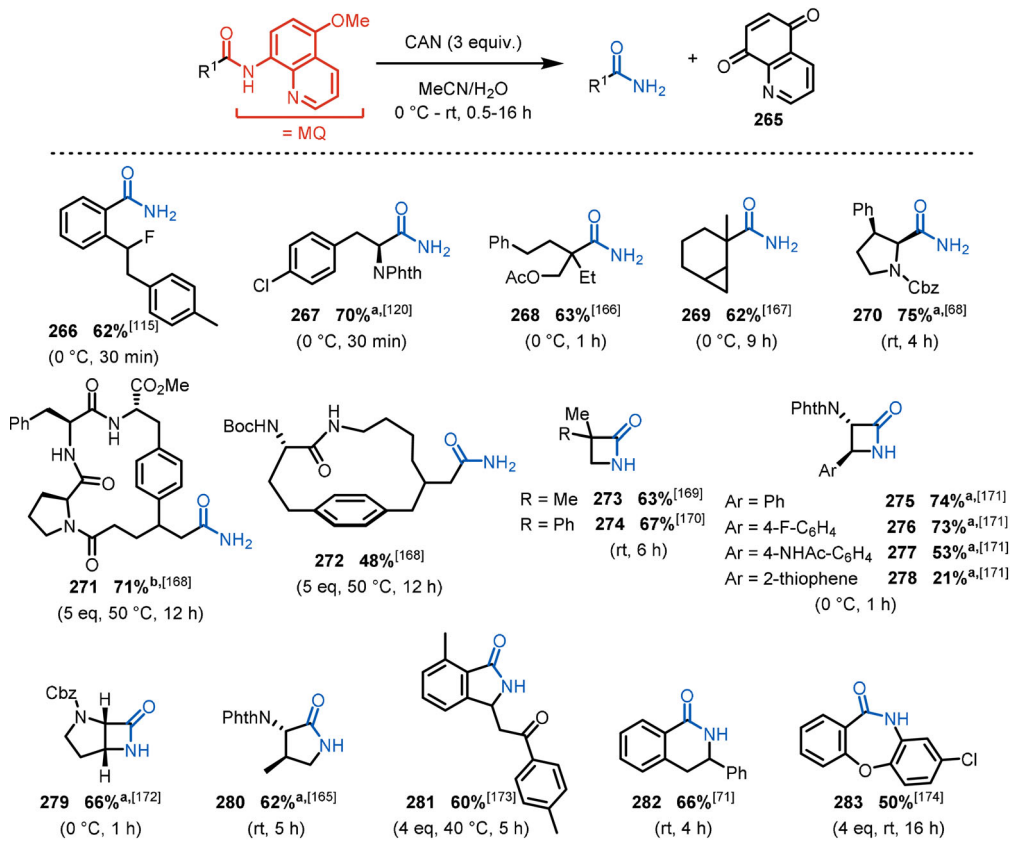
However, while hydrolysis of *N*-Boc imides occurs on the desired AQ-amide bond with high levels of selectivity due to the steric bulk of the *tert*-butyl group (see Section 1.2.1.1), the imide generated by this method (**231**/**232**) is less sterically shielded. In some cases, this can lead to low selectivity, with substantial amounts of the undesired amide product formed in addition to the desired carboxylic acid upon hydrolysis (Scheme 39).[45] Schreiber *et al.* have had some success in controlling product outcome by varying steric bulk around the AQ amide: for less bulky amides, hydrolysis was found to be more favorable at the AQ-amide bond, affording the expected carboxylic acid product (**46 b**, **47 b**) (shown by blue arrows in Scheme 39), while bulkier AQ-amides reacted at the pyridine amide bond giving the 'undesired' amide product (**258**, **259**) (red arrows in Scheme 39).[45] When Maulide *et al.* carried out the hydrolysis step under acidic conditions, the major product was the primary amide (**260**–**263**).[54] Boger *et al.* were able to avoid formation of the undesired amide by-product in their synthesis of **264** by addition of pyridine to the ozonolysis step.[160,163]

2.2. Oxidative removal of MQ (8-amino-5-methoxyquinoline)

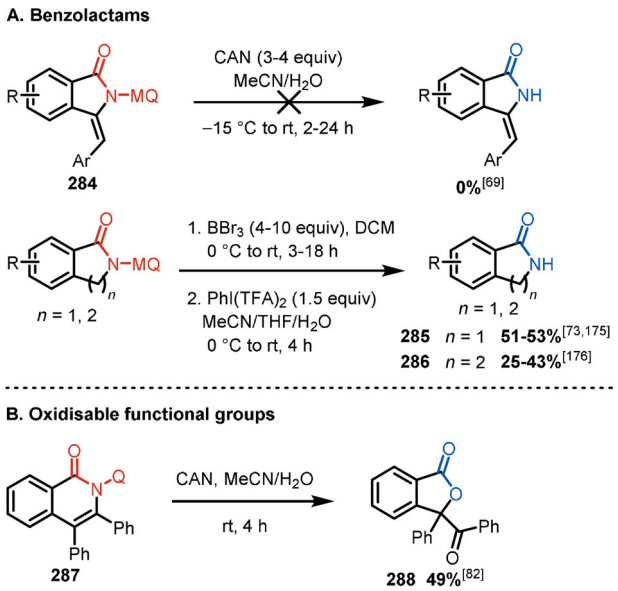
While ozonolysis offers a powerful protocol for AQ removal, giving access to carboxylic acids and primary amines in high yields, a potential limitation of this methodology is the presence of functional groups that can be oxidized by ozone, for which milder oxidative conditions would be advantageous.

Para-methoxyphenyl (PMP) is an electron-rich amine protecting group that can be removed under very mild oxidative conditions by forming a charge-transfer complex with electron-deficient cerium ammonium nitrate (CAN).[164] Taking inspiration from this chemistry, Chen and co-workers developed a popular derivative of the AQ directing group: 8-amino-5-methoxyquinoline (MQ),[165] that can be removed upon treatment with CAN at room temperature, furnishing primary amides in moderate to good yields (Scheme 40). For aromatic amides (such as **266**), basic hydrolysis of AQ often occurs with similar yields.[115] However, the MQ derivatives becomes highly advantageous on sterically encumbered substrates for which AQ-hydrolysis is sluggish or indeed not practically possible: bulky *alpha*-substituents (**267**–**268**),[120,166] bulky cyclohexane (**269**)[167] and pyrrole substrates (**270**)[68] as well as peptide macrocycles (**271**–**272**)[168] that are resistant towards AQ-removal and cyclic amides (**273**–**283**)[71,165,169–174] are tolerated under these conditions. However, not all lactams are successfully cleaved. While benzolactam **281** was successfully deprotected—albeit under elevated reaction temperatures—all attempts to remove the MQ or AQ directing groups from benzolactam **284** failed (Scheme 41 A).[69] Miura *et al.* found that removal of MQ from benzolactams **285**/**286** was possible in moderate yields, but only when more forcing conditions were used (BBr_3 followed by a hypervalent iodine oxidant).[73,175,176] Interestingly, Daugulis *et al.* have reported one example of successfully removing the less electron-rich AQ directing group (**287**) using Chen's oxidative CAN conditions (Scheme 41 B).[101] However, this example highlights one of the major limitations of this method: as with Maulide's ozonolysis, functional groups that are easily oxidized are not tolerated under these conditions. In this example, the double bond in the isoquinoline product is also oxidized causing rearrangement to the ketolactone (**288**).

Due to its ease of removal, the MQ directing group has received much attention in recent years and many methodology papers using 8-aminoquinoline (AQ) demonstrate directing group removal on the MQ-derivative.[68,170,177,178] However, this directing group is significantly more expensive than 8-amino-

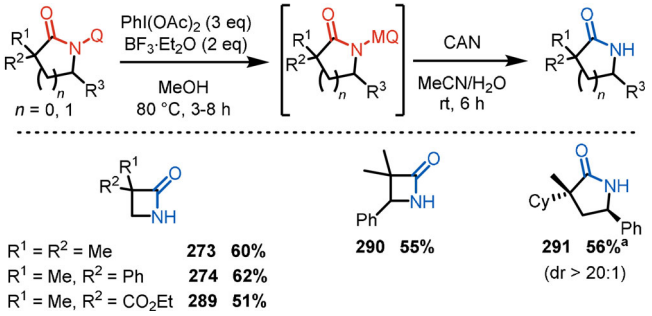


Scheme 40. Oxidative cleavage of 8-amino-5-methoxyquinoline (MQ): Scope. [a] *ee* not reported. [b] *dr* not reported.



Scheme 41. Oxidative cleavage of 8-amino-5-methoxyquinoline (MQ): Limitations.

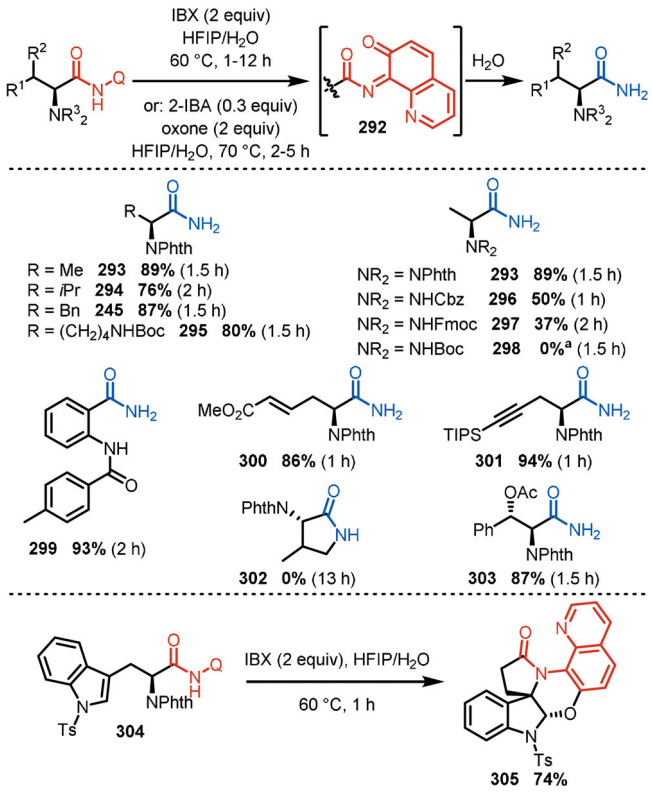
quinoline (Sigma Aldrich catalogue, September 2020: MQ 76.40 €/g, AQ 9.04 €/g), its synthesis from cheap 5-chloro-2-nitroaniline is low yielding (39% over 3 steps) and while AQ can be recovered and recycled after most cleavage reactions, MQ is oxidized to quinolone **265** during removal with CAN and can thus not be reused (Scheme 40).[165] In addition, MQ-derivatives often give lower yields in the functionalization/C–H activation step than their AQ equivalents.[68,170,177,178] A possible solution to these problems was developed by Li and Ge who demonstrated a one-pot protocol for the methoxylation of AQ to MQ and subsequent removal of the directing group with CAN in yields that are comparable to those reported for one-step MQ removal (Scheme 42).[179]



Scheme 42. One-pot transformation of AQ to MQ and oxidative removal. [a] Step one at 50 °C; no erosion of *dr*.[179]

2.3. IBX oxidation

Zhang, Zhang and Chen recently reported the IBX-mediated oxidative cleavage of AQ from α-amino acid derivatives

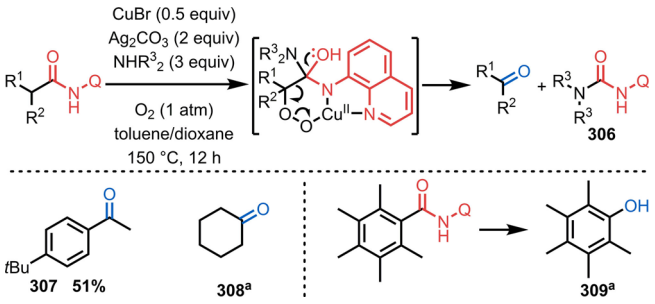


Scheme 43. Oxidative removal of AQ from α-amino acid derivatives (*ee* values not reported).[180] [a] Complex mixture.

(Scheme 43).[180] Oxidative dearomatization of 8-aminoquinoline is proposed to form an *o*-iminoquinone (**292**) which is highly susceptible to hydrolysis. Aromatic and aliphatic AQ-amides are thus transformed to primary amides at 60–70 °C with only a slight erosion of *ee* (from >99% to 96% for **293**). Bulky *alpha*-substituents are tolerated and do not need to be derivatized, even in the presence of a *beta*-substituent (**303**). A screen of common protecting groups for α-amino acids found excellent yields for *N*-Phth derivatives (**293**), lower yields for Cbz (**296**) and Fmoc (**297**) protected compounds, and decomposition of *N*-Boc protected α-amino acids (**298**). The method was selective for 8-aminoquinoline cleavage over other amides (**299**), carbamates (**295**), and esters (**300**, **303**). Bulky, *ortho*-substituted aromatics (**299**) were tolerated, but electron-rich phenylalanine derivatives underwent spirocyclization instead of AQ-cleavage. A similar side-reaction was observed for tryptophan derivative **304**. Lactams (**302**) were completely unreactive under these conditions (see section 1.1.1.2 for more information on the reactivity of AQ-amides bearing lactam substituents).

2.4. Copper-mediated oxidation

While we were preparing this manuscript, Guo and Cai published a radical oxidation mediated by Cu^{I} and molecular oxygen (Scheme 44).[181] The paper focuses on the formation of AQ-ureas **306**, however it is also a rare example of AQ-removal that cleaves the C–C(O) bond, rather than the (O)C–N bond



Scheme 44. Oxidative C–C cleavage for AQ removal.[181] [a] Detected by GC/MS.

discussed in most of the examples given in this review. As such, we are confident it will pave the way for further development of interesting oxidative AQ-removal protocols via C–C bond cleavage that will vastly expand the scope of accessible products.

3. Reductive Cleavage of the Amide Bond

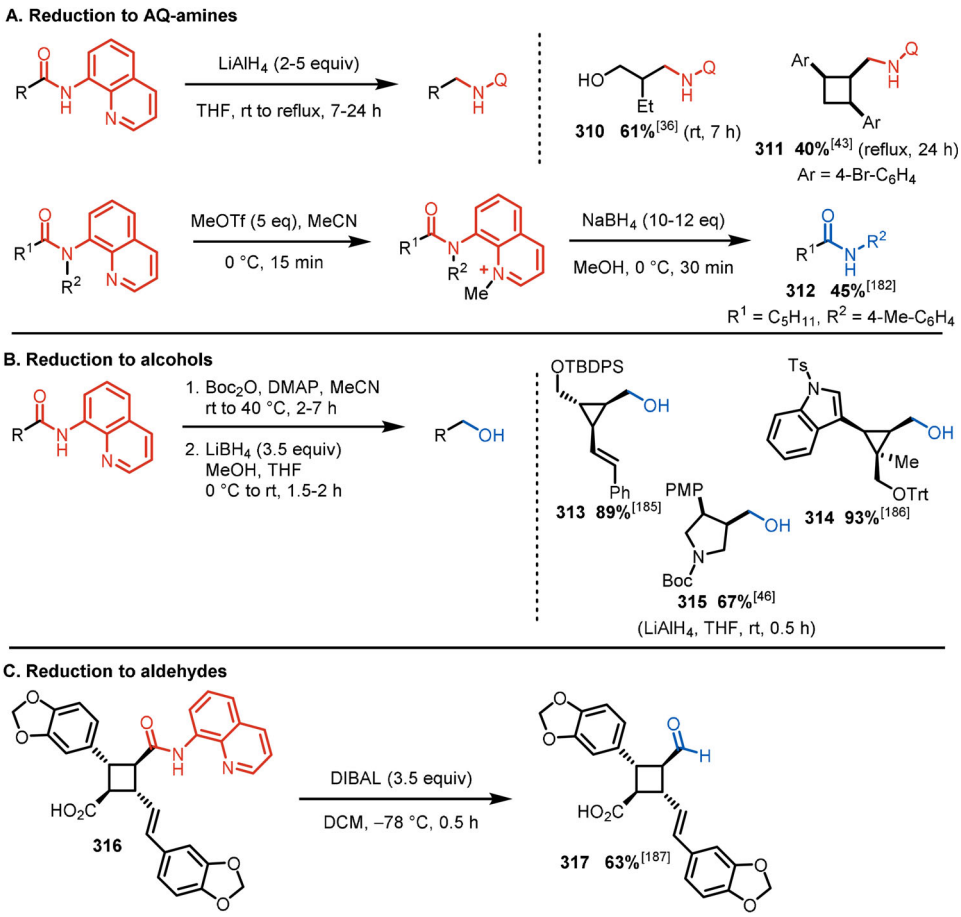
3.1. Metal hydrides

Reduction of secondary amides with $LiAlH_4$ affords amines (**310**, **311**),[36,43] and is therefore not useful for the removal of directing groups (Scheme 45 A). Tertiary amides can be activated by *N*-methylation of the quinoline ring and reduced to give a secondary amide (**312**) from which the AQ group has been cleaved.[182–184] Reduction to the alcohol is generally achieved by pre-activation of the amide bond with Boc_2O followed by treatment with $LiAlH_4$ or $LiBH_4$ (**313**–**314**, Scheme 45 B),[46,185,186] though a small number of examples exist where direct reduction of the AQ-amide without pre-activation was successful.[22,56] Baran *et al.* demonstrated the reduction of highly encumbered AQ-amide **316** to the corresponding aldehyde with concomitant removal of the AQ directing group using DIBAL (Scheme 45 C).[187] Crucial for the success of this reaction were the coordinating AQ directing group in combination with a non-coordinating solvent.

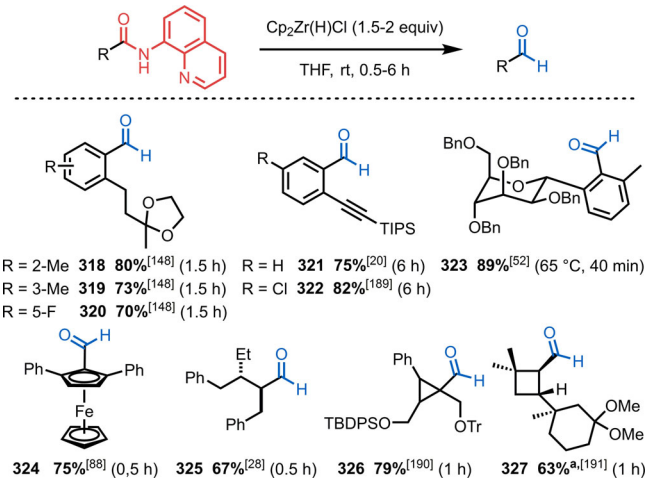
A more robust and versatile method to convert AQ-amides to aldehydes uses Schwartz's reagent, $Cp_2Zr(H)Cl$ (Scheme 46). First demonstrated to selectively transform amides to aldehydes by Georg *et al.* in 2007,[188] this reagent must be stored and handled under strictly inert and anhydrous conditions (generally achieved in a glovebox), but the reduction reaction itself proceeds quickly and reliably outside the glovebox at room temperature, providing aromatic (**318**–**324**)[20,52,88,146,189] and aliphatic (**325**–**327**)[28,190,191] aldehydes in good to excellent yields. The stereochemistry of the starting material is preserved (**325**, **327**) and sterically hindered cyclobutane substrates (**327**) are tolerated.

3.2. Directing group modifications

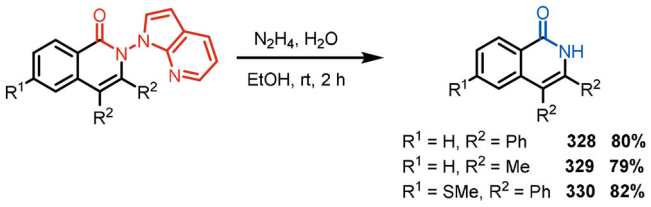
A full overview of alternative directing groups is outside the scope of this review, but two interesting AQ-modifications will



Scheme 45. Reduction of AQ-amides with metal hydrides: **A.** to AQ-amines, **B.** to alcohols (PMP = *para*-methoxyphenyl, Trt = trityl/ triphenylmethyl), **C.** to aldehydes (*ee* values not reported).



Scheme 46. Reduction of AQ-amides with Schwartz's reagent. [a] *ee* not reported.

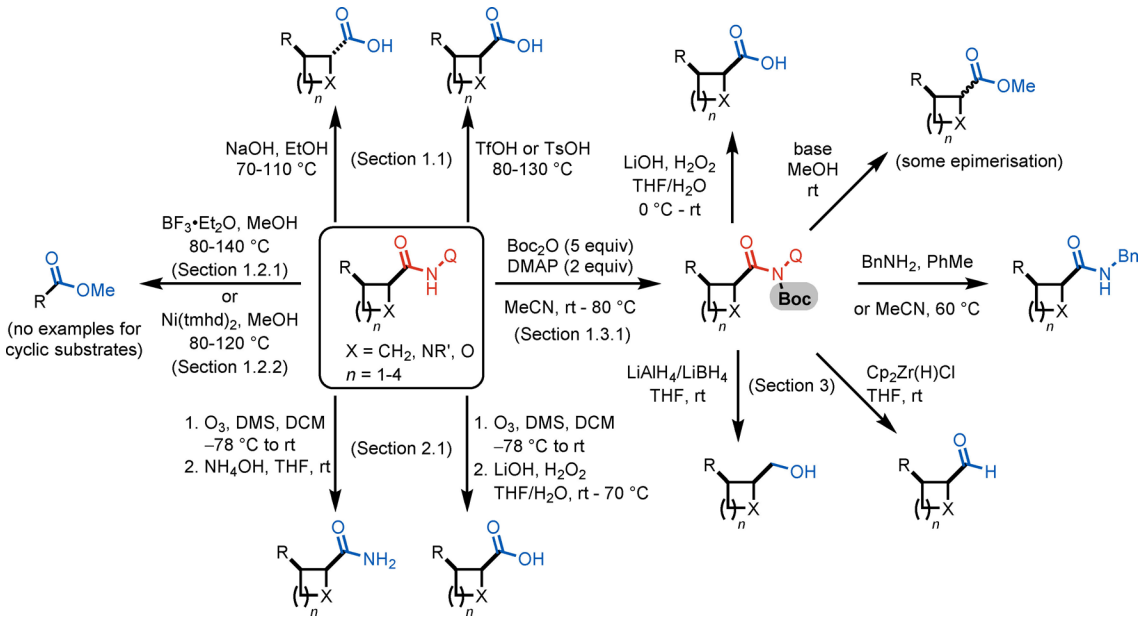


Scheme 47. Reductive cleavage of *N*-amino-7-azaindole.[72]

be mentioned here. While Chen's 8-amino-5-methoxyquinoline (MQ) modification provides a more easily oxidized directing group (see Section 2.2), Ravikumar and co-workers introduced *N*-amino-7-azaindole as an easily reduced AQ-variant (Scheme 47).[72] This directing group, which can be synthesized in 97% yield from commercially available 7-azaindole (Sigma Aldrich catalogue, September 2020, 11.88 €/g),[192] showed the same directing group ability in ruthenium catalyzed C–H annulation of benzamides as AQ, but reductive cleavage of the weak N–N bond with hydrazine was much easier than removal of AQ, which can be extremely difficult on lactam substrates (see Section 1.1.1.2, Scheme 14).

Summary and Conclusion

8-Aminoquinoline is one of the most powerful and versatile directing groups in transition metal-catalyzed methodologies and while its installation and use are well understood, its removal can pose a frustrating challenge.



Scheme 48. Divergent removal of AQ directing group.

The choice of deprotection conditions is influenced by (1) substrate structure and (2) the functional group that is required in the target molecule. Classic hydrolysis in refluxing acid or base can be successful for simple, unhindered substrates. Alternatives have been developed to tolerate a wider range of functional groups, activate less reactive substrates, and access a variety of different products, allowing for divergent syntheses of substrate libraries. Some of the strategies discussed in this review are summarized in Scheme 48, including their stereochemical outcome when applied to cycloalkyl AQ-amides. However, due to the low reactivity of the amide bond, some selectivity issues and unreactive substrates remain. Inspiration for their AQ deprotection may be found in the amide activation literature that has been referenced throughout this review or in one-pot transition metal-catalyzed C–O, C–N and C–C annulation reactions with concomitant AQ removal.

Recent efforts have focused on transient auxiliaries or a combination of coordinating functional groups and exogenous ligands as a powerful alternative for selective functionalization that circumvent the need for harsh cleavage steps. A full discussion of this field is beyond the scope of this review and we would like to point the reader towards excellent recent publications in this area.[193–196] These approaches are often complementary to covalent directing group chemistry, and there is clearly still a need for mild, efficient methods for directing group cleavage at this time.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H activation · directing groups · homogeneous catalysis · hydrolysis · synthetic methods

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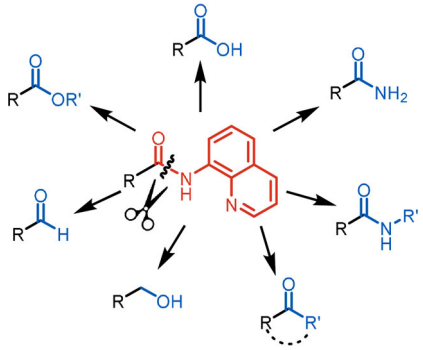
REVIEW

Synthetic Methods

*L. S. Fitzgerald, M. L. O'Duill**

■■ – ■■

A Guide to Directing Group Removal: 8-Aminoquinoline



Obstinate auxiliaries: How can directing groups be removed after successful C–H activation or transition metal-catalyzed functionalization? This Review discusses different strategies for 8-aminoquinoline removal to access a wide variety of products. Challenges and limitations are highlighted and alternative approaches are suggested to provide a comprehensive end-users' guide to directing group removal.

8-Aminoquinoline is one of the most powerful and versatile directing groups in transition metal-catalyzed methodologies and while its installation and use are well understood, its removal can pose a frustrating challenge. In their review on page ■■ ff., L. S. Fitzgerald and M. L. O'Duill discuss different strategies for 8-aminoquinoline removal to access a wide variety of products. Challenges and limitations are highlighted and alternative approaches are suggested to provide a comprehensive end-users' guide to directing group removal.

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Liam S. Fitzgerald
Dr. Miriam L. O'Duill http://orcid.org/0000-0002-8312-824X

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