**Direct Imine Acylation: a Versatile Method for the Synthesis of Nitrogen Containing Heterocycles, Spirocycles and Natural Products**

|  |  |
| --- | --- |
| William P. Unswortha\*  Richard J. K. Taylora\*  a Department of Chemistry, University of York, Heslington, York, YO10 5DD (UK)..  william.unsworth@york.ac.uk; [richard.taylor@york.ac.uk](mailto:e-mail_address@address.com)  Click here to insert a dedication. |  |
|  |

Received:   
Accepted:   
Published online:   
DOI:

Abstract Diverse nitrogen-containing heterocyclic compounds can be synthesised *via* the *N*-acylation of imines using functionalised carboxylic acids (Direct Imine Acylation, DIA). The carboxylic acids are activated *in situ* using coupling agent T3P, before reacting with the imine coupling partner to generate *N*-acyliminium ions *in situ*, that can then be trapped by oxygen-, nitrogen-, sulfur- or carbon-based nucleophiles built into the carboxylic acid. This versatile, convergent method has been used to generate a wide range of products, including aromatic and aliphatic heterocycles, β-lactams, azaspirocycles and natural products.

**Table of contents**

1 Introduction

2 DIA in the total synthesis of ‘Upenamide

3 DIA with benzoic acid derivatives

4 DIA with aliphatic carboxylic acids

5 DIA in the synthesis of β-lactams

6 DIA in the synthesis of azaspirocycles

7 Mechanistic Studies

8 Conclusion

**Key words** *N*-heterocycles, spirocycles, natural products, *N*-acyliminium ions, diversity, ‘upenamide, evodiamine, cavidine.

**1. Introduction**

The efficient synthesis of functionalised, small organic molecules is of paramount importance in the identification of novel lead compounds in medicinal and agrochemical discovery programmes.1 Within these vital research fields, nitrogen-containing heterocycles are amongst the most prevalent structural classes used, hence novel methods which expedite their synthesis will always be of high interest.

This Account describes a research program developed in our group at the University of York to generate such compounds, based on a series of processes collectively referred to as ‘Direct Imine Acylation’ (DIA) reactions. Since our first report of a DIA reaction in 2013,2 a further six articles have been published by our York group,3-8 in which DIA has been used to access a broad range of nitrogen-containing heterocycles, spirocycles and natural products.

As the methodology has evolved, an increasing number of modified reaction protocols have emerged, enabling the synthesis of increasingly diverse substrate classes, but fundamentally, all DIA processes are based on a single, simple concept, the cornerstone of which is the improved synthesis of functionalised *N-*acyliminium ions **1** (Figure 1). These valuable reactive intermediates, which have been used in synthetic chemistry for several decades, are characterised by their high electrophilicity, and consequently the majority of their reactions are based on coupling reactions with nucleophiles.9

The high reactivity *N-*acyliminium salts means that they cannot be synthesised directly and isolated, and instead they must be formed *in situ* from a suitable precursor. Typically, this is done *via* the reversible extrusion of a suitable leaving group (most commonly a hydroxy, alkoxy or halogen substituent), usually under acidic conditions, from a precursor of the form **2** (Figure 1).9 The requisite precursor **2** can itself be formed*via* a number of routes, the two most common being either a regioselective partial reduction of an imide (**3 → 2**), or the α-oxidation of an amide (**4 → 2**). These approaches (and others) have been used to good effect to generate *N-*acyliminium ions, but poor regiocontrol in these processes, as well as functional group incompatibility, can be problematic in some substrates.



**Figure 1.** Traditional approaches to generate *N*-acyliminium ions **1** and DIA.

An alternative way to access reactive intermediate **1** is using our DIA methodology, which refers to the direct acylation of an imine *via* the reaction of the sp2 hybridised imine nitrogen with an activated carboxylic acid derivative (**5 → 6**, Figure 1).2-8 This convergent method to form *N*-acyliminium ions has a number of important synthetic advantages compared with previous approaches, and these are discussed throughout this Account. The strengths and weaknesses of the methodology are detailed, along with its successful application in natural product synthesis, a discussion of the mechanism of DIA and future perspectives. The ordering of the synthetic sections is roughly chronological in order that a sense of how the method evolved can be gained, beginning with its inception in a complex natural product synthesis.

**2. DIA in the total synthesis of ‘upenamide**

Unusually, the first example of a DIA reaction that we performed remains by far the most complex.3-4 At the time of this experiment, we did not envisage that DIA would be extended into the broad synthetic method that it has become, instead, it was devised as a solution to a synthetic problem in a long-standing project in the group to complete the total synthesis of the two proposed structures of ‘upenamide **7a** and **7b** (Figure 2).10,11



**Figure 2.** The proposed structures of ‘upenamide **7a** and **7b**.

Before the development of DIA, a key step in our planned syntheses of compounds **7a** and **7b** was a SnCl2·2H2O mediated oxa-quinolizidinone formation, in which it was planned to form the A and B rings of the target molecules in a single synthetic step (*e.g.* **8** → **11**,Scheme 1A).11g The synthetic method had been validated in simpler model studies,11g,12 but progress on this route was thwarted by difficulties accessing large amounts of a suitable precursor of the form **8**. This prompted us devise an alternative strategy, focusing on the formation of *N-*acyliminium ion **10** *via* a convergent route, in the hope that breaking down the starting material into two smaller fragments would simplify the synthesis. We realised that the most direct route to generate such an *N-*acyliminium ion was *via* the *N*-acylation of an imine **12** with an activated carboxylic acid derivative of the form **13**. At the time, precedent for the *N-*acylation of imines was limited, although a few examples of imines reacting with acid chlorides fluorides or anhydrides (**13a-c**) had been published,13 providing reassurance that this approach was at least feasible. However, concerns that some of the acid-sensitive moieties present in ‘upenamide (*e.g.* the DE ring system) would be incompatible with acid chlorides, fluorides or anhydrides led us to consider whether the same transformation could be performed directly from an imine **12** and carboxylic acid **13d**,which would require the use of a coupling agent to activate the acid *in situ* (Scheme 1B)*.*14



**Scheme 1.** SnCl2·2H2O mediated cyclisation (**A**) and Direct Imine Acylation (**B**) strategies for the construction of the ‘upenamide AB ring system **11**.

To test this idea, imine **14** and carboxylic acid **15** were synthesised3 and their coupling was attempted using a selection of standard peptide coupling reagents.15 Following brief optimisation, propylphosphonic acid anhydride16 (T3P, a mild, readily available reagent, with the additional benefit that its by-products are water soluble and hence are easily removed during work-up) emerged as the best reagent to promote this transformation; imine **14** and acid **15** were stirred at RT in the presence of NEt(*i*-Pr)2 and T3P (presumably forming an *N*-acyliminium adduct **16**) before excess SnCl2·2H2O was used to cleave the silyl protecting group and promote cyclisation, forming pentacycle **17** in 66% yield, as a single diastereoisomer following column chromatography (Scheme 2). Subsequent steps completed the synthesis of one the proposed structures of ‘upenamide **7a** while the same sequence of reactions was also used to form diastereoisomer **7b**.3



**Scheme 2.** DIA in the synthesis of ‘upenamide precursor **17**. TIPS = triisoproylsilyl; TBS = *tert-*butyldimethylsilyl; Boc = *tert-*butyloxycarbonyl.

Unfortunately, the spectroscopic data of neither synthetic compound matched those reported for the natural product, suggesting that the natural product may have been incorrectly assigned.3,4,10 After several years of effort, there is no denying that there was not some degree of frustration at this outcome, and if the synthesis of the natural product is taken as being the overarching goal of the project, it was a somewhat disappointing ending. However, this point of view fails to acknowledge that so often in natural product synthesis, the knowledge acquired in solving problems encountered along the way is more important than the target itself, and from this perspective, the project was certainly worthwhile, in view of the subsequent new methodology that it helped to inspire.2-8,12

**3. DIA with benzoic acid derivatives**

We soon came to realise that if DIA could be applied successfully in complex natural product synthesis, then surely it would also be applicable on simpler systems, hence attention then turned to its development as a more general method.2,5 These studies started by examining the coupling of imines with *ortho*-substituted benzoic acids, exemplified by the coupling of imine **18** with salicylic acid **19a** (Scheme 3).2 This transformation was achieved by heating the two components at 90 °C in toluene with NEt(*i*-Pr)2 and T3P, furnishing product **21a** in high yield. The necessary increase in temperature in this case (compared to the earlier examples above) is thought to be a consequence of the reduced electrophilicity of the activated acid compared with aliphatic acid **15**. However, despite the need to use a higher reaction temperature, these acid coupling partners proved to be particularly well-suited to take part in DIA reactions. First, many such compounds are readily available (especially salicylic acid derivatives) with a range of substitution patterns. Second, and perhaps more importantly, there is no requirement to protect the nucleophile on the carboxylic acid component, as its nucleophilicity is naturally curtailed *via* conjugation into the adjacent electron withdrawing acid group; this means that the phenol was not sufficiently reactive to take part in competing *O*-acylation, but was reactive enough to trap the *N*-acyliminium ion once it formed (**20 → 21a**).



**Scheme 3.** Direct Imine Acylation of imine **18** with salicylic acid **19a**.

The versatility of DIA to generate diverse heterocyclic scaffolds using *ortho­*-substituted benzoic acid derivatives has been well demonstrated, with 35 examples now published.5 The wide substrate scope is demonstrated below, starting by varying the acid coupling partner and coupling with imine **18**.Benzoic acids bearing*O*- *N*- *S*- and *C*-centred nucleophiles were all found to be compatible with the same basic procedure (Figure 3).



**Figure 3.** Direct Imine Acylation of imine **18** with *ortho­*-substituted benzoic acid derivatives. a Reaction performed at 120 °C.

A wide range of salicylic acid derivatives **19a**–**p** were found to react well under the DIA conditions described above, affording products **21a**–**p** in good to excellent yields.2,5 In the case of products **21e** and **21g** a higher reaction temperature (120 °C) was required in order to achieve full conversion into the respective products, which was proposed to result from the activated carboxylic acid being less electrophilic than the other systems tested, in view of its electron-rich methoxy groups. Naphthalene and pyridine derivatives were also well tolerated, with products **21j** and **21k** both being formed in high yield. Similarly, efficient reactions of thiosalicylic acid and two anthranilic acid derivatives were also performed (forming **21m**–**21o**) and all three proceeded in excellent yield. Furthermore, 1,3-dicarbonyl compounds can also be used as carbon pro-nucleophiles in DIA to produce lactam **21p**, which demonstrated that C–C bond formation can also be achieved in good yield. Importantly, these reactions are unoptimised, highlighting the operational simplicity and broad utility of the process for the rapid synthesis of diverse heterocycles.

Next, the substrate scope with respect to the imine component was examined (Figure 4).2,5 Broad substrate scope was demonstrated across a range of imines, which were reacted with benzoic acid derivatives bearing*O*- *N*- *S*- and *C*-centred nucleophiles. Many of the reactions proceeded in excellent yield, with little or no optimisation required, including the synthesis of natural product evodiamine **23**, which was formed cleanly,in 95% yield, as a white crystalline solid.2,17,18 Products **21ad**–**21af** are also noteworthy as they were made from acyclic imines; acyclic *N*-acyliminium ions are far less stable than their cyclic counterparts, particularly with respect to hydrolysis,19 and hence are difficult to prepare and handle using traditional methods, but DIA overcomes this problem by forming and trapping the unstable *N*-acyliminium ions *in situ*.



**Figure 4**. Direct Imine Acylation of imines **22** with *ortho­*-substituted benzoic acid derivatives. a Reaction performed at 120 °C.

It is also important to highlight examples in which the DIA reactions proceeded less effectively. In some cases, the (unoptimised) yields are lower than those using imine **18** illustrated in Figure 3, and we believe this to be primarily a consequence the comparative stabilities of the products. Another factor which typically leads to a reduction in reaction yield is the stability of the imine precursor; for example, products **21aa** and **21ab** were each formed in comparatively low yield, and this is likely to be because the requisite imine exists primarily in its trimeric form (dodecahydro-4a,8a,12a-triazatriphenylene).20 It should also be noted that all of the highest yielding examples of DIA (*i.e.* those with yields >80%) were performed on imines that cannot tautomerise to enamines, which is an important consideration when designing new syntheses involving DIA. Ketimines are also generally not tolerated in DIA. A notable exception is the reaction of 1-methyl-4,5-dihydroisoquinoline with thiosalicylic acid, which produced **21ac** in high yield, but analogous reactions using benzoic acids substituted with *O*-, *N*- and *C*-nucleophiles did not furnish the expected products, and instead underwent *C*-acylation (*via* the enamine tautomer of the imine), resulting in the predominant formation of *Z*-enaminones **25a**, **25n** and **25p** (Scheme 4).21 Other ketimines (*e.g.* 1-phenyl-4,5-dihydroisoquinoline) were found to be unreactive under standard DIA conditions, presumably as a result of increased steric hindrance around the imine.



**Scheme 4.** The formation of *Z*-enaminones **25a**, **n**, **p**.

An interesting, successful example is the DIA reaction of isoquinoline **26** with anthranilic acid **19n** (Scheme 5). This reaction is significant given that it proceeded in high yield despite the loss of aromaticity in the ‘imine’ component. Unfortunately, this dearomatising DIA reaction appears not to be general; the analogous reactions of isoquinoline **26** with *ortho*-substituted benzoic acids bearing *O*-, *S*- and *C*-nucleophiles all failed to form any products under the same reaction conditions. Other aza-aromatics containing C=N bonds that could theoretically serve as the ‘imine’ coupling partner (quinolone, pyridine, DMAP, pyrimidine, pyrazine, oxazole, thiazole, *N*-Boc imidazole and 1,3,5-triazine) also failed to react when treated with the standard DIA reagents and *N-*methyl anthranilic acid at 120 °C. We believe that these are thermodynamic outcomes; even if *N-*acylation and cyclisation (**28 → 29 → 30**) does take place, these steps are likely to be reversible, and we propose that in the unsuccessful cases the equilibrium is biased towards the aromatic starting materials and acids. Intuitively, this thermodynamic outcome appears to reasonable; indeed, it is arguably more difficult to explain why the reaction of imine **26** and acid **19n** to form dearomatised product **27** worked so well, rather than why the others failed.22



**Scheme 5.** DIA with aza-aromatics as the ‘imine’ component.

The final example in this section is another natural product synthesis. Cavidine **34**, which was first isolated from a *Corydalis* plant in 1964, is a member of a large family of biologically active alkaloids known as protoberberines.23,24 It was thought that DIA methodology could be used as a key step in its total synthesis, and we were pleased to find that when acid **32** was reacted with imine **31** using our standard DIA procedure (see Figure 1 for conditions), lactam **33** was formed, albeit in relatively low yield (39%).25 Pleasingly, we were able to improve the yield significantly (up to 69%) by switching the reaction solvent to chloroform, running the reaction at RT rather than 90 °C and by adding BCl3 to the crude reaction mixture following *N*-acylation (Scheme 6). In examples were the cyclisation step is sluggish, we have found that the addition of Lewis or Brønsted acid directly into the reaction mixture can lead to significant improvements in the overall yield of the DIA reaction. Several more examples of the use of additives in this way are discussed in Section 4.



**Scheme 6.** The total synthesis of (±)-cavidine **34**.

**4. DIA with aliphatic carboxylic acids**

Having already established that aliphatic carboxylic acids bearing protected alcohols can be used in DIA in a single reaction system (during the synthesis of ‘upenamide precursors **7a** and **7b**, see Section 2), attention turned to examining the scope of this DIA variant using other aliphatic acids, starting with hydroxy acid derivatives.5 Although the fundamental processes involved are the same as those in the benzoic acid variants described in Section 3, there are major differences in reactivity, meaning that the reactions are generally performed under different conditions. First, the activated carboxylic coupling partners aresignificantly more electrophilic than analogous benzoic acid derivatives (as they are not conjugated to an electron-donating group through the aromatic ring) and second, the nucleophile is also more reactive than in the benzoic acid systems for the same reason.

The increased electrophilicity of the activated acid is a useful feature, as it means that the initial *N*-acylation step can be performed at a much lower temperature (typically RT). However, the increased reactivity of the nucleophilic component is a potential problem, as a result of it becoming more competitive with the imine in the acylation step. Both of these features must be balanced when designing DIA processes with aliphatic acids, as demonstrated by the reactions of imine **18** with hydroxy-acid **35a**, and its TBDMS protected analogue **35b** (Scheme 7). Positively, both reactions proceeded at RT (compared to 90 °C using salicylic acid) highlighting the significantly increased electrophilicity of the activated acids**.** However, in the case of unprotected hydroxy-acid **35a**, the yield was low due to competing *O*-acylation of the hydroxy-acid. Thankfully, this problem is easily solved by using a protected alcohol derivative; the reaction was achieved by first by performing the *N-*acylation of imine **18** with protected acid **35b** in the usual way, before treating the resulting *N*-acyliminium adduct with SnCl2∙2H2Oin CH2Cl2 at room temperature,12 which resulted in concomitant silyl cleavage and cyclisation, affording product **36** in a much improved 68% yield.



**Scheme 7.** DIA of imine **18** with hydoxyacid derivatives **35a** and **35b**.

The scope of this protocol was then explored using other imines **37** and hydroxy acids **38** (Figure 5). This DIA variant furnishes various *N*,*O*-acetal scaffolds **39a**–**f**,26 which have potential uses in the agrochemical industry as herbicides,13h,27 and importantlyincludes examples of DIA based on challenging unsubstituted and acylic imine substrates.



**Figure 5.** DIA with aliphatic hydroxyacids. a TfOH used in place of SnCl2·2H2O.

Next, the analogous amine-containing coupling partners were examined (Figure 6).5 In this case, we did not attempt to perform the DIA using free amino acids (which almost certainly would have undergone self-condensation) and instead explored the reactions of imines **37** with commercially available *N*-Boc or *N*-Cbz-protected amino acids **40**. Thus, following the T3P coupling in the usual way and aqueous work-up, cleavage of the *N*-protecting group (using TFA in CH2Cl2 for Boc cleavage or H2/Pd(OH)2 in MeOH for Cbz cleavage) resulted in cyclisation and formation nitrogen-containing heterocycles **41a**–**e** in high yields.



**Figure 6**.DIA with protected amino acids (protecting group used in brackets). TFA = trifluoroacetic acid.

The sulfur-variant of this class of DIA reaction is extremely efficient,5 affording biologically relevant28 thiazolidinone scaffolds **43a–f** in high yields in a one-pot procedure, with no protecting group required on the thiol in any of the examples tested (Figure 7).29



**Figure 7.** DIA with aliphatic thioacids.

The syntheses of products **43c** and **43d** are especially noteworthy as they are derived from ketimines, which typically do not undergo DIA reactions (see earlier, Scheme 4). Indeed, the only other ketimine DIA described so far (the formation of product **21ac**, see earlier, Figure 4) also used thiosalicylic acid **19m**, indicating that the thiol substrates are a special case. Furthermore, the coupling of imine **18** and thiosalicyclic acid **19m** was found to go to 20% conversion, even in the absence of T3P, whereas T3P is essential in all of the examples tested that use *O*-, *N*- or *C*-nucleophiles. These observations suggest that these sulfur variants likely proceed *via* a different (or combined) reaction mechanism to the other DIA processes described; rather than initial *N-*acylation, followed by nucleophilic attack onto the resulting *N*-acyliminium ion, we propose that in thiol system, the imine is attacked by the nucleophilic thiol group, and that *N-*acylation takes place intramolecularly (*e.g.* **44 → 46 → 47**, Scheme 8).29b-c This offers some explanation for how the *N-*acylation could proceed in the absence of an activating acid (the intramolecular condensation of an amine and carboxylic acid appears far more plausible than an intermolecular coupling between an imine and carboxylic acid). For more detailed mechanistic discussions, see Section 7.



**Scheme 8.** Alternative mechanism in the formation of thiazolidinones.

The final examples in this section demonstrate that *N*-acyliminium ions formed *via* DIA can also be intercepted by carbon-centred pro-nucleophiles (Figure 8).5 In these examples, in order to generate the lactam products in a one-pot process, it was necessary to include a Lewis acid additive to promote cyclisation, following *N*-acylation in the usual way.9 For example, carboxylic acids tethered to a diester or diketone were used to generate an *N*-acyliminium ion, and the subsequent addition of AlCl3 then promoted cyclisation to generate lactams **50a** and **50b**. Electron-rich aromatics can also be used as the pro-nucleophile in Freidel–Crafts-type processes to form lactams **50c–f**, with BF3∙OEt2 used to effect cyclisation. Alkenyl carboxylic acids can also be used with either TFA or BF3∙OEt2 as the activating agent to form lactams **50g** and **50h** respectively.



**Figure 8.** DIA with aliphatic acids bearing carbon pro-nucleophiles.

The examples in Figure 8 are particularly important; the core product structures are prevalent in a number of natural products30 and medicinally useful frameworks,31 and they demonstrate that reaction systems in which the nucleophilic component is relatively unreactive can still be used in DIA processes. The mild nature of the reagents used in the initial *N*-acylation is important, as this means that a range of acids can used in a one-pot process, with no problems concerning reagent incompatibility having been observed to date. The ability to tune the reaction conditions in this way is a key feature of the DIA method, dramatically increasing its potential scope.

**5. DIA in the Synthesis of β-lactams**

The value of β-lactams in medicinal chemistry has been well documented,32 in particular in the field of antibiotics,33 which is of significant importance in view of rising anti-microbial resistance to existing drugs.34 While many routes to prepare β-lactams are known,35 DIA provides an attractive alternative synthesis in view of the simplicity of the method and mild reagents, allowing access to a range of predominantly *trans*-orientatedβ-lactams **53a–53p** (Figure 9).7



**Figure 9.** DIA in the Synthesis of β-lactams **53a–53p**.

In contrast to our earlier work on DIA, these reactions typically proceed most effectively with simple, acylic imine starting materials, which is unusual for any methodology based on *N-*acyliminium ion chemistry.9 It is also noteworthy that no acid additives are required to promote cyclisation in these C–C bond forming reactions (the imine **51** and acid **52** are simply refluxed in chloroform with the standard DIA reagents). Indeed, the absence of an acidic additive is crucial in ensuring that β-lactam formation takes place rather than competing δ-lactam formation, which could also take place *via* a Friedel-Crafts-type reaction, similar to those shown earlier in Figure 8. This is demonstrated by the fact that β-lactam **53o** (Figure 9) was formed selectively under the Lewis acid free conditions, whereas we had previously shown that δ-lactam **50c** (Figure 8) is formed in high yield from the same starting materials if BF3·Et2O is included as an additive.5

Also of interest is the observed *trans-­*selectivityin the majority of the examples, given that *cis*-β-lactams are usually formed preferentially in related studies.35 It is unlikely that there is a single explanation for the predominance of *cis*-β-lactams in these earlier studies, as ring closure is possible *via* a number of related pathways; for example, the activated carboxylic acid derivative may react directly with the imine to form an *N*-iminium ion (similar to DIA) or proceed *via* an intermediate ketene intermediate, while this in turn opens up the possibility of β-lactam formation *via* a direct [2+2]-cycloaddition process. We cannot say with confidence which process operates in our case, but based on selective formation of *trans­-*β-lactams we feel that this indicates a degree of reversibility in the process. It is possible that following *N-*acylation*,* the zwitterionic intermediate undergoes isomerisation before ring-closure, thus leading to predominantly the *trans*-β-lactams as the major diastereoisomers.35e In addition, isomerisation of the β-lactam products themselves, or isomerisation of the starting acylic imine geometry, cannot be ruled out.

**6. DIA in the synthesis of azaspirocycles**

In 2016, the DIA method was extended to allow the preparation of spirocyclic products.36 The investigation of underexplored regions of chemical space is an important goal in the search for new pharmaceutical lead compounds and rigid, three-dimensional scaffolds are valuable in this regard.37 Dearomatisation reactions are a useful way to access such compounds from comparatively simple precursors,38 and DIA was adapted for use in a series of dearomatisation processes.39

We began by examining the reactions of indole acetic acid derivatives.8 At this time, we had already performed a single example of a DIA reaction using indole-tethered acid, but this did not deliver a spirocyclic product; the reaction of indole acetic acid **54a** and imine **48** with T3P, NEt(*i*-Pr)2 in chloroform at RT, followed by the addition of BF3·OEt2 as an acidic additive furnished ring-annulated δ-lactam **50d** in good yield. However, we were pleased to find that by simply omitting the BF3·OEt2 additive and switching the solvent to THF, the same coupling partners could also be converted into spirocycle **55a**, also in good yield and also with high diastereoselectivity (Scheme 9).



**Scheme 9.** Contrasting reactivity of imine **48** and acid **54a** with and without BF3·OEt2.

The successful formation of spirocycle **55a** suggested that in our previous formation of compound **50d**, spirocycle **55a** was a likely intermediate, but underwent subsequent 1,2-migration under the alternative reaction conditions. This opened up a whole new area of investigation for the DIA method, and a range spirocyclic scaffolds were assembled by varying both the imine and acid coupling partner. The substrate scope with respect to the acid coupling partner is illustrated in Figure 10.8



**Figure 10.** DIA spirocyclisation reactions of imine **44**.

Several substituted indole acetic acid derivatives were found to be compatible with the basic DIA procedure, furnishing spirocycles (**55b–55i**) in good yields and with generally high diastereoselectivity. The relative stereochemistry of the major diastereoisomer is the same in most cases, with the observed diastereoselectivity believed to be kinetically determined, arising from nucleophilic attack of the indole onto the intermediate *N*-acyliminium ion proceeding *via* an intermediate of the form **56**, which may be stabilised by π-stacking (Scheme 10, for more details, see our previous publication).8 Longer chain homologue **55j** was also formed under the same conditions and furthermore, aza-indole and pyrrole derivatives could also be used, affording unusual spirocycles **55k–n** with minor modifications to the standard procedure.



**Scheme 10.** Diastereoselectivity in the DIA spirocyclisation of imine **44** with acid **54b**; potential for π-stacking.

The substrate scope with respect to the imine coupling partner was also examined (Figure 11). A range of functionalised imines **57a–g** was used to generate diverse scaffolds **58a–58g** in generally high yields. Further transformations were also performed on some of the spirocyclic products, and 3D shape analysis of all of the products formed indicated that a significant proportion occupy chemical space that is relatively under-represented in most compound screening libraries (for more detail, see our earlier publication).8



**Figure 11.** DIA spirocyclisation reactions of indole acetic acid derivatives.

**7. Mechanistic studies**

With a few notable exceptions, all of the reactions described in this Account are thought to proceed *via* an initial *N*-acylation reaction (**44 → 61**), followed by intramolecular trapping of the resulting *N*-acyliminium ion (**61 → 62,** route **A**, Scheme 11). However, in theory, the same reaction products could also be obtained *via* an alternative mechanism, in which order of events is reversed; *i.e.* nucleophilic attack into the imine takes place first (**44 → 63**), before intramolecular acylation (**63 → 62,** route **B**, Scheme 11). In DIA variants in which the *N-*acylation and cyclisation steps are performed in a stepwise manner (*e.g.* Figures 5, 6 and 8) the order of events is clear, as adducts of the *N-*acyliminium ioncan be formed and isolated, but in examples in which the product is obtained directly without an additional cyclisation step, the mechanism is less obvious.

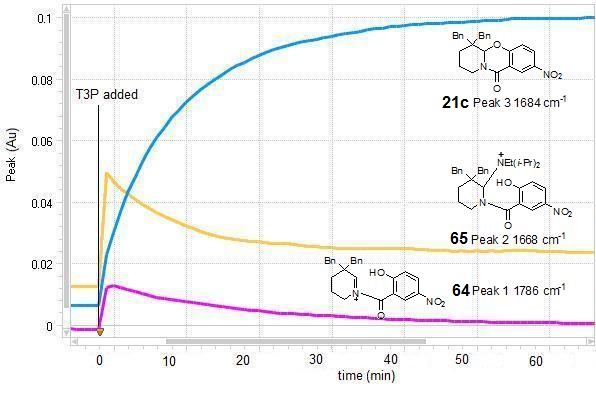


**Scheme 11.** Mechanistic possibilities for the coupling of imine **44** with acid **60**.

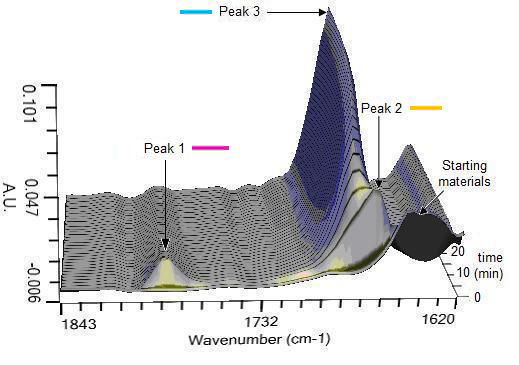
To shed light on the mechanism an *in situ* ReactIR™ study was carried out on the DIA reaction of imine **18** with 5-nitro-salicylic acid **19c**. A mechanism consistent with our findings is summarised below (Scheme 12), with more details included in our earlier publication.2 The ReactIR™ results suggest that activation of the carboxylic acid with T3P is fast on the reaction time scale and that *N*-acyliminium ion **64** is quickly formed (Peak 1, Figures 12 and 13), within the first few minutes of the reaction. Note that due to their high reactivity, spectroscopic data for *N*-acyliminium ions are extremely rare, but with ReactIRTM we were able to observe this reactive intermediate in real time (albeit in low concentration). Unsurprisingly, *N*-acyliminium ion **64** is short-lived, and is mainly converted into a second intermediate, believed to be ammonium salt **65** (Peak 2, Figures 12 and 13), *via* a reversible trapping reaction with excess NEt(*i-*Pr)2 present in the reaction. Finally, over the course of around 1 hour, intermediate **65** breaks down, presumably *via* the extrusion of NEt(*i-*Pr)2 to regenerate *N*-acyliminium ion **64**, which can then cyclise to form the product **21c** (Peak 3, Figures 12 and 13)in high yield,*via* intramolecular trapping with the nucleophilic phenol group.



**Scheme 12.** Mechanistic possibilities for the coupling of imine **18** with acid **19c**.



**Figure 12.** 2D ReactIRTM plot of atomic absorption units of the wavenumbers 1786 cm-1, 1668 cm-1 and 1684 cm-1 against time for the DIA reaction of imine **18** and acid **19c**.



**Figure 13.** 3D ReactIRTM plot of atomic absorption against wavenumber and time for the DIA reaction of imine **18** and acid **19c**.

Of course, just because this particular reaction appears to proceed *via* a DIA-type mechanism, it does not mean that this applies to all cases; indeed, for reasons described earlier (see Figure 7 and Scheme 8), we believe that variants involving thiol substituted acids are more likely proceed *via* the alternative ‘route **B**’ shown in Scheme 11. Neither should it be assumed that an ammonium salt of the form **65** is necessarily an intermediate in all DIA reactions, although its formation is consistent with much of what is known about *N-*acyliminium ion chemistry. Thus, based on our findings and experience in this field, we feel that the mechanism shown in Scheme 12 is the most likely pathway for all of the DIA reactions presented, with the exception of the aforementioned sulfur variants.

**8. Conclusion**

Since its first use towards the total synthesis ‘upenamide, DIA has been expanded significantly and used to construct a range of diverse structural types; in this Account the syntheses of 103 distinct products are described.2-8 The mild nature of the reagents and simple operating conditions are key features of the method, which is relatively insensitive to both air and moisture. The versatility of the DIA method is also important, a key advantage being the ability to tune the reactivity by use of a suitable additive. The DIA reactions developed can be separated into three categories depending on the type of additives used:

1) **Additive-free**. Many DIA reactions require no additive at all; these processes are the easiest to perform, and are characterised by the fact that the nucleophilic component on the carboxylic acid is not sufficiently reactive to undergo competitive acylation, but is reactive enough to add to the *N*-acyliminium ion once formed. Examples include the reactions of imines with *ortho-*substituted benzoic acids (Figures 3 and 4) and indole acetic acid derivatives to make spirocyclic products (Figures 10 and 11).

2) **Protecting group cleavage**. DIA reactions in this category are those in which the nucleophilic component on the carboxylic acid must be masked by a suitable protecting during the *N*-acylation stage and is then revealed to complete the cyclisation. These included examples with acids containing aliphatic alcohols and amines (Figures 5 and 6) that would react with the activated carboxylic acid more readily than the imine nitrogen if a protecting group was not include.

3) **Acidic additives**.Finally, relatively poor nucleophiles can also be made to react in DIA processes, in these cases by the addition of a Lewis or Bronsted acid to increase the electrophilicity of the *N*-acyliminium ion. This technique is especially useful for the formation of new C–C bonds (Scheme 6 and Figure 8)

The ability to use choose one of these variants means that DIA is possible whether or not the nucleophile is strong, weak or ‘just-right’. A number of different additives are compatible with the reagents used to promote the *N*-acylation, meaning that the two steps can easily be telescoped into a single high yielding process. We are currently seeking to further extend the DIA method, in particular for use in multi-component reactions,40 for the synthesis of medium-sized and macrocyclic scaffolds41 and in target synthesis.42

Acknowledgment

The authors would like to thank the following people for their valuable efforts on the development of DIA at the University of York: Dr. Christiana Kitsiou, Dr. Graeme Coulthard, Sarah J Chambers, Prof. Peter O’Brien and Dr. Katherine A Gallagher. We are also grateful to Elsevier for funding (W. P. U.) and Euticals for regular donations of the reagent T3P, which underpins all of the chemistry described herein.

References

1. (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, 103, 893; (b) Comprehensive Heterocyclic Chemistry III; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Oxford, **2008**, and references therein.
2. Unsworth, W. P.; Kitsiou C.; Taylor, R. J. K. *Org. Lett*. **2013**, *15*, 258.
3. Unsworth, W. P.; Gallagher, K. A.; Jean, M.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Org. Lett*. **2013**, *15*, 262.
4. Unsworth, W. P.; Taylor, R. J. K. *Org. Biomol. Chem*. **2013**, *11*, 7241.
5. Unsworth, W. P.; Coulthard, G.; Kitsiou C.; Taylor, R. J. K. *J. Org. Chem*. **2014**, *79*, 1368.
6. Kitsiou C.; Unsworth, W. P.; Coulthard, G.; Taylor, R. J. K. *Tetrahedron* **2014**, *70*, 7172.
7. Coulthard, G.; Unsworth, W. P.; Taylor, R. J. K. *Tetrahedron Lett.* **2015**, *56*, 3113.
8. Chambers. S. J.; Coulthard, G.; Unsworth, W. P.; O’Brien, P.; Taylor, R. J. K. *Chem*. *Eur. J.* **2016**, doi: 10.1002/chem.201600823
9. (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, 41, 1985, 4367; (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, 56, 3817; (c) Maryanoff, B. E.; Zhang, H-C. Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev*. **2004**, 104, 1431; (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339; (e) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513; (f) Le Quement, S. T.; Petersen, R.; Meldal, M.; Nielsen, T. E. *Biopolymers* (Peptide Science), **2010**, *94*, 242; (g) Daïch, A.; Ghinet, A.; Rigo, B. Addition to N-Acyliminium Ions of Heteroatoms such as Oxygen, Nitrogen, Sulfur and Selenium as Internal Nucleophiles, In: Gary A. Molander and Paul Knochel (eds.), Comprehensive Organic Synthesis, 2nd edition, Vol 2, Oxford: Elsevier; **2014**. pp. 682.
10. For the isolation paper for ‘upenamide, see: Jiménez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelley, M. *J. Org. Chem.* **2000**, 65, 8465.
11. For synthetic work towards the synthesis of ‘upenamide prior to the development of DIA, see: (a) Reid, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, 45, 4181; (b) Mons, S.; Malves Maia, A.; Mons, S.; Pereira de Freitas Gil, R.; Marazano, C. *Eur. J. Org. Chem.* **2004**, 1057; (c) Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, 7, 5163; (d) Han. J. L.; Ong, C. W. *Tetrahedron* **2007**, 63, 609; (e) Cayley, A. N.; Cox. R. J.; Ménard-Moyon, C.; Schmidt, J. P.; Taylor, R. J. K. *Tetrahedron Lett.* **2007**, 48, 6556; (f) Ménard-Moyon, C.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2007**, 3698; (g) Schmidt, J. P.; Beltran-Rodil, S.; Cox, R. J.; Mcallister, G. D.; Reid. M.; Taylor, R. J. K. *Org. Lett.* **2007**, 20, 4041; (h) Luo, Z.; Peplowski, K.; Sulikowski, G. A. *Org. Lett.* **2007**, 9, 5051.
12. Cayley. A. N.; Gallagher, K. A.; Ménard-Moyon, C.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Synthesis* **2008**, 3846.
13. (a) Ziegler, E.; Hanus, H. D. *Monatsh. Chem.* **1965**, 96, 411; (b) Ziegler, E.; Kollenz, G.; Kappe, T. *Monatsh. Chem.* **1968**, 99, 804; (c) Kametani, T.; Higa, T.; Van Loc, C.; Ihara, M.; Koizumi, M.; Fukumoto, K. *J. Am. Chem. Soc*. **1976**, 98, 6186; (d) Castagnioli, N., Jr. *J. Org. Chem*. **1969**, 34, 3187; (e) Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1997**, *38*, 4327; (f) Wang, H.; Ganesan, A. *Org. Lett*. **1999**, *1*, 1647; (g) Strumberg, D.; Pommier, Y.; Paull, K.; Jayaraman, M.; Nagafuji, P.; Cushman, M. *J. Med. Chem*. **1999**, 42, 446; (h) Sieck, O.; Ehwald, M.; Liebscher, J. *Eur. J. Org*. *Chem*. **2005**, 663; (i) Chen, Z.; Hu, G.; Chen, J.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. *Bioorg. Med. Chem*. **2009**, 17, 2351; (j) Johannes, K.; Martens, J. *Tetrahedro*n **2010**, 66, 242; (k) Zarei, M *Tetrahedron Lett*. **2014**, *55*, 5354.
14. For related processes involving the coupling of imines with *in situ* activated carboxylic acids, see: (a) Smith, M. W.; Hunter, R.; Patten, D. J.; Hinz, W. *Tetrahedron Lett.* **2009**, *50*, 6342; (b) Pin, F.; Comesse, S.; Daϊch, A. *Tetrahedron* **2011**, 67, 5564.
15. Successful coupling was also achieved using HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) or DCC (*N,N'*-dicyclohexylcarbodiimide) under the same conditions, albeit in lower yield.
16. Wissmann, H.; Kleiner, H.-J. *Angew. Chem. Int. Ed*. **1980**, 19, 133.
17. (a) Nakasato, T.; Asada. S.; Murai. K. *J. Pharm. Soc. Jpn*. **1962**, 82, 619; (b) Kobayashi, Y.; Nakano, Y.; Kizaki, M.; Hoshikuma, K.; Yokoo, Y.; Kamiya, T. *Planta Medica* **2001**, 67, 628; (c) Dong, G.; Sheng, C. S.; Wang, S.; Miao, Z.; Yao, J.; Zhang, W. *J. Med. Chem*. **2010**, 53, 7521.
18. For a related total synthesis of dievodiamine, see: Unsworth, W. P.; Kitsiou C.; Taylor, R. J. K. *Org. Lett*. **2013**, *15*, 3302.
19. Böhme, H.; Hartke, K. *Chem. Ber*. **1963**, *96*, 600.
20. (a) Schöpf, C; Komzak, A.; Braun, F.; Jacobi, E.; Bormuth, M.-L.; Bullnheimer, M.; Hagel, I. *Liebigs Ann*. **1948**, 559, 1; (b) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O’Brien, P. *J. Org. Chem*. **2011**, 76, 5936.
21. Dannhardt, G.; Bauer, A.; Nowe, U. *J. Prakt. Chem.* **1998**, *340*, 256.
22. For a similar synthesis of related scaffolds *via* a dearomatisation approach, see: Surygina, O.; Ehwald, M.; Liebscher, J. *Tetrahedron Lett*. **2000**, *41*, 5479.
23. For general considerations on berberine alkaloids, see: (a) Gear, J. R.; Spenser, I. D. *Can. J. Chem*. **1963**, *41*, 783; (b) Beecher, C. W. W.; Kelleher, W. J. *Tetrahedron Lett*. **1984**, *25*, 4595; (c) Kobayashi, M.; Frenzel, T.; Lee, J. P.; Zenk, M. H.; Floss, H. G. *J. Am. Chem. Soc*. **1987**, *109*, 6184; (d) Jendrzejewski, S. *Phytochemistry* **1990**, *29*, 135; (e) Amann, M.; Nagakura, N.; Zenk, M. H. *Eur. J. Biochem*. **1988**, *175*, 17; (f) Kametani, T.; Takemura, M.; Ihara, M.; Takahashi, K.; Fukumoto, K. *J. Am. Chem. Soc*. **1976**, *98*, 1956; (g) Jeﬀs, P. W.; Scharver, J. D. *J. Am. Chem. Soc*. **1976**, *98*, 4301; (h) Bhakuni, D. S.; Gusta, S.; Jain, S. *Tetrahedron* **1983**, *39*, 4003; (i) Grycova, L.; Dostal, J.; Marek, R. *Phytochemistry* **2007**, *68*, 150; (j) Niu, X-F.; Xu, H-B.; Liu, X.; Fan, T.; Qi, L. *Chem. Nat. Compd.* **2013**, *49*, 187; (k) Hughes, D. W.; Holland, H. L.; Maclean, D. B. *Can. J. Chem.* **1976**, *54*, 2252.
24. For the isolation, structural assignment and previous syntheses of cavidine, see: (a) Taguchi, H.; Imaseki, I.; *Yakugaku Zasshi* **1964**, *84*, 955; (b) Yu, C. K.; Maclean, D. B.; Rodrigo, R. G. A.; Manske, R. H. F. *Canad. J. Chem.* **1970**, *48*, 3673; (c) Ninomiya, I.; Takasugi, H.; Naito, T. *Heterocycles* **1973**, *1*, 17; (d) Ninomiya, I.; Naito, T.; Takasugi, H. *J. Chem. Soc., Perkin Trans. I* **1975**, 1791; (e) Iwasa, K.; Gupta, Y. P.; Cushman, M. *J. Org. Chem*. **1981**, *46*, 4744; (f) Bhakuni, D. S.; Jain, S.; Gupta, S. *Tetrahedron* **1986**, *42*, 675.
25. For a recent publication of similar scaffolds *via* a Redox-Mannich approach, see: Ma, L.; Seidel, D. *Chem. Eur. J.* **2015**, *21*, 12908.
26. For a more recent synthesis of similar *N,O*-acetal scaffolds *via* a similar approach, see: Shymanska, N. V.; An, I. H.; Pierce, J. G. *Angew. Chem. Int. Ed*. **2014**, *53*, 540.
27. Ohno, K.; Ueki, T.; Fushikida, K.; Okita, T.; Komori, S.; Tazawa, Y.; Kumakura, Y.; Izakura, K. PCT Int. Appl. **2013**, WO2013061973; A1 20130502.
28. Verma, A.; Saraf, S. K., *Eur. J. Med. Chem*. **2008**, *43*, 897.
29. For alternative syntheses of similar scaffolds, see: (a) Johnson, M. R.; Fazio, M. J.; Ward, D. L.; Sousa, L. R. *J. Org. Chem*. **1983**, *48*, 494; (b) Jarvis, C. L.; Richers, M. T.; Breugst, M.; Houk, K. N.; Seidel, D. *Org. Lett.* **2014**, *16*, 3556; (c) Wen, L.-R.; Yuan, W.-K.; Li, M. I. *J. Org. Chem*. **2015**, *50*, 4942.
30. (a) Iwasa, K.; Gupta, Y. P.; Cushman, M. *J. Org. Chem.* **1981**, *46*, 4744; (b) Herlé, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, *76*, 8907; (c) Cao, M.; Muganga, R.; Tits, M.; Angenot, L.; Frederich, M., *Planta. Med.* **2011**, *77*, 2050.
31. Negoro, T.; Murata, M.; Ueda, S.; Fujitani, B.; Ono, Y.; Kuromiya, A.; Komiya, M.; Suzuki, K.; Matsumoto, J. *J. Med. Chem.* **1998**, *41*, 4118.
32. (a) The Organic Chemistry of *β*-Lactams; Georg, G. I., Ed.; Verlag Chemie: New York, **1993**; (b) Broccolo, F.; Cainelli, G.; Caltabiano, G.; Cocuzza, C. E. A.; Fortuna, C. G.; Galletti, P.; Giacomini, D.; Musumarra, G.; Musumeci, R.; Quintavalla, A. *J. Med. Chem.* **2006**, *49*, 2804.
33. King, A. M.; Reid-Yu, S. A.; Wang, W.; King, D. T.; De Pascale, G.; Strynadka, N. C.; Walsh, T. R.; Coombes, B. K.; Wright, G. D. *Nature* **2014**, *510*, 503.
34. (a) D’hooghe, M.; Dekeukeleire, S.; Mollet, K.; Lategan, C.; Smith, P. J.; Chibale, K.; De Kimpe, N. *J. Med. Chem.* **2009**, *52*, 4058; (b) D’hooghe, M.; Mollet, K.; De Vreese, R.; Jonckers, T. H. M.; Dams, G.; De Kimpe, N. *J. Med. Chem.* **2012**, *55*, 5637.
35. For selected, relevant examples and stereochemical studies, see: (a) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51; (b) Cossío, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925; (c) Crichfield, K. S.; Hart, J. E.; Lampert, J. T.; Vaid, R. K. *Synth. Commun*. **2000**, *30*, 3737; (d) Zarei, M. *Monatsh. Chem.* **2014**, *145*, 1495; (e) Jiao, L.; Liang, Y.; Xu, J. *J. Am. Chem. Soc*. **2006**, *128*, 6060.
36. (a) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257; (b) Hung, A. W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6799; (c) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257; (d) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem*. *Lett*. **2014**, *24*, 3673; (e) M. J. James, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856.
37. (a) Reymond, J.-L.; van Deursen, R.; Blum, L. C.; Ruddigkeit, L. *MedChemComm* **2010**, *1*, 30–38; (b) Reymond, J.-L.; Awale, M. *ACS Chem. Neurosci.* **2012**, *3*, 649; (c) Hung, W.; Ramek, A.; Wang, Y.; Kaya, T.; Wilson, J. A.; Clemons, P. A.; Young, D. W. *Proc. Natl. Acad. Sci.* **2011**, *108*, 6799.
38. For recent dearomatisation reactions, see: (a) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem. Int. Ed*. **2012**, *51*, 1680; (b) Gao, R. D.; Liu, C.; Dai, L.-X.; Zhang, W.; You, S.-L. *Org. Lett*. **2014**, *16*, 3919; (c) Zhu, Y.; Rawal, V. H*. J. Am. Chem. Soc*. **2012**, *134*, 111; (d) James, M. J.; Cuthbertson, J. D.; O’Brien, P.; Taylor, R. J. K.; Unsworth, W. P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7640; (e) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O’Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2015**, *17*, 4372.
39. For a recent example of a spirocyclisation method using *N*-acyliminium ion intermediates, see: Ledovskaya, M. S.; Stepakov, A. V.; Molchanov, A. P.; Kostikov, R. R. *Tetrahedron*, **2015**, *71*, 7562.
40. Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
41. Kitsiou, C.; Hindes, J. J.; I’Anson, P.; Jackson, P.; Wilson, T. C.; Daly, E. K.; Felstead, H. R.; Hearnshaw, P.; Unsworth, W. P. *Angew. Chem. Int. Ed*. **2015**, *54*, 15794.
42. Efforts towards the total synthesis of berberine alkaloid pallimamine will be reported in due course, see: Sheng-Teh, L.; Jeng-Fen, H.; Tian-Shung, W.; McPhail, D. R.; McPhail, A. T.; Lee, K-H. *Phytochemistry* **1989**, *28*, 1245.

**Biosketches**

|  |  |
| --- | --- |
| C:\Users\Will\Desktop\Photo of me.jpg | William P. Unsworth studied chemistry at the University of Oxford, where he remained to complete his Ph.D. studies, in the group of Prof. Jeremy Robertson. He completed his Ph.D. in 2010 and then began work at the University of York, first as a postdoctoral research associate in the group of Prof. Richard J. K. Taylor, before being appointed to a Research and Teaching Fellowship in 2013. He has recently been awarded a Leverhulme Trust Early Career Fellowship to develop new procedures to synthesise functionalised macrocycles. His current research interests include the construction of diverse spirocyclic scaffolds, cascade reactions, macrocylisation and total synthesis. |
| Richard Taylor | Richard J. K. Taylor obtained his B.Sc. and Ph.D. from the University of Sheffield. Postdoctoral periods were followed by lectureships at the Open University and then UEA, Norwich. In 1993 he moved to the Chair of Organic Chemistry at the University of York. Taylor's research interests centre on the synthesis of bioactive natural products and the development of new synthetic methodology. His awards include the RSC's Pedler (2007), Synthetic Organic Chemistry (2008) and Natural Product Chemistry (2012) prizes. Taylor is a past President of the International Society of Heterocyclic Chemistry and of the RSC Organic Division and is the current UK Editor of Tetrahedron. |

**Checklist (have these on hand for manuscript submission in ScholarOne):**

* cover letter, including a statement of the work’s significance
* full mailing address, telephone and fax numbers, and e-mail address of the corresponding author
* email address for each author
* original Word file
* original graphics files zipped into one zip file
* eye-catching graphical abstract as an individual file
* 5–8 key words