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Bridging C-H activation: Mild and versatile cleavage of the 8-Aminoquinoline directing group

Martin Berger,[a] Rajan Chauhan,[a] Catarina A. B. Rodrigues,[a] and Nuno Maulide*[a]

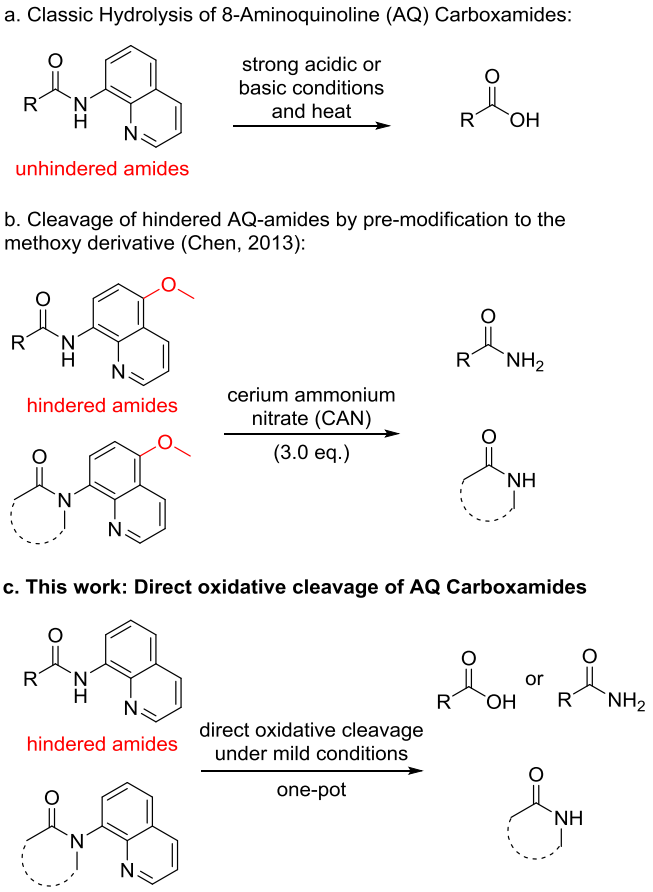
8-Aminoquinoline has emerged as one of the most powerful bidentate directing groups in history of C-H activation within the last decade. However, cleavage of its robust amide bond has shown to be challenging in several cases, thus jeopardising the general synthetic utility of the method. To overcome this limitation, we herein report a simple oxidative deprotection protocol. This transformation rapidly converts the robust amide to a labile imide, allowing subsequent cleavage in a simple one-pot fashion to rapidly access carboxylic acids or amides as final products.

Transition metal catalyzed CH-activation utilizing bidentate directing groups has attracted much attention over the past decade.[1] After its introduction by Daugulis *et al.* in 2005, 8-Aminoquinoline (AQ) has become perhaps the most efficient and popular structure among such directing groups.[2] Indeed, more than 150 publications to date report its use for directed C-H activation, it being compatible with a large number of transition metal catalysts and substrate classes.[3] Clearly, the removal of a directing group is of critical importance, since a remaining, recalcitrant auxiliary in the product essentially voids any methodology of its synthetic utility. Although the cleavage of this auxiliary is most often not demonstrated in methodology publications, AQ is generally considered to be a removable directing group as demonstrated by some protocols employing strong acidic or basic conditions at high temperatures (Scheme 1a).[4] At the same time, several examples have been reported where attempted cleavage met with failure. In certain cases, prior *N*-Methylation[5] or *N*-Boc protection[6] was found to facilitate cleavage under basic conditions; in other cases, unsuccessful cleavage was reported and even resulted in a necessary change of the directing group.[7]

A pre-modified directing group was introduced by Chen *et al.* in 2013 with 8-Amino-5-methoxyquinoline (MQ) (Scheme 1b).[8] This auxiliary provides similar results to AQ in C-H activation and can be removed by oxidation with superstoichiometric CAN (cerium ammonium nitrate; usually 3.0 equivalents are required). Interestingly, several protocols demonstrate the cleavage of MQ on hindered carboxamides[9] and *β*- or *γ*-lactams,[10] although the C-H activation scope of the methodologies in question is investigated using AQ. This fact can be explained by the higher cost[11] or lengthy 3-step preparation which is associated with MQ. Additionally, only the carboxamide product can be obtained upon removal of MQ (Scheme 1b).

Statements such as "(…) the AQ group proved highly resistant to a wide variety of reagents (…)"[9a] are not uncommon in the literature, and significantly hinder the synthetic promise that C-H activation holds for organic chemistry in general.

Herein we wish to report a mild and simple method for cleavage of this high-performance auxiliary into amides or carboxylic acids (Scheme 1c).



Scheme 1. (a) Classic cleavage of AQ directing group by harsh acidic or basic conditions, (b) Cleavage of the modified *5*-Methoxy-*8*-Aminoquinoline (MQ) directing group by CAN and (c) Direct oxidative cleavage of *8*-Aminoquinoline (AQ) in the present work.

We reasoned that the classic approach for cleavage of secondary amides like AQ is a nucleophilic attack on the carbonyl group, which can be achieved by force using harsh conditions. Nevertheless, since several classes of amides can be expected to resist this attack, a different approach is needed in order to develop a general deprotection methodology. We

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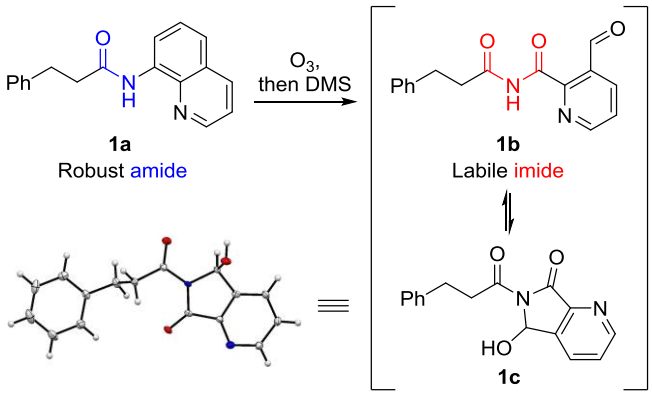
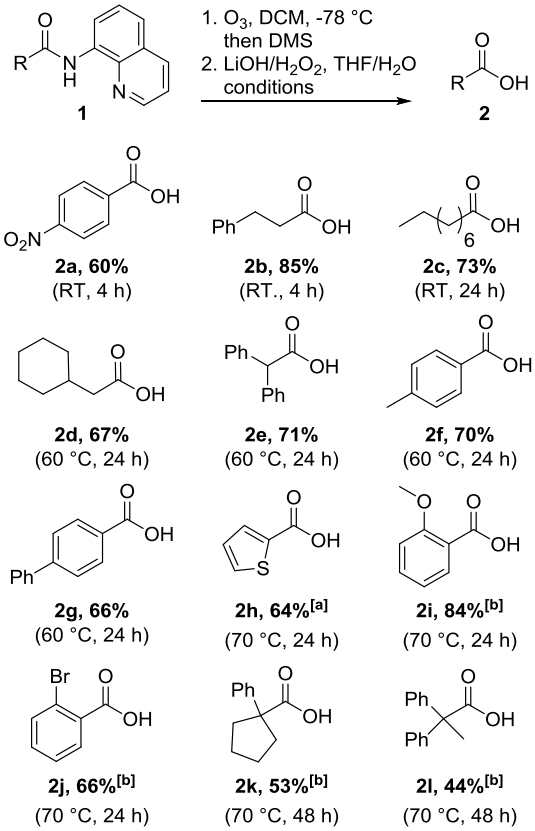
aimed for pre-weakening of the amide[12] by partial oxidative fragmentation of the quinolyl moiety, which can be achieved by ozonolysis typically within five minutes.[13] Reductive work-up affords a fragile *imide* intermediate (cf. **1b**, in equilibrium with **1c**). (Scheme 2, confirmed by X-ray analysis). The latter might be easily cleaved in a one-pot operation.



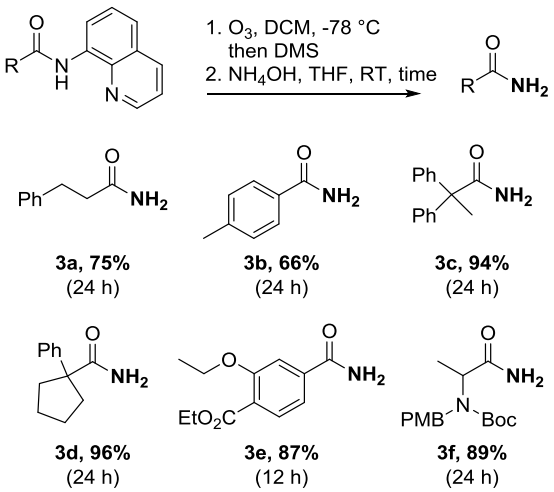
Scheme 2. Ozonolytic weakening of the robust AQ-amide into a labile imide. X-ray crystallographic structure of **1c** is enclosed.

In the event, we found that while the reported oxidative cleavage of MQ only provides to access primary amides, ozonolysis followed by hydrolysis of AQ-amides **1** can yield either the amide or the carboxylic acid. As depicted in Scheme 3, ozonolysis was performed in dichloromethane at -78 °C. Selective cleavage of the quinolyl moiety was completed within a few minutes, indicated by the appearance of the characteristic blue color and resulting often in the precipitation of the desired imides. Following a survey of conditions (see SI for details), LiOOH was chosen as a convenient reagent for hydrolysis. It is important to note that, in our hands, ozonolysis was generally a very clean process. The carboxylic acid products can be obtained analytically pure without the need for chromatography, by a simple acid-base extraction procedure. While electron-deficient aryl- (**2a**) and simple alkylamides (**2b-c**) are converted to the acids already at room temperature in good yields, more sterically demanding or electron-rich amides were cleaved at 60 or 70 °C (**2d-g, 2i-j**), respectively. Notably, thiophene **2h** was isolated in good yield without undesired decomposition by ozone. The cleavage of very hindered amides was successfully demonstrated with **2k** and **2l**.

Alternatively, if the primary amide is the desired product, simple treatment of the imide linkage with aqueous ammonia affords the desired product already at RT in typically very good yields (Scheme 4). Even the highly hindered amides **3c** and **3d** gave excellent yields, and also **3a** and **3b** were obtained in high yields, similar to the yields of the corresponding acids **2b** and **2f,** obtained by treatment with LiOOH.



Scheme 3. Mild cleavage of AQ-directing group under basic conditions. Reaction conditions: Ozonolysis of **1** (0.2 mmol) in DCM (4 mL) at -78 °C, then DMS, 2 h at room temperature. Hydrolysis with LiOH * H_2O (1.2 mmol) and H_2O_2 (2 mmol) in THF (2.4 mL) and water (0.6 mL), but [a] no H_2O_2 and [b] 2.4 mmol LiOH * H_2O and 4.0 mmol H_2O_2 was used.

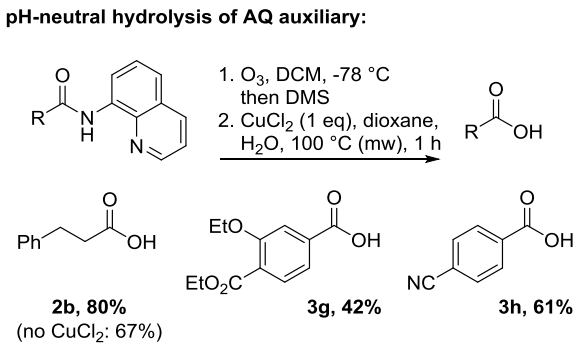


Scheme 4. Aminolysis of AQ directing group at room temperature. Reaction conditions: Ozonolysis of **1** (0.2 mmol) in DCM (4 mL) at -78 °C, then DMS, 2 h at room temperature. Aminolysis with NH_4OH (1.5 mL) and THF (1.5 mL).

Under these conditions, chemoselective aminolysis can occur even in presence of an ester function, as demonstrated by

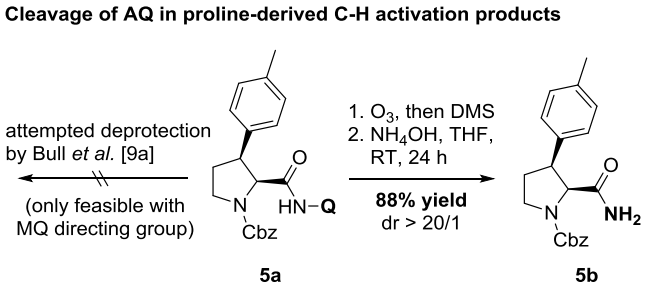
3e which was obtained in high yield. Additionally, high chemoselectivity is observed in presence of a *p*-methoxybenzyl protecting group (PMB) with isolation of aminoamide **3f** in very high yield.

The labile character of the obtained imides also allows hydrolysis to be carried out under pH-neutral conditions. In the event, heating of **1b/c** in a mixture of water and dioxane at 100 °C for 1 hour under microwave irradiation afforded the carboxylic acid **2b** in 67% yield. Addition of $CuCl_2$ (1 equivalent) slightly improved the yield to 80%, with the metal salt possibly acting as Lewis acid.



Scheme 5. Hydrolysis of AQ directing group under pH-neutral conditions.

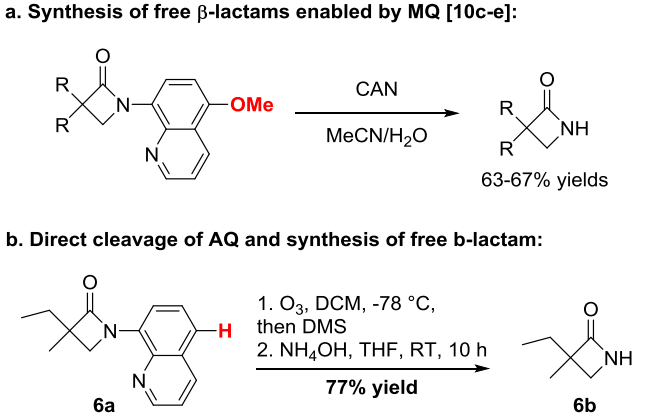
In order to fully assess the utility of this method, specific examples of problematic deprotections were selected from the literature. In the first showcase (Scheme 6). Bull *et al.* reported a *syn*-diastereoselective Pd-catalyzed CH-arylation on *N*-protected proline derivatives utilizing the AQ directing group.[9a]



Scheme 6. Successful cleavage of AQ in a recalcitrant example (Bull *et al.*, ref 9a) enabled by ozonolysis.

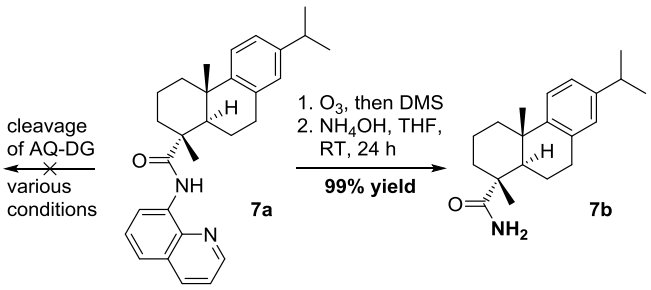
The authors reported that the AQ-motif was highly resistant towards cleavage (Scheme 6), and had to resort to a 3-step preparation of the MQ auxiliary[8,9a] in order to accomplish deprotection to the primary amides after the C-H activation step. In contrast, application of our aminolysis protocol to **5a** led to smooth removal of the AQ linkage yielding the product **5b** at room temperature in very high yield and without epimerization (Scheme 6).

Another illustration of the usefulness of the method presented herein is the cleavage of the AQ directing group after intramolecular CH-amination, yielding lactam products. To the best of our knowledge, all reported procedures employ MQ when demonstrating the cleavage of the auxiliary (Scheme 7a).[10] Attempts have been made to shorten the synthetic route by installation of the methoxy-group directly on the AQ moiety prior to cleavage with CAN, but this still results in an overall cumbersome sequence.[14] In the event, ozonolytic cleavage and subsequent aminolysis applied to lactam **6a** smoothly afforded the desired product **6b** in very good yield, without noticeable lactam ring-opening.



Scheme 7. (a) Previous cleavage of the aminoquinoline directing group on *β*-lactam utilizing MQ and (b) direct cleavage of the actual AQ-directing group enabled by ozonolysis.

A final demonstration was carried out on the natural diterpene dehydroabietic acid (DHAA). DHAA and its derivatives were found to have a wide range of biological activities.[15] Interestingly, only few examples of modification of this resin acid on positions in close proximity to the carboxylic acid can be found. Thus, C(sp^3)-H-activation on this substrate as enabling methodology was already the subject of prior investigations by Yu *et al.*, demonstrating the feasibility of C-H-alkylation,[16] amination[17] and borylation.[18] Not demonstrated is the cleavage of the amide directing groups in order to generate acid or amide analogues. Unsurprisingly for a hindered carboxylic acid derivative, the methylester of DHAA was already shown to be very resistant to hydrolysis even under harsh conditions.[19] In our hands, the amide **7a** proved extraordinarily robust.



Scheme 8. Room-temperature cleavage of AQ directing group on highly hindered dehydroabietylamide.

A large survey of conditions including many strong acids or bases at high temperatures resulted mainly in recovered starting material. Strikingly, pre-ozonolysis of the quinolyl moiety allowed the cleavage to occur even at room temperature in very high yield (Scheme 8).

In summary, we have reported herein a new method for the easy cleavage of the ubiquitous aminoquinoline directing group in C-H activation chemistry. This protocol employs mild conditions and enables the preparation of either the carboxylic acid or the amide derivative, relying on ozonolytic weakening of the amide function. It is our belief that the conditions herein shall be deemed useful and widely adopted by the practitioners of C-H activation at large.

Experimental Section

A stream of ozone is passed through a solution of *N*-Quinolylamide (0.2 mmol) in dichloromethane (4 mL) at -78 °C until the characteristic blue color appears. A stream of oxygen is passed through until decolorization occurs and the mixture is quenched with dimethylsulfide (0.05 mL). The mixture was allowed to warm to RT, stirred for 2 hours and concentrated under high vacuum to complete dryness. The crude imides were subjected to the specific hydrolysis or aminolysis conditions followed by an extraction with DCM (see SI for details and conditions). Drying with $MgSO_4$ and removal of solvents affords the desired amides or carboxylic acids.

Acknowledgements

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Keywords: C-H activation • 8-aminoquinoline • directing group • cleavage • ozonolysis

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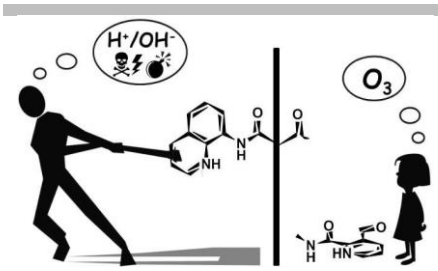

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