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C – H Arylation of Heterocyclic *N* Oxides Through *In-Situ* Diazotisation Of Anilines Without Added Promoters: A Green And Selective Coupling Process

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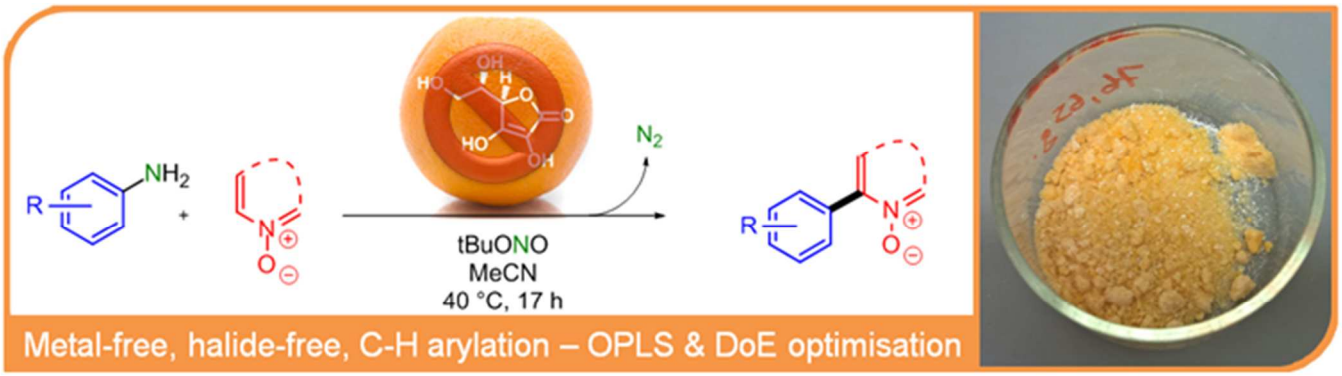


ABSTRACT: A green and selective method for the generation of bi-aryl compounds through C—H arylation of heterocyclic *N*-oxides is presented in which the addition of ascorbic acid as a promoter is not required for either the generation of an aryldiazonium species or the subsequent arylation. Reaction conditions were optimised through Multivariate Data Analysis, including Orthogonal Projections to Latent Structures (OPLS) and Design of Experiments (DoE) methodologies resulting in further sustainability improvements, and were then applied to a range of substrates to establish the scope and limitations of the process. The reaction was studied using *in-situ* infra-red spectroscopy and a mechanism is presented that accounts for the available data from this and previous studies. The reaction was also performed on a multigram scale, with calorimetry studies to support further scale-up of this promoter-free transformation.

Keywords: Radical arylation, Aryldiazonium salts, Green Chemistry, *N*-oxide heterocycles, Design of Experiments, Calorimetry

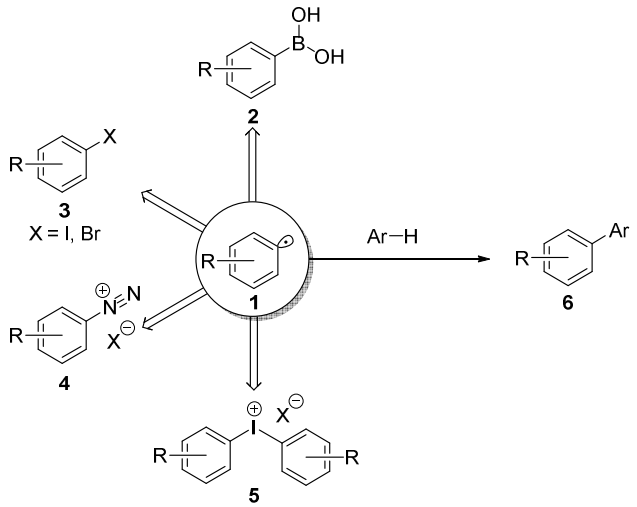
INTRODUCTION

Palladium catalysed cross-coupling reactions have become a staple of organic synthesis since their discovery in the 1970s and have been extensively studied in the intervening decades.[1] Partly as a consequence of their wide use, a number of drawbacks with these methods have been highlighted including: the preparation of the aryl halide and aryl metal coupling partners; the use of some-times exotic palladium – ligand combinations and the requirement for elevated reaction temperatures in many cases. Each of these considerations can have a significant impact on the length, cost and sustainability of any new synthetic route, especially during scale-up, and can reduce the substrate scope when highly functionalised or sensitive substrates are to be employed.

New methodologies focusing on the insertion of a metal complex into aromatic C—H bonds have recently emerged in an attempt to address some of these issues but the majority still require the use of a transition metal catalyst,[2–9] the long-term sustainability of which, particularly in the case of the platinum-group metals, is an area of considerable concern.[10]

A potentially more sustainable approach is the direct arylation of aromatic rings employing an aryl radical species generated *in-situ*.[11,12] Aryl radical species **1** can be obtained from the corresponding arylboronic acids **2**,[13–16] arylhalides **3**,[17] aryldiazonium salts **4**[18–21] and diaryliodonium salts **5**[22–24] (Figure 1).

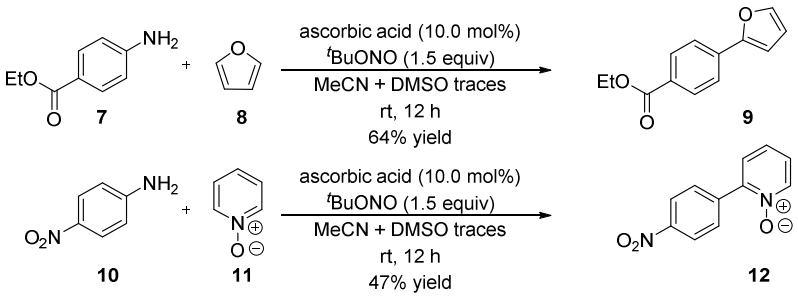
Figure 1. Radical-mediated C-H arylation



Addition of the aryl radical to a second aryl species (Ar—H) followed by oxidation / rearomatisation then leads to a biaryl product **6**. Amongst the methods for the generation of biaryls, Gomberg and Bachmann described one of the first radical-mediated arylations of aromatic rings through the *in-situ* generation of an aryl radical by reaction of an aryldiazonium salt with a base in water.[25–27] Although conceptually simple, a major limitation of this transformation arises when the aryl radical is reacted with complex aromatics, leading to chaotic additions and mixtures of regioisomeric products.[28] For example, whereas unsubstituted heterocyclic substrates such as furan, thiophene and pyrrole exclusively led to the 2-arylated product,[18,20,22,23] reactions with pyridine provided a mixture of regioisomers,[28] albeit in reasonable yields. Along with problems arising due to the high reactivity of the aryl radical intermediates, an additional challenge is the handling of the potentially unstable aryldiazonium precursors. Although these high energy species are routinely handled on large scale,[29–32] safety concerns[33] still inhibit their adoption among the wider synthetic community.

Recently, Carrillo and co-workers described an elegant method telescoping a diazotisation and a radical-mediated arylation reaction using ascorbic acid as the sole promoter for both steps (Scheme 1).[34]

Scheme 1. Telescoped diazotisation / arylation



7 8 9 10 11 12

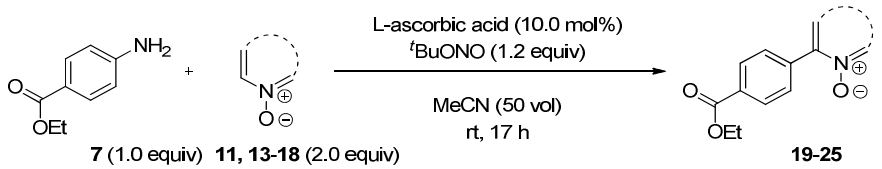
The *in-situ* generation of the aryldiazonium salt from a cheap and readily available aniline helps to address safety concerns around the isolation of these species, while the use of an organic promoter (ascorbic acid) provides an intriguing alternative to standard metal-catalysed couplings. As well as sub-

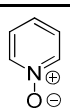
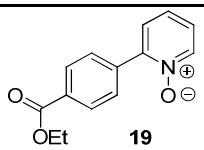
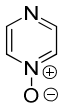
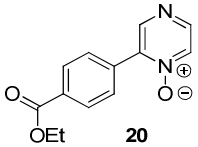
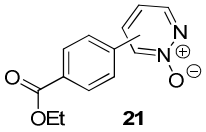
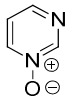
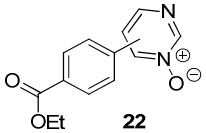
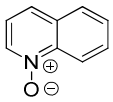
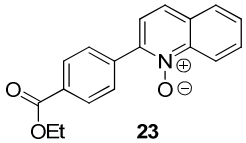
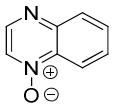
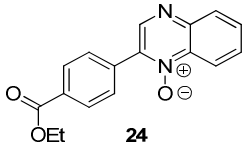
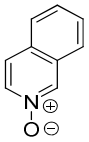
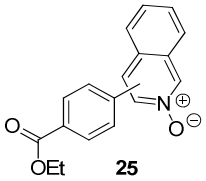
strates such as furan **8** which undergo addition of an aryl radical at the 2-position to give the biaryl product **9**, they showed that pyridine *N*-oxide **11** also underwent a regioselective addition of the aryl radical derived from aniline **10** to give the product **12** (Scheme 1). This single example of such an important heterocyclic structure is significant and represents a major advance in this class of coupling reaction. Attracted by the reactivity of an aryl radical species with pyridine *N*-oxide **11** and in line with our interest in aryldiazonium compounds,[32] we sought to expand this methodology to other pharmaceutically relevant nitrogen heterocycles. Within this paper we show that quinoline *N*-oxides and their derivatives are effective coupling partners for arylation with aryldiazonium species and that ascorbic acid is not required as an additive in this reaction, contrary to previous reports. We also demonstrate how industry-standard statistical and experimental tools can be used to rapidly optimise the reaction and provide additional mechanistic understanding.

RESULTS AND DISCUSSION

As a starting point to our research we examined a series of nitrogen containing heterocycles of relevance to the pharmaceutical industry to establish if the reaction was also applicable to these scaffolds (Table 1). For the initial screening process the reaction conditions reported by Carrillo and co-workers[34] were adapted, reducing the excess of *tert*-butyl nitrite to 1.2 equivalents and omitting the DMSO cosolvent. The reaction was found to be remarkably substrate specific; whilst pyridine *N*-oxide **11** and pyrazine *N*-oxide **13** could be arylated with outstanding regioselectivity but disappointing yield (Table 1, entries 1 and 2), only traces of the possible regioisomeric adducts **21** and **22** were detected by LC/MS when pyridazine *N*-oxide **14** and pyrimidine *N*-oxide **15** were evaluated as potential substrates (Table 1, entries 3 and 4). Although single ring nitrogen heterocycles did not react in high yield, we were delighted to observe that fused ring systems displayed significantly more promise. For example, quinoline *N*-oxide **16** and quinoxaline *N*-oxide **17** were both successfully arylated under our standard conditions in 60% and 71% yield respectively (Table 1, entries 5 and 6). Surprisingly, the isomeric isoquinoline *N*-oxide **19** gave only traces of the arylated products **25** under these standard conditions (Table 1, entry 7).

Table 1: Screening of heterocyclic *N*-oxides

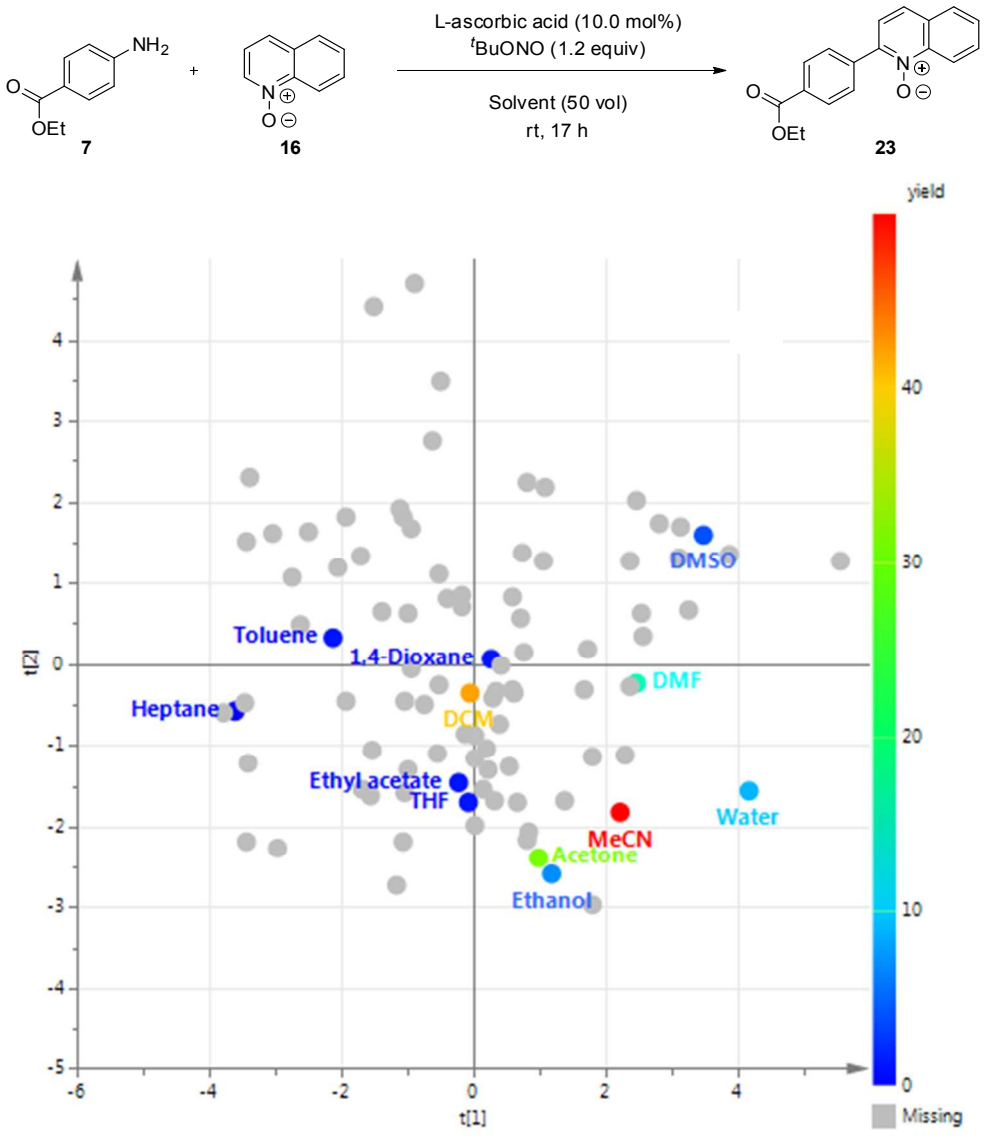


Entry	Substrate	Product	Yield[a]
1	 11	 19	22%
2	 13	 20	19%
3	 14	 21	Traces[b]
4	 15	 22	Traces[b]
5	 16	 23	60%
6	 17	 24	71%
7	 18	 25	Traces[b]

[a]Isolated yield after purification by column chromatography. [b]A mixture of regioisomers was observed by LC/MS.

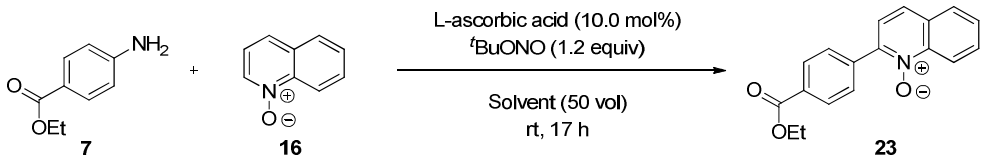
Whilst not exhaustive, this initial series of heterocyclic *N*-oxides suggested this transformation should have significantly broader scope than the single example reported by Carrillo and co-workers[34] and provided a number of interesting trends that warranted further investigation. These promising preliminary results encouraged us to screen different organic solvents in order to evaluate the impact of the reaction medium on the yield through OPLS analysis.[35] The solvent screening results required by this statistical method were obtained through the evaluation of inexpensive benzocaine **7** and commercially available quinoline *N*-oxide **16** as model substrates for this transformation in a series of common organic solvents (Table 2) selected from a PCA model (Figure 2).[36]

Figure 2: PCA solvent model



These reaction media were selected according to their difference in terms of physico-chemical properties, also referred to as solvent descriptors. These inherent descriptors were identified and reported by Carlson and co-workers[36] to describe each solvent through numerical values in nine dimensions: melting point, boiling point, dielectric constant, dipole moment, refractive index, normalised Reichardt-Dimroth parameter, lipophilicity (logP) and water solubility. The spatial position of a solvent in the PCA solvent model in Figure 2 is representative of the combination of those descriptors.

Table 2: Solvent screening for the radical arylation of quinoline *N*-oxide **16**

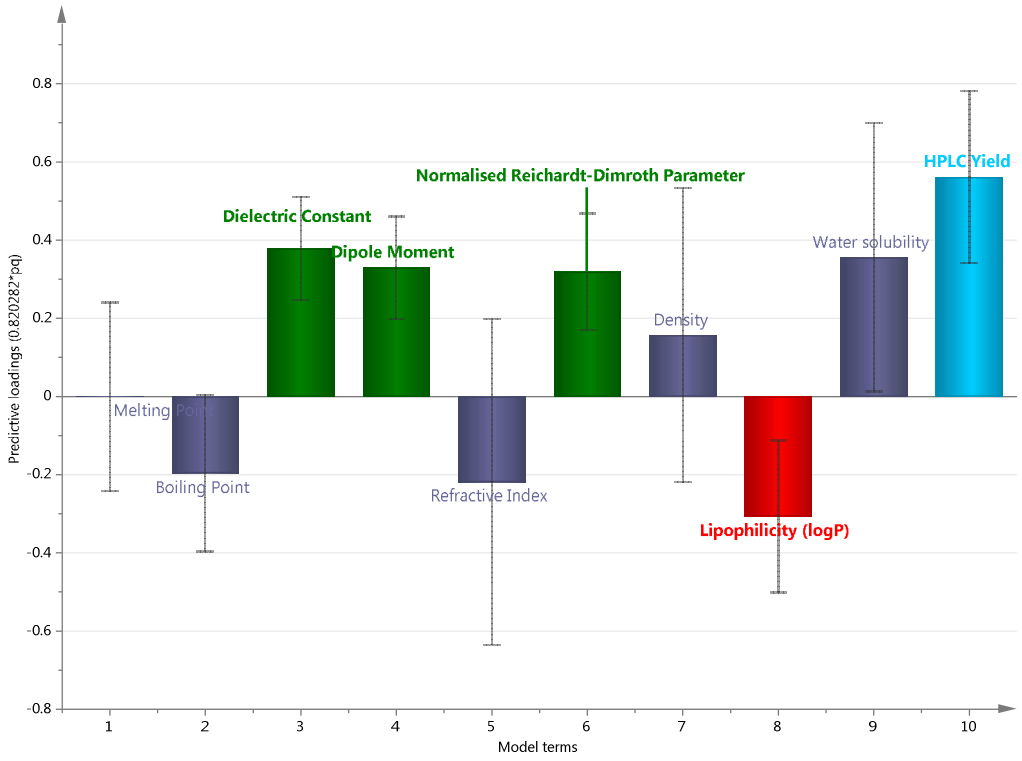


Entry	Solvent	HPLC yield[a]	Isolated yield[b]
1	Heptane	0%	-
2	Toluene	1%	-
3	1,4-Dioxane	1%	-
4	THF	1%	-
5	EtOAc	1%	-
6	DMSO	4%	-
7	EtOH	7%	-
8	Water	9%	-
9	DMF	16%	19%
10	Acetone	31%	33%
11	CH_2Cl_2	42%	40%
12	MeCN	50%	60%

[a]HPLC yield calculated with calibration curve. [b]Isolated yield after purification by column chromatography.

The reaction did not proceed well in heptane, toluene, 1,4-dioxane, tetrahydrofuran, ethyl acetate, DMSO, ethanol and water as only low yields were observed by HPLC (Table 2, entries 1-8). DMF, acetone and dichloromethane gave 16%, 31% and 42% yield of the biaryl product **23** respectively (Table 2, entries 9–11). Among all the solvents screened, acetonitrile gave the product in 60% isolated yield (Table 2, entry 12). As mentioned previously, these screening results were used to build the OPLS regression model describing reaction yield as a function of solvent properties in order to increase process understanding. This regression method aims to find the multidimensional direction in the solvent descriptors space that explains the maximum variance in the yield (Figure 3).

Figure 3: OPLS regression model



Descriptors highlighted in green show a statistically-significant positive correlation with reaction yield; those in red show a statistically-significant negative correlation with reaction yield; and those in dark blue/grey show a correlation that is not statistically significant (95% confidence interval). The model (R^2X=63.9%, R^2Y=74.8%, Q^2=43.7%) revealed that solvents with high dipole moment, dielectric constant and normalised Reichardt-Dimroth[37] parameters resulted in high yield whereas increased lipo-

philicity of the solvent was detrimental to the yield (Figure 3). Accordingly, this model highlights the clear affinity of the reaction for polar, polarisable solvents, which is consistent with the large number of charged intermediates involved in the transformation (*vide infra*). Although the PCA model used contains a wide variety of "green" alternatives, the only solvents predicted to give similar or better yields than acetonitrile were nitromethane and trifluoroethanol, which are both less desirable from a sustainability perspective. Therefore acetonitrile was chosen for the further development of this transformation through Design of Experiment methodology.

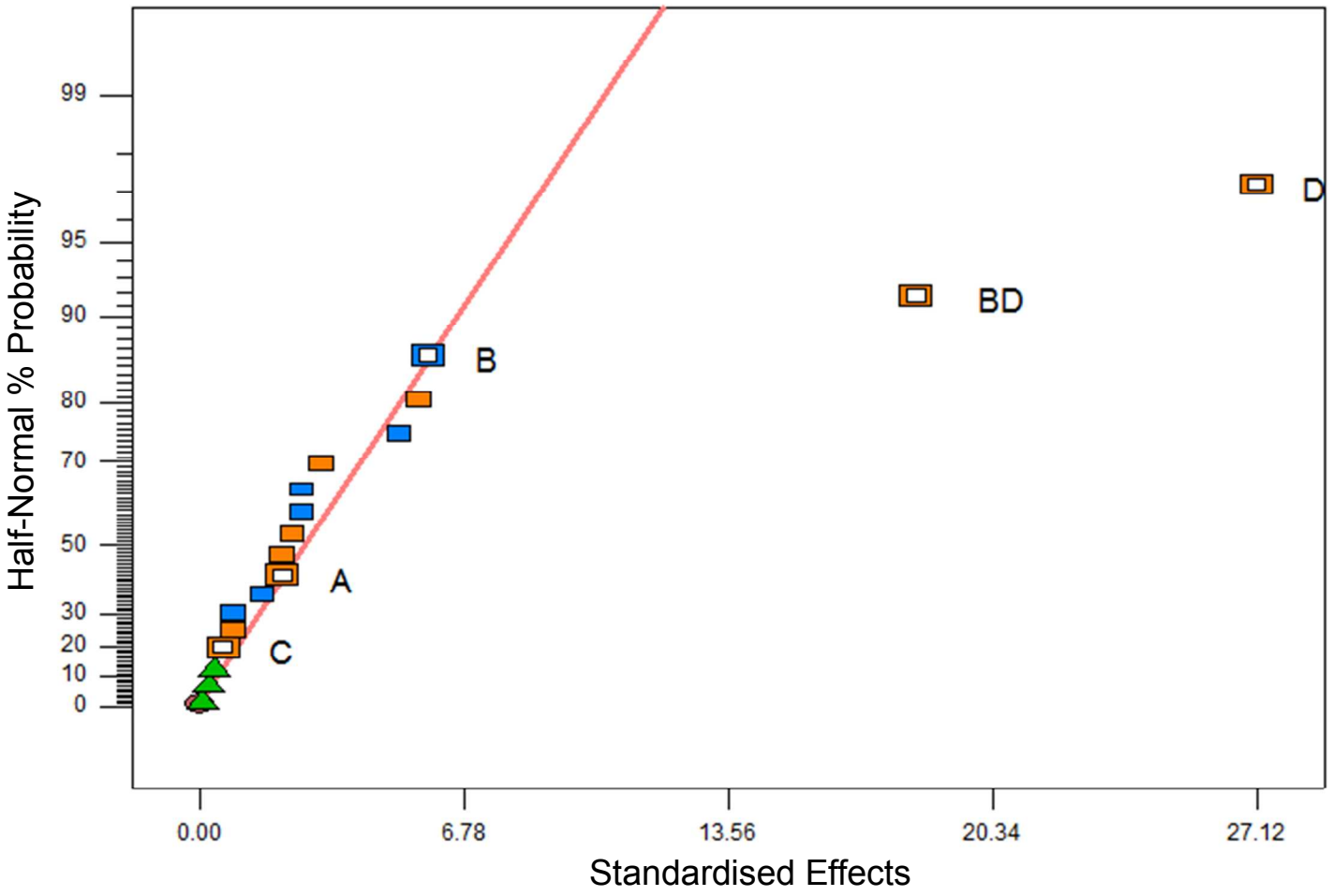
Design of Experiments is a multifactorial analysis technique allowing the identification of key reaction parameters within a previously defined space. With suitable solvent and model substrates established, it was decided to evaluate the impact of other reaction parameters (Table 3), including the ascorbic acid loading (A), the number of equivalents of quinoline *N*-oxide **16** (B), the solvent volumes (C) and the temperature (D) through 20 runs using a full factorial model where HPLC yield was used as the response (see supporting information).

Table 3: Design of Experiment summary with optimised conditions

Entry	Settings	Ascorbic acid (mol %) (A)	Quinoline *N*-oxide 17 (equiv) (B)	Solvent volumes (vol) (C)	Temperature (°C) (D)
1	Minimum	1%	1.0	10	0 °C
2	Centre	10.5%	2.0	55	20 °C
3	Maximum	20%	3.0	100	40 °C
4	Selected	-	2.0	10	40 °C

The results were interpreted using Design-Expert (version 7.1.1, Stats-Ease, Inc) software without transformation in order to obtain the half-normal plot (Figure 4) of this accurate but not predictive model due to the significant curvature detected (R^2 = 0.9104, Adj R^2 = 0.8760, Pred R^2 = 0.7795).

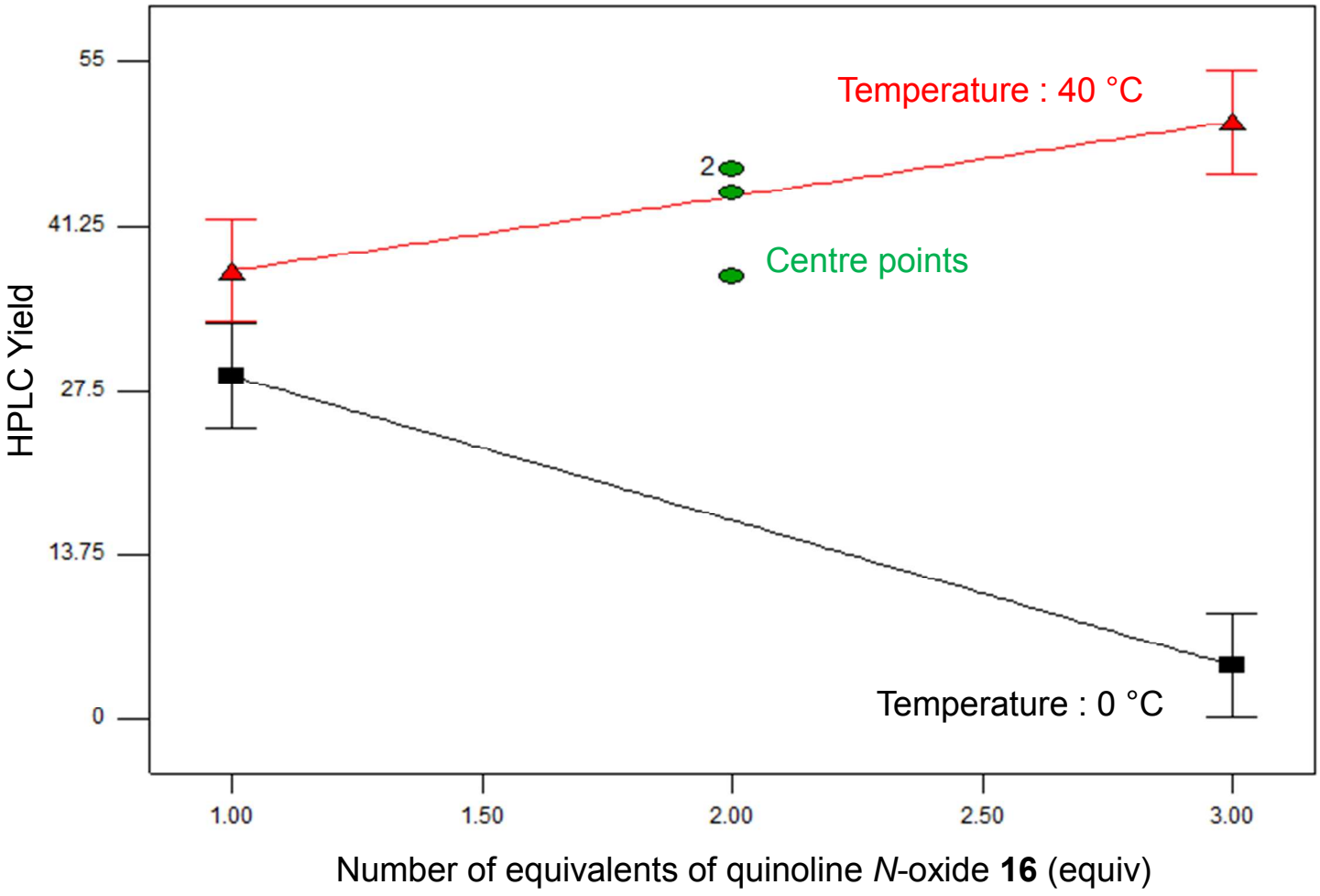
Figure 4: Half-normal plot using HPLC yield as response



Orange: positive effects; Blue: negative effects; Green: error from replicates

The half-normal plot revealed that the temperature (D) had the greatest influence as reactions performed at elevated temperatures gave the best results (Figure 4). This study also revealed that the interaction between the amount of quinoline *N*-oxide **16** (B) and the temperature (D) also had a significant impact on the reaction (Figure 5): whilst a high loading of quinoline *N*-oxide **16** was beneficial to the reaction at high temperature (red line), it was found to be detrimental at low temperature (black line). Although this result does not seem intuitive, it was reproducible and was believed to be symptomatic of the mechanistic complexity of the reaction. A response surface design to estimate the curvature would be required in order to fully understand the actual effect of the curvature on this interaction.

Figure 5: Quinoline *N*-oxide equivalents / temperature interaction plot

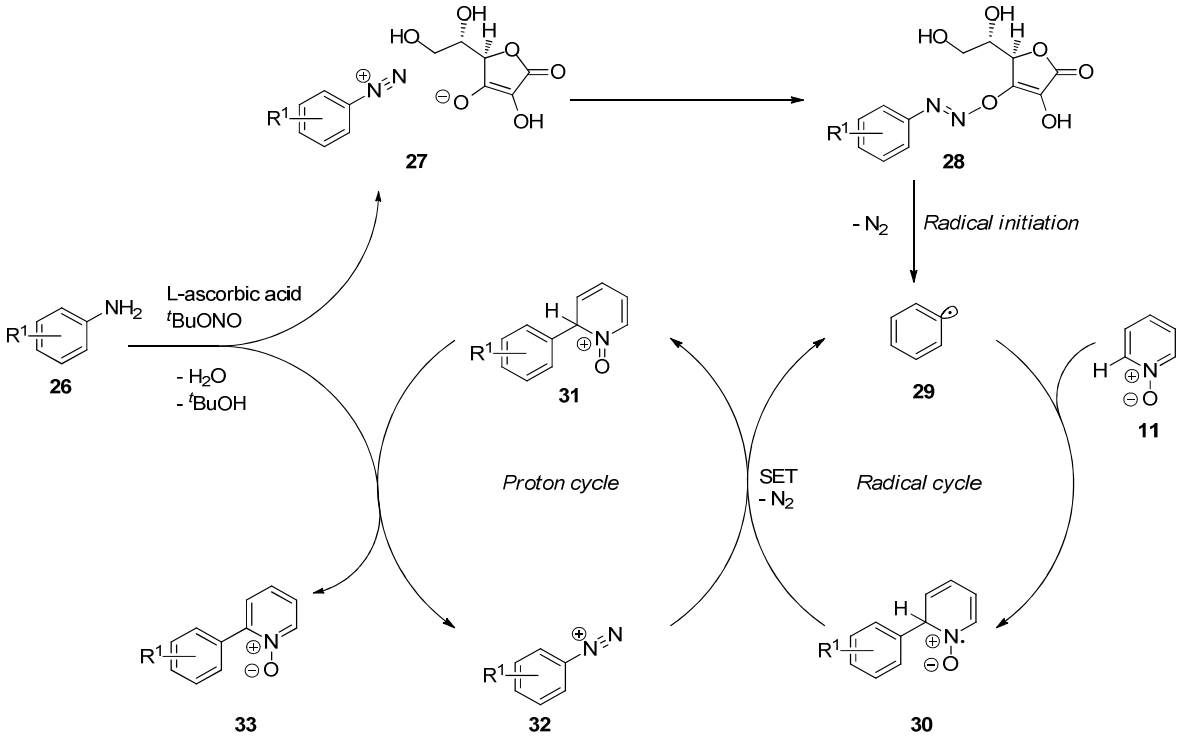


While the amount of quinoline *N*-oxide **16** (B) and the temperature (D) were found to have a pronounced impact on the yield, the number of solvent volumes (C) and more surprisingly, the loading of ascorbic acid (A) had no impact on the reaction outcome within the ranges studied and as a consequence of these results, minimum quantities of these reagents could be used to render this metal-free process even more sustainable. A compromise consisting of two equivalents of the *N*-oxide heterocycle at 40 °C in 10 volumes of solvent was selected as exhibited in Table 4, entry 4. The unexpected result obtained in this study with regards to the impact of ascorbic acid (A) loading on this transformation

raised the intriguing possibility of reducing the loading still further and warranted additionnal investigation of its role in this radical arylation.

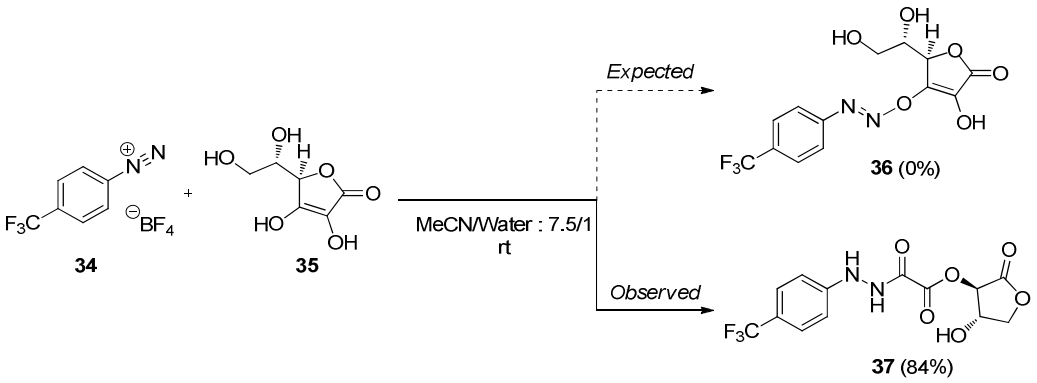
Carrillo and co-workers[34] hypothesised the possible role of ascorbic acid in this radical arylation of heterocycles as shown in Figure 6.

Figure 6: Hypothetical role of ascorbic acid



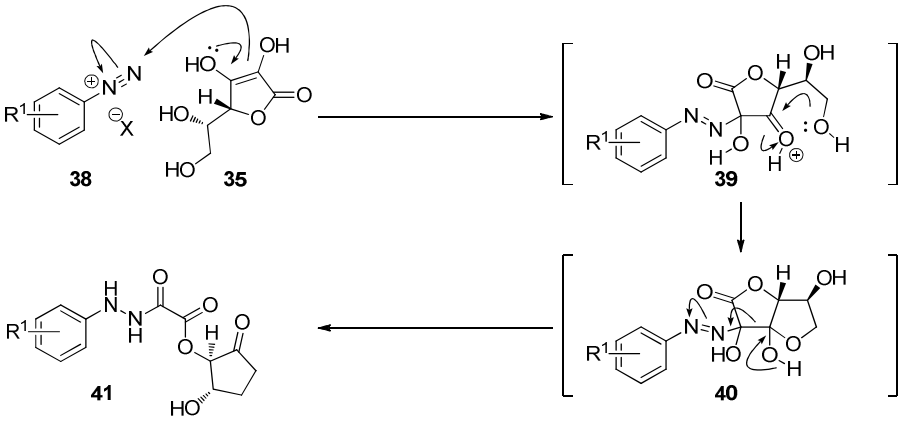
In this proposed mechanism, aniline **26** is diazotised in the presence of *tert*-butyl nitrite and ascorbic acid to form the aryldiazonium ascorbate salt **27** which reacts to generate the key intermediate **28**[38] which was believed to generate aryl radicals through spontaneous dediazotisation and generation of a stable ascorbate radical.[38] In order to probe this hypothesis, we elected to prepare the compound **36** according to the method published by Doyle and co-workers[39] and to study its behaviour under the reaction conditions (Scheme 2).

Scheme 2: Tentative synthesis of diazoether **36**



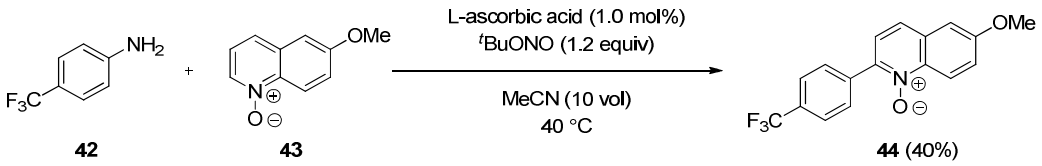
The reaction of 4-(trifluoromethyl)benzenediazonium tetrafluoroborate **34** with ascorbic acid **35** in aqueous acetonitrile led to the formation of a precipitate which was isolated by filtration. While standard analysis of the precipate by ^{1}H NMR, ^{13}C NMR and mass spectrometry were consistent with the reported structure **36**,[39] the IR spectrum exhibited three distinct bands in the carbonyl region (1781 cm^{-1}, 1760 cm^{-1} and 1693 cm^{-1}) which did not match the single carbonyl functionality of **36**. While this result was unexpected, a detailed study[40] by Ley and co-workers has shown that rather than **36**, the isolated product was **37**, arising from a Japp-Klingemann rearrangement (Figure 7).

Figure 7: Japp-Klingemann rearrangement for hydrazine formation[40]



The proposal from Carrillo and co-workers[34] involving the formation of a diazoether intermediate[38] was inconsistent with this observation and we decided to monitor the reaction with an infrared probe and LC/MS in order to identify potential reaction intermediates. Optimal reaction conditions previously established through DoE were thus adapted with minimal amounts of ascorbic acid used (1.0 mol%) in a reaction where the product could be easily isolated by precipitation and filtration (Scheme 3).

Scheme 3: Reaction for IR and LC/MS monitoring

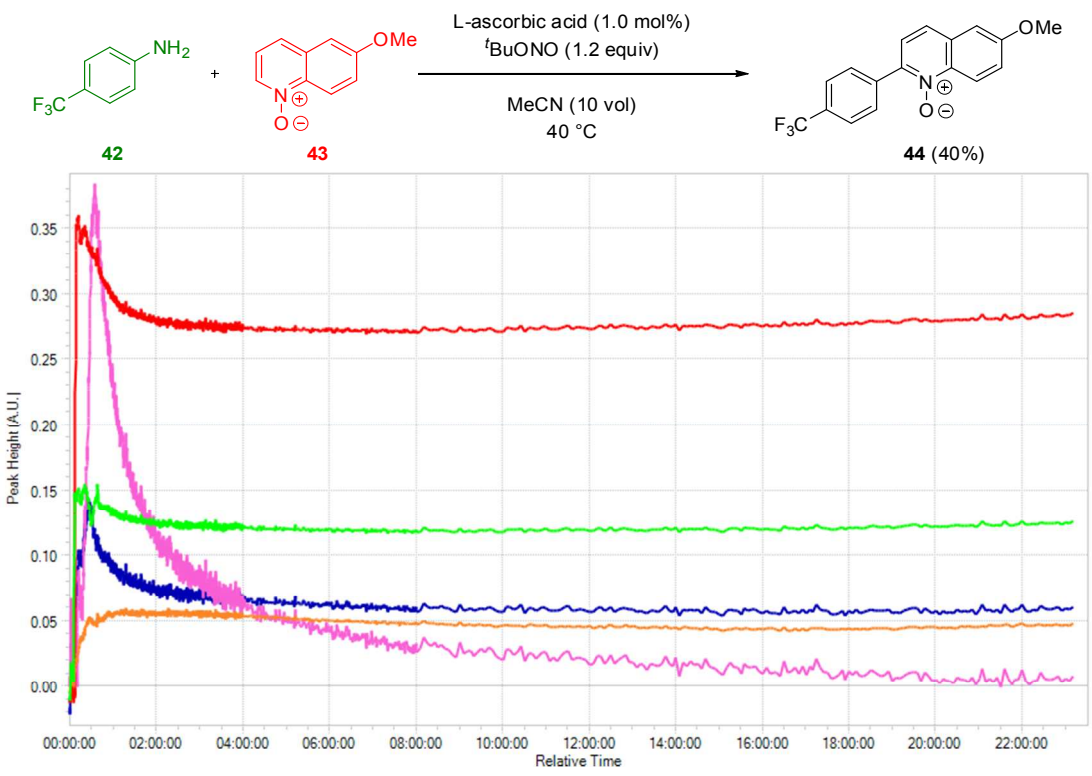


The infrared trace of the reaction mixture was analysed with the software iC IR (version 4.3, Mettler Toledo) with the attribution of representative wavenumber for every component involved in this arylation, except for the product **44** as no characteristic band could be identified to monitor its formation (see supporting information).

The identification of characteristic wavenumbers for each reagent allowed the monitoring of their behavior over the course of the reaction (Figure 9). As expected, 4-(trifluoromethyl)aniline **42**, 6-methoxyquinoline *N*-oxide **43** and *tert*-butyl nitrite were consumed while the formation of

4-(trifluoromethyl)benzenediazonium intermediate **34** was observed. Further analysis of the infrared spectra collected during this experiment allowed the identification of a potential intermediate with a 99.2% fit through the predicative function ConcIRT (pink line, Figure 8). It is noteworthy that the trend observed for this predicted intermediate is consistent with the behavior of a reaction intermediate as it is formed and consumed at the same time. In addition to the prediction of possible intermediates involved in the transformation, a predicted infrared spectrum was also generated for this intermediate (Figure 9).

Figure 8: Wavenumbers monitoring and potential intermediate identification

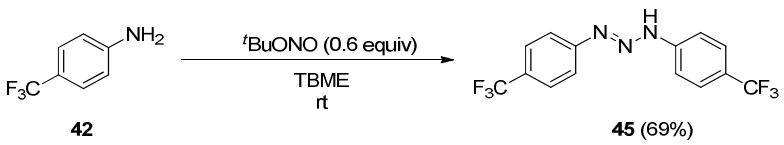


Entry	Component	Wavenumber

1	4-(Trifluoromethyl)aniline **42**	1125 to 1097 cm^{-1}
2	4-(Trifluoromethyl)benzenediazonium **34**	725 to 711 cm^{-1}
3	6-Methoxyquinoline *N*-oxide **43**	1232 to 1199 cm^{-1}
4	*tert*-Butyl nitrite	1656 to 1540 cm^{-1}
5	Simulated intermediate	Calculated

Moreover, a compound exhibiting a similar behavior to the intemediate identified through ReactIR analysis was also detected by LC/MS with a molecular weight of 333 $g.mol^{-1}$. As similarities were observed between the infrared spectrum of the intermediate and those of the aniline **42**, and the aryldiazonium **35** (Figure 10, bands at 1616 cm^{-1}, 1320 cm^{-1}, 1168 cm^{-1}, 1116 cm^{-1} and 1062 cm^{-1}), a structure derived from these scaffolds was envisaged for this intermediate. In addition to this observation, the molecular weight obtained by LC/MS allowed us to postulate that this intermediate was the triazene **45**, arising from the reaction of aryldiazonium **34** with the aniline **42.** This theory was supported by the the ready preparation and isolation of **45** using conditions similar to those in the coupling reaction (Scheme 4).

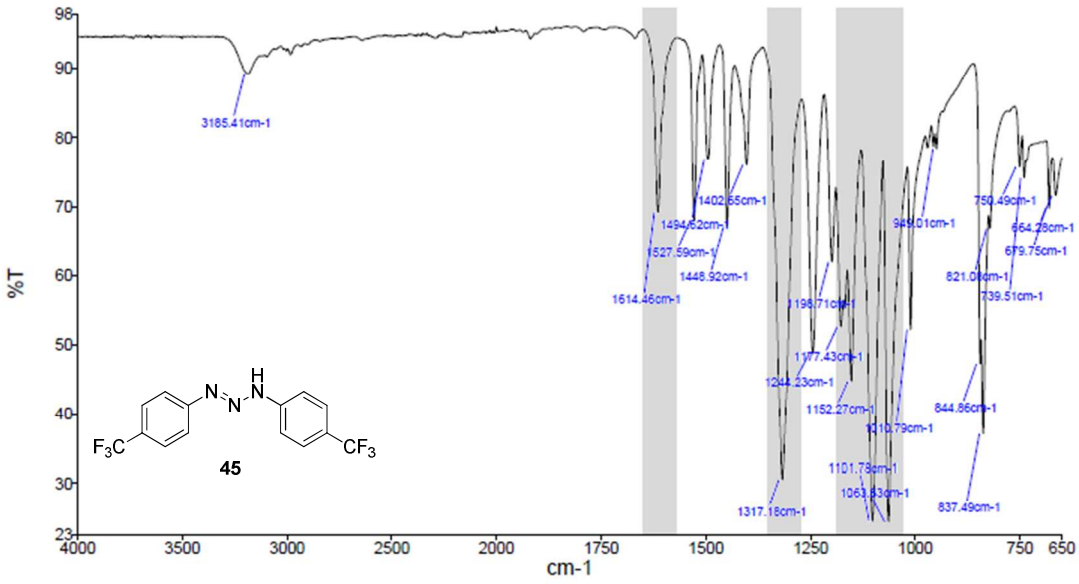
Scheme 4: Preparation of triazene intermediate **45**

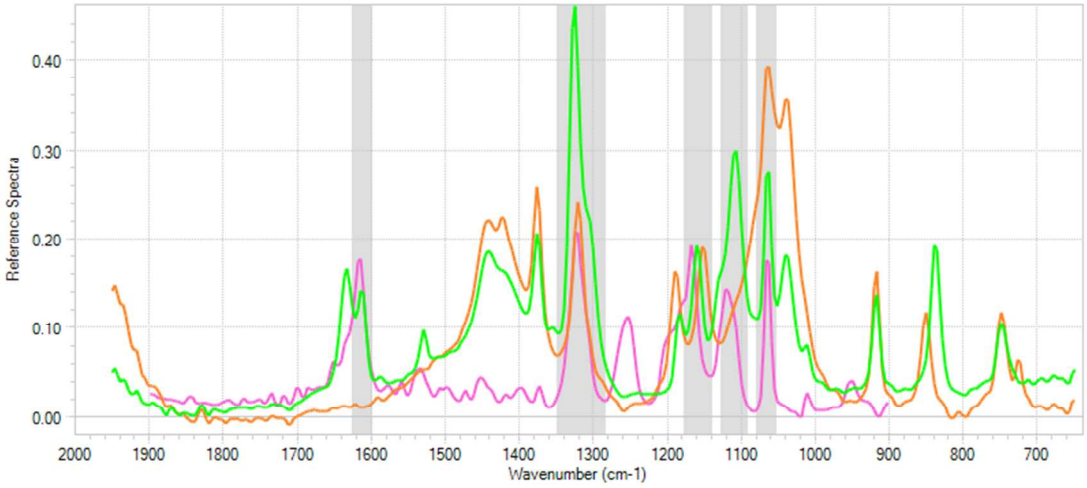


42 **45** (69%)

Comparison of the infrared spectrum of isolated triazene **45** (see supporting information) with the calculated spectrum of the predicted intermediate showed a high degree of similarity (Figure 9).

Figure 9: Comparison of triazene **45** with other reaction components by IR

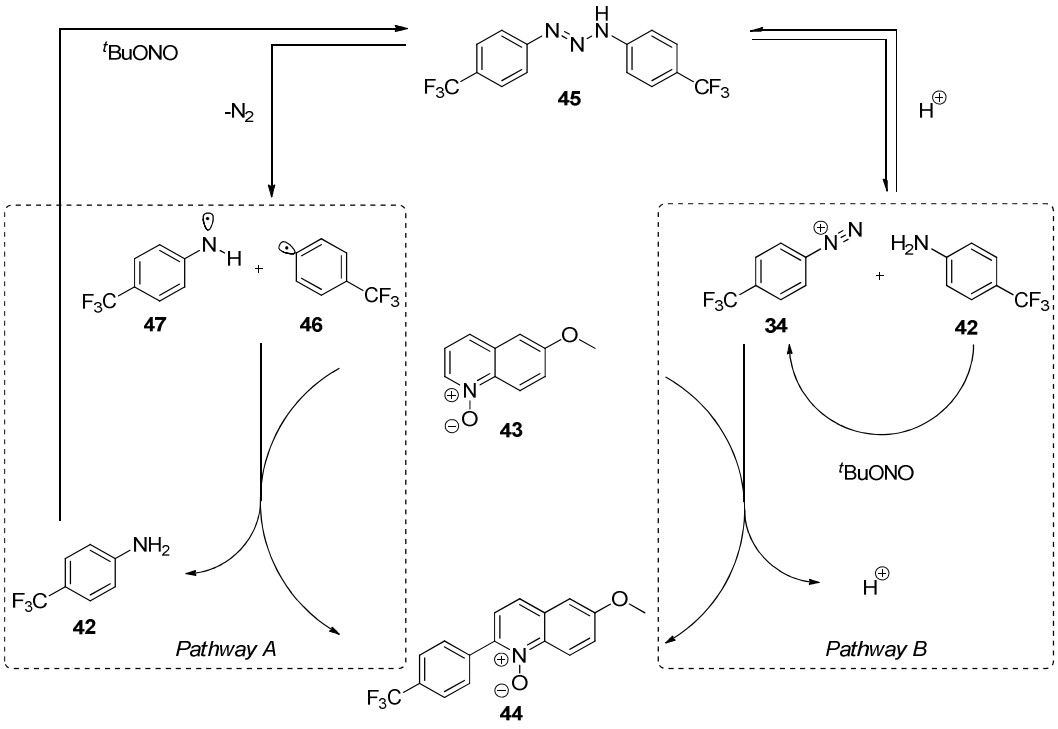




Entry	Aniline 174	Aryl diazonium 185	Simulated intermediate	Triazene 264
1	1614 cm^{-1}	N.A.	1614 cm^{-1}	1614 cm^{-1}
2	1324 cm^{-1}	1318 cm^{-1}	1322 cm^{-1}	1317 cm^{-1}
3	1159 cm^{-1}	1150 cm^{-1}	1167 cm^{-1}	1152 cm^{-1}
4	1109 cm^{-1}	N.A.	1118 cm^{-1}	1101 cm^{-1}
5	1064 cm^{-1}	1064 cm^{-1}	1064 cm^{-1}	1063 cm^{-1}

Selected among the similarities exhibited by the spectra, a significant medium band at 1614 cm^{-1} corresponding to the N—H bend and a strong band around 1320 cm^{-1} corresponding to the aromatic amine C—N stretch were observed. This result provides strong evidence of a triazene intermediate which could either be involved on the catalytic pathway (Figure 10, Pathway A) or simply acts as an aryldiazonium reservoir (Pathway B).

Figure 10: Postulated reaction pathways from the triazene compound **45**

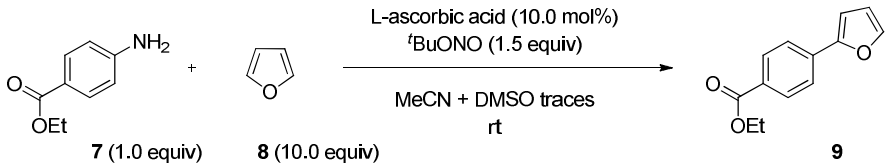


Hence, in Pathway A, triazene **45** acts as a radical initiator in an analogous manner to methodologies involving triazene intermediates[41] to generate a reactive aryl radical **46** and a stabilised aniline radical **47**, the release of nitrogen providing a driving force of this process (Figure 10). These radical species may then be involved in the arylation shown in Figure 6 to generate the product **44**, with the aniline radical **47** being reduced during the process. Alternatively the triazene may act as an off-cycle reservoir of aryldiazonium **34** which can react with the *N*-oxide **43** through a yet unknown mechanism (Pathway B), in which ascorbic acid may or may not be involved. While we feel that Pathway B is most likely to be radical in nature, an ionic mechanism cannot be ruled out at this stage. The difficulty of investigating these reactions is compounded by the fact that a radical mechanism would require only a trace amount of an initiator, following which the chain propogating species may be intermediates in the mechanism from **43** to **44** as shown in Figure 6 (radical cycle).

During their investigations using furan as the coupling partner, Carrillo and co-workers[34] showed that ascorbic acid had a benificial impact on the reaction when starting from a pre-formed diazonium salt, but no control reaction was reported starting from the aniline. It is possible that the *N*-

oxide functionality itself can somehow promote formation of an aryl radical such as **46** when ascorbic acid is not present (Figure 10, Pathway B). We therefore elected to conduct control reactions with furan as the coupling partner using the conditions reported by Carrillo and co-workers in the presence and absence of ascorbic acid (Table 4).[34]

Table 4: Control reactions



7 (1.0 equiv) **8** (10.0 equiv) **9**

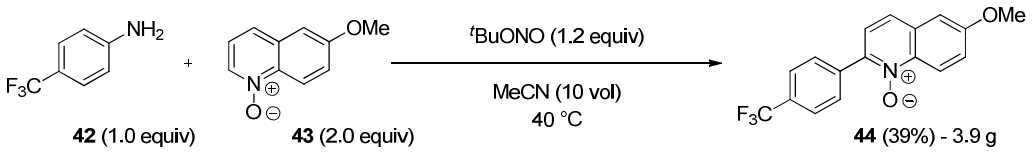
Entry	Conditions	Yield
1	Literature[34]	64%
2	With ascorbic acid	52%
3	Without ascorbic acid	53%

While the yields were lower than those reported in the literature, identical results were obtained regardless of the presence or absence of ascorbic acid and confirm that neither the ascorbic acid, nor the *N*-oxide functionality are required to promote the generation of an aryl radical intermediate. To add to the confusion, a number of groups have reported reactions involving the reaction of aryldiazonium salts in the presence of ascorbic acid where control reactions without this reagent show significantly inferior results, although some product is often observed.[42] What is clear is that the mechanism of these reactions warrants further investigation, and is likely to be significantly more complex than first thought.

The true test of any new green methodology often comes during scale-up where the sustainability advantages become more important. We therefore decided to study this radical arylation using reaction calorimetry in order to demonstrate the synthetic potential of this methodology while generating data which could support our mechanistic hypothesis. Reaction of 4-(trifluoromethyl)aniline **42** with 6-methoxyquinoline *N*-oxide **43** under optimised conditions (Scheme 5) was carried out on a 5 gram

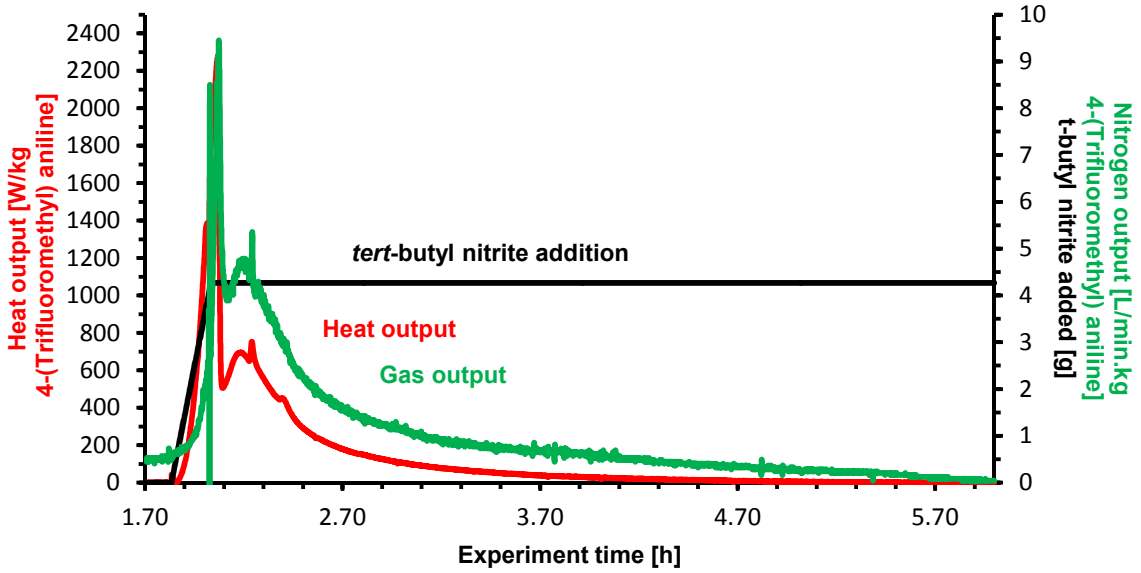
scale in a reaction calorimetry vessel equipped with a gas flow monitor with the aim to monitor the energy of the system and to identify potentially hazardous exothermic and gas-evolving events. It is noteworthy that the product of this arylation precipitated spontaneously from the reaction mixture and was isolated by filtration in 39% yield, thus delivering 3.9 grams of the target compound **44** (Scheme 5).

Scheme 5: Reaction for scale-up and calorimetry study



The dropwise addition of 4-(trifluoromethyl)aniline **42** to a mixture containing 6-methoxyquinoline *N*-oxide **43** in acetonitrile at 40 °C proved to be very mildly exothermic with a 3 °C predicted adiabatic temperature rise. Subsequent controlled addition of *tert*-butyl nitrite to the reaction mixture over 10 minutes correlated with a strongly exothermic event and substantial gas evolution (Figure 11) with a calculated 81 °C adiabatic temperature rise. Accumulation (of reagent or intermediates) was also a concern with 88% of the total heat output occurring after the addition of *tert*-butyl nitrite was complete, implying that the reaction was intrinsically slower than the rate of addition. This issue could be addressed by increasing the rate of reaction (for example by increasing reaction temperature) or by reducing the rate of *tert*-butyl nitrite addition and will be examined prior to further scale-up.

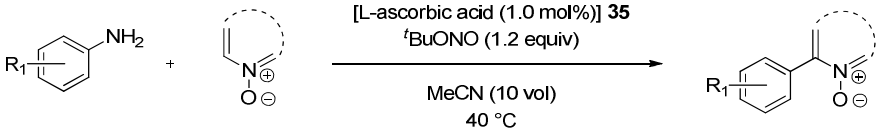
Figure 11: Gas and heat output of experiment shown in Scheme 5

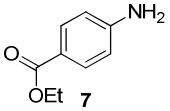
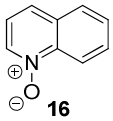
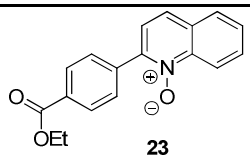
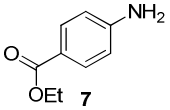
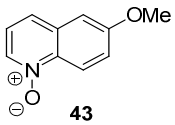
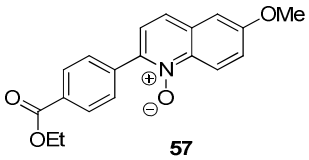
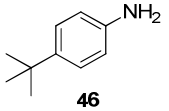
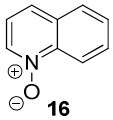
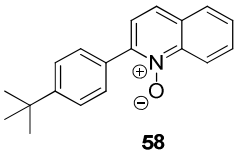
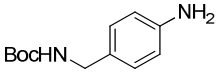
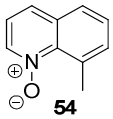
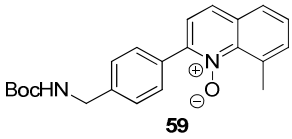
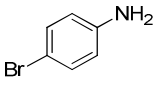
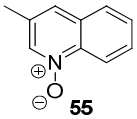
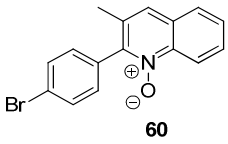
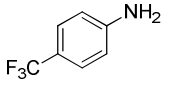
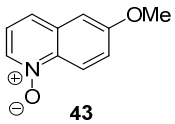
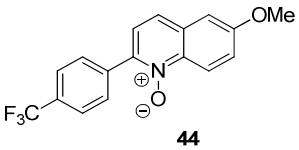
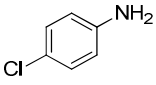
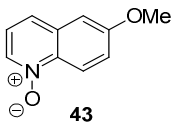
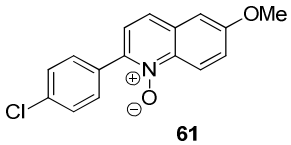


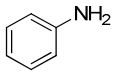
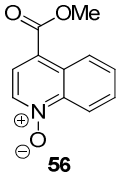
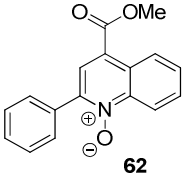
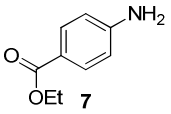
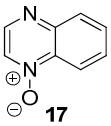
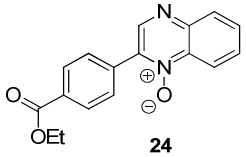
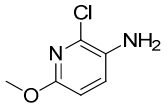
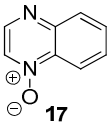
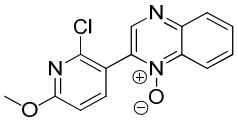
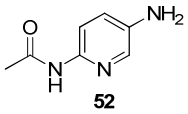
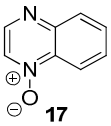
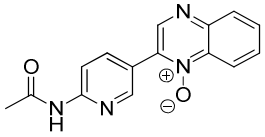
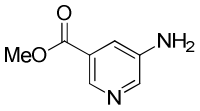
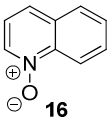
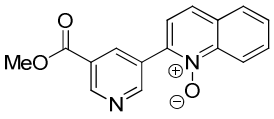
In addition to these results, the chart presented in Figure 11 is consistent with the formation of the intermediate discussed previously as two distinct peaks were observed during the calorimetry study. We suspect that the sharp peak between 1.9 and 2.5 hours corresponds to the direct reaction of the aryldiazonium species, while the second peak, between 1.9 and 4.7 hours, which was broader than the first, could be attributed to the consumption of the triazene intermediate **45**. However, given the relatively modest yield of the reaction, it is also possible that the two peaks correspond to the desired reaction and an as yet unknown side reaction.

The previous studies allowed the identification of optimal reaction conditions excluding ascorbic acid which were applied to a range of functionalised anilines and *N*-oxide heterocycles in order to define the scope and the limitations of this reaction (Table 5).

Table 5: Scope of the C-H arylation of *N*-oxide heterocycles



Entry	Aniline	*N*-oxide heterocycle	Product	Yield without 35[a]	Yield with 35[a]
1	 **7**	 **16**	 **23**	52%	53%
2	 **7**	 **43**	 **57**	52%	54%
3	 **46**	 **16**	 **58**	55%	51%
4	 **47**	 **54**	 **59**	44%	58%
5	 **48**	 **55**	 **60**	52%	51%
6	 **42**	 **43**	 **44**	52%	50%
7	 **49**	 **43**	 **61**	53%	51%

Entry	Aniline	*N*-oxide heterocycle	Product	Yield without 35[a]	Yield with 35[a]
8	 **50**	 **56**	 **62**	70%	65%
9	 **7**	 **17**	 **24**	74%	N.A.
10	 **51**	 **17**	 **63**	15%	22%
11	 **52**	 **17**	 **64**	43%	43%
12	 **53**	 **16**	 **65**	35%	34%

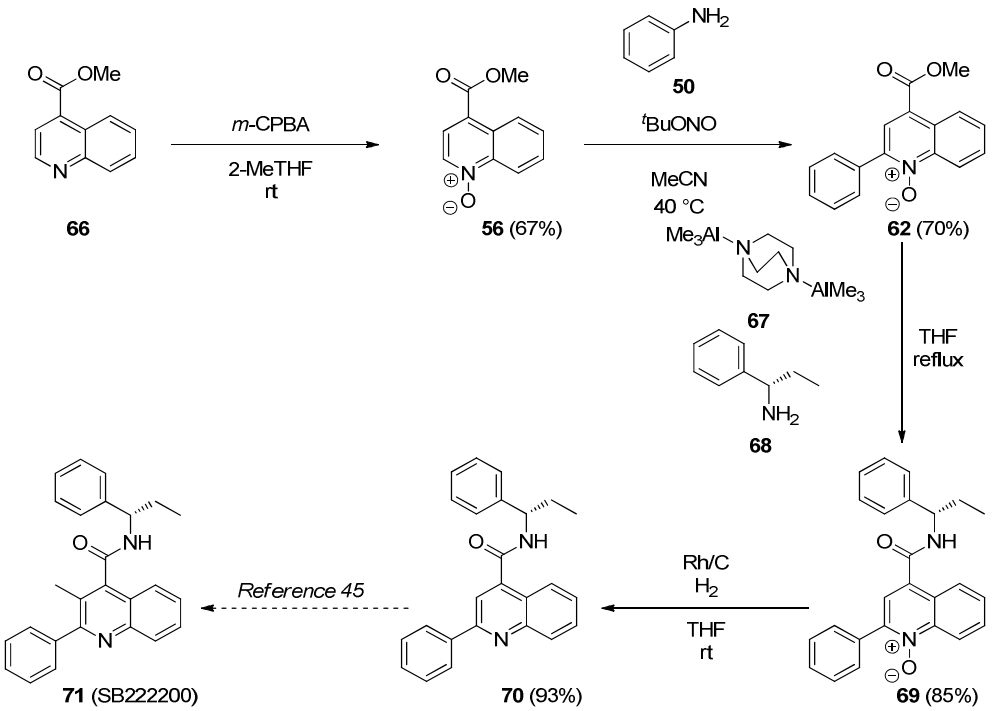
[a]Isolated yield after chromatography.

The electronic properties of both the aniline and the *N*-oxide heterocycle did not appear to affect the reaction as all combinations gave similar results with yields around 50%. Nevertheless it is noteworthy that aminopyridine derivatives were much less efficient coupling partners compared to their otherwise similar aniline counterparts (Table 5, entries 1 and 12). This observation is consistent with our experience of pyridyldiazonium species exhibiting lower stability than the corresponding phenyldiazonium compounds.[32] In contrast, the arylation proved to be compatible with a representative range of functional groups used in medicinal chemistry such as amide (Table 5, entry 11), esters (Table 5, entries 1,

2 and 12), a *N*-Boc protected amine (Table 5, entry 4) and halides (Table 5, entries 5 and 7), which provide significant opportunity for further elaboration. In addition, steric encumbrance of the *N*-oxide coupling partner was well tolerated (Table 5, entry 5) with the presence of an *ortho*-methyl group having no apparent impact on the yield of the transformation. This study also confirmed the observation of regiospecificity for the 2-position of the *N*-oxide heterocycle as only traces of the potential regioisomeric adducts were observed by LC/MS during this work. The close similarity between the yields obtained with and without ascorbic acid provides strong evidence that this additive is not required for the reaction to proceed.

While arylated heterocyclic substrates could be prepared in moderate to good yields through this radical C-H arylation reaction, we elected to apply this methodology to the pharmaceutically relevant substrate SB222200 **71**, a selective, reversible and competitive antagonist of human NK-3 receptor (Figure 12).[43]

Figure 12: Formal synthesis of SB222200



The C-H arylation developed in this work required the preparation of the *N*-oxide substrate **56** which was achieved in 67% yield by oxidation of methyl 4-carboxy-quinoline **66** using *m*-CPBA. This example showed the ease of introduction of the *N*-oxide group on quinoline substrates as this com-

pound was obtained in good yield with unoptimised reaction conditions. Subsequent arylation of *N*-oxide heterocycle **56** was carried out in 70% yield and the methyl ester of **62** was directly converted to the corresponding amide **69** (85%) in the presence of DABAl-Me_3 **67** and chiral amine **68**.[44] The *N*-oxide group was then easily removed through unoptimised hydrogenation conditions catalysed by rhodium on activated charcoal and delivered the arylated quinoline **70** in 93% yield. The conversion of **70** to **71** has been reported in the literature[45] so our work represents a formal total synthesis of SB222200.

CONCLUSION

In conclusion, we have developed a sustainable C-H radical arylation of quinoline *N*-oxide derivatives using a variety of industry-standard tools (Multivariate Data Analysis, Design of Experiments, IR monitoring and reaction calorimetry) to accelerate the research while simultaneously providing valuable mechanistic insights. The understanding provided by the careful use of these tools can be used to support decision making processes when choices and compromises need to be made and we hope that this demonstration will stimulate their wider adoption within the chemistry community. In our hands, the use of ascorbic acid as a putative promoter of the reaction is not necessary as very similar yields were observed in the presence or absence of this material. The use of *in-situ* monitoring and supporting analytical techniques has allowed the identification of a triazene intermediate which could potentially act as a precursor to the active radical species and has highlighted the need for further detailed investigation of the reaction. Our optimised process releases nitrogen, *t*-butanol and water as the only co-products; is compatible with a wide range of functional groups and was successfully performed on a multigram scale. While the *N*-oxide functionality is required for high regioselectivity, it is unlikely to be present in the final product and can be removed under catalytic conditions to afford the corresponding 2-arylquinoline, providing expedient access to this pharmaceutically important family of compounds. Current work is focused on expanding our understanding of the mechanistic course of this intriguing reaction and we will report on our findings in due course.

EXPERIMENTAL SECTION

General Procedure for the screening of *N*-oxide heterocycles and solvents (Tables 1 and 2): To a round bottom flask containing ethyl 4-aminobenzoate **7** (250 mg, 1.513 mmol), *N*-oxide heterocycle (3.03 mmol) and L-ascorbic acid **35** (27 mg, 0.151 mmol) under a nitrogen atmosphere was added de-gassed solvent (12.5 mL), followed by *tert*-butyl nitrite (0.240 mL, 1.816 mmol) and the reaction mixture was stirred for 17 hours at 20 °C. After this time, reaction mixture was evaporated to dryness and the crude product was purified by silica gel chromatography eluting with either heptane/ethyl acetate or CH_2Cl_2/MeOH mixtures to yield the target compound.

2-(4-(Ethoxycarbonyl)phenyl)pyridine *N*-oxide (19): Orange solid (81 mg, 22% yield), Mp 119–120 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.39-8.38 (m, 1H), 8.07 (d, 2H, *J* = 8.6 Hz), 8.00 (d, 2H, *J* = 8.6 Hz), 7.72-7.67 (m, 1H), 7.45-7.48 (m, 2H), 4.37 (q, 2H, *J* = 7.1 Hz), 1.36 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.3 (C_{IV}), 146.6 (C_{IV}), 140.2, 137.2 (C_{IV}), 130.2 (C_{IV}), 129.6, 128.7, 127.7, 126.1, 125.5, 60.9, 14.1 ppm. HRMS (ESI$^+$): calculated for $C_{14}H_{14}NO_3$ $[M + H]^+$ 244.0960, found 244.0968.

2-(4-(Ethoxycarbonyl)phenyl)pyrazine *N*-oxide (20): Orange solid (69 mg, 19% yield), Mp 154–159 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.83 (s, 1H), 8.55 (d, 1H, *J* = 4.1 Hz), 8.48 (d, 1H, *J* = 4.1 Hz), 8.08 (d, 2H, *J* = 8.5 Hz), 8.01 (d, 2H, *J* = 8.5 Hz), 4.36 (q, 2H, *J* = 7.1 Hz), 1.35 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.2 (C_{IV}), 148.4, 146.9, 142.5 (C_{IV}), 134.5, 133.7 (C_{IV}), 130.9 (C_{IV}), 129.7, 128.9, 61.0, 14.1 ppm. HRMS (ESI$^+$): calculated for $C_{13}H_{13}N_2O_3$ $[M + H]^+$ 245.0924, found 245.0921.

2-(4-(Ethoxycarbonyl)phenyl)quinoline *N*-oxide (23): Pale pink solid (264 mg, 60% yield), Mp 196–200 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.67 (d, 1H, *J* = 8.8 Hz), 8.19 (d, 2H, *J* = 8.6 Hz), 8.15 (d, 1H, *J* = 8.7 Hz), 8.12 (d, 2H, *J* = 8.6 Hz), 8.05 (d, 1H, *J* = 8.5 Hz), 7.90 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.5 Hz), 7.81-7.78 (m, 2H), 4.39 (q, 2H, *J* = 7.1 Hz), 1.38 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.3 (C_{IV}), 142.8 (C_{IV}), 141.5 (C_{IV}), 137.8 (C_{IV}), 130.8, 130.3 (C_{IV}), 129.9, 129.7 (C_{IV}), 128.9, 128.7, 128.6, 124.9, 123.4, 119.4, 61.0, 14.2 ppm. HRMS (ESI$^+$): calculated for $C_{18}H_{16}NO_3$ $[M + H]^+$ 294.1127, found 294.1125.

2-(4-(Ethoxycarbonyl)phenyl)quinoxaline *N*-oxide (24): Beige solid (317 mg, 71% yield), Mp 212–215 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.93 (s, 1H), 8.70 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 8.24 (d, 2H, J = 8.5 Hz), 8.18 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.4 Hz), 8.09 (d, 2H, J = 8.5 Hz), 7.89-7.80 (m, 2H), 4.45 (q, 2H, J = 7.2 Hz), 1.44 (t, 3H, J = 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.9 (C_{IV}), 147.0, 144.6 (C_{IV}), 138.6 (C_{IV}), 137.6 (C_{IV}), 134.1 (C_{IV}), 132.0 (C_{IV}), 131.6, 130.7, 130.0, 129.8, 129.4, 119.4, 61.4, 14.4 ppm. HRMS (ESI^+): calculated for $C_{17}H_{15}N_2O_3$ $[M + H]^+$ 295.1076, found 295.1077.

General Procedure for the Design of Experiments (Table 3): To a round bottom flask containing ethyl 4-aminobenzoate **7** (250 mg, 1.513 mmol, 1.0 equiv.), quinoline *N*-oxide hydrate **16** (80% w/w, desired number of equivalents) and L-ascorbic acid **35** (desired loading) under a nitrogen atmosphere was added degassed acetonitrile (desired volume), followed by *tert*-butyl nitrite (0.240 mL, 1.816 mmol) and the reaction mixture was stirred for 17 hours at the desired temperature. The reaction mixture was then diluted in a 50 mL volumetric flask with ethyl acetate to dissolve the solids and the solution was analysed by HPLC by diluting 250 µL into 1250 µL of acetonitrile. Yields were calculated from a calibration curve (see Supporting Information for full details).

Procedure for the synthesis of the hydrazine derivative 37 (Scheme 2): L-ascorbic acid **35** (346 mg, 1.96 mmol) was added to a round bottom flask containing 4-(trifluoromethyl)benzenediazonium tetrafluoroborate **34** (510 mg, 1.96 mmol) dissolved in a mixture of acetonitrile (1 mL) and water (7.5 mL) and the resulting mixture was stirred at room temperature for 30 minutes. A precipitate was formed and was filtered off the reaction mixture to give the hydrazine derivative **37** as a white solid (575 mg, 1.65 mmol, 84% yield).

(3*R*,4*S*)-4-Hydroxy-2-oxotetrahydrofuran-3-yl-2-(2-(4-(trifluoromethyl)phenyl)hydrazinyl)-2-oxoacetate (37): White solid (575 mg, 84% yield), Mp 195–200 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.13 (s, 1H), 8.67 (s, 1H), 7.51 (d, 2H, J = 8.5 Hz), 6.86 (d, 2H, J = 8.5 Hz), 6.17 (bs, 1H), 5.70 (d, 1H, d = 7.8 Hz), 4.71 (aq, 1H J = 7.6 Hz), 4.52 (at, 1H, J = 8.0 Hz), 4.08 (at, 1H, J = 8.3 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 170.2 (C_{IV}), 158.6 (C_{IV}), 155.9 (C_{IV}), 155.2 (C_{IV}), 126.4, 126.3, 124.9 (C_{IV}, q,

J = 270.3 Hz), 118.9 (C_{IV}, q, *J* = 31.8 Hz), 111.7 (at, *J* = 29.5 Hz), 76.0, 69.4 ppm. HRMS (ESI^+): Calculated for $C_{13}H_{12}F_3N_2O_6$ $[M + H]^+$ 349.0642, found 349.0653

Procedure for IR and LC/MS monitoring experiment (Scheme 3): To a 400 mL EasyMax 402 (Mettler Toledo) reactor fitted with an IR probe (Mettler Toledo ReactIR iC 10 with MCT detector using HappGenzel apodization fitted with a DiComp (Diamond) probe connected with AgX 6mm x 2m Fiber (Silver Halide)) under a nitrogen atmosphere was charged L-ascorbic acid **35** (6 mg, 0.31 mmol) diluted in previously degassed acetonitrile (100 mL), followed by 6-methoxyquinoline *N*-oxide **43** (10.87 g, 62.1 mmol) and 4-(trifluoromethyl)aniline **42** (3.91 mL, 31.0 mmol). The resulting mixture was stirred at 40 °C and monitored by IR and LC/MS for 21 hours. 6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinoline *N*-oxide **44** precipitated spontaneously during the course of the reaction and was isolated by filtration to give a beige solid (3.92 g, 12.3 mmol, 40% yield).

6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinoline *N*-oxide (44): Beige solid (3.92 g, 40% yield), Mp 218–223 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, 1H, *J* = 9.5 Hz), 8.09 (d, 2H, *J* = 8.4 Hz), 7.77 (d, 2H, *J* = 8.3 Hz), 7.69 (d, 1H, *J* = 8.6 Hz), 7.46 (d, 1H, *J* = 8.6 Hz), 7.43 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.14 (d, 1H, *J* = 2.4 Hz), 3.98 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6 (C_{IV}), 141.8, 137.80, 137.1, 131.3, 131.0 (q, *J* = 32.6 Hz), 130.0, 125.2 (q, *J* = 3.8 Hz), 124.5, 124.0 (q, *J* = 272.2 Hz), 123.40, 122.9, 122.0, 105.9, 55.8 ppm. HRMS (ESI^+): Calculated for $C_{17}H_{13}F_3NO_2$ $[M + H]^+$ 320.0893, found 320.0895.

Preparation of 1,3-bis(4-(trifluoromethyl)phenyl)triazene (45) (Scheme 4): To a round bottom flask containing a stirr bar and 4-(trifluoromethyl)aniline **42** (0.195 mL, 1.552 mmol) in TBME (5 mL) was added *tert*-butyl nitrite (0.123 mL, 0.931 mmol) and the resulting mixture was stirred for 2 hours at room temperature. The solvent was then removed under reduced pressure and the resulting solid was triturated in heptane. Filtration of the slurry afforded 1,3-bis(4-(trifluoromethyl)phenyl)triazene **45** (178 mg, 0.534 mmol, 69 % yield) as an orange solid.

1,3-Bis(4(-trifluoromethyl)phenyl)triazene (45):[46] Orange solid (178 mg, 69% yield), Mp 114–116 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 13.07 (bs, 1H), 7.78-7.60 (m, 8H) ppm. HRMS (ESI$^+$): Calculated for $C_{14}H_{10}F_6N_3$ $[M + H]^+$ 334.0773, found 334.0773

Control reactions – synthesis of ethyl 4-(furan-2-yl)benzoate 9 (Table 4): To a glass tube containing benzocaine **7** (83 mg, 0.5 mmol) under a nitrogen atmosphere was added previously degassed acetonitrile (5 mL), followed by furan **8** (0.36 mL, 5.00 mmol), *tert*-butyl nitrite (0.1 mL, 0.750 mmol) and a previously prepared solution of DMSO (0.1 mL) with or without L-ascorbic acid **35** (0.88 mg, 5.0 µmol). The resulting mixture was stirred for 14 hours at room temperature and was evaporated to dryness under reduced pressure. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give ethyl 4-(furan-2-yl)benzoate **9** (56 mg, 0.26 mmol, 52% yield with L-ascorbic acid **35**; 57 mg, 0.27 mmol, 53% yield without L-ascorbic acid **35**) as a white solid.

Ethyl 4-(furan-2-yl)benzoate (9): White solid (56 mg, 52% yield with L-ascorbic acid **35**; 57 mg, 53% yield without L-ascorbic acid **35**), Mp 57–60 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, 2H, J = 8.6 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.53 (d, 1H, J = 1.3 Hz), 6.80 (d, 1H, J = 3.4 Hz), 6.52 (dd, 1H, J_1 = 3.5 Hz, J_2 = 1.7 Hz), 4.40 (q, 2H, J = 7.1 Hz), 1.42 (t, 3H, J = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.4 (C_{IV}), 153.0 (C_{IV}), 143.1, 134.7 (C_{IV}), 130.1, 129.0 (C_{IV}), 123.4, 112.0, 107.2, 61.0, 14.4 ppm. HRMS (ESI$^+$): Calculated for $C_{13}H_{13}O_3$ $[M + H]^+$ 217.0859, found 217.0852.

Scale-up and calorimetry study (Scheme 5): To a 100 mL Reaction Calorimetry 1 (RC 1, Mettler Toledo) reactor under a nitrogen atmosphere was charged 6-methoxyquinoline *N*-oxide **43** (10.87 g, 62.1 mmol), followed by previously degassed acetonitrile (50 mL). The solution was then stirred at 40°C and a first calibration was performed (Cp = 2221 J/[Kg.K]).

Aniline addition: 4-(trifluoromethyl)aniline **42** (3.91 mL, 31.0 mmol) was added dropwise with a syringe pump over 10 minutes to the previous solution at 40°C and a second calibration was performed (Cp = 1948 J/[Kg.K]). The RC 1 instrument indicated a total heat output of 0.33 kJ and a predicted adiabatic temperature rise of 3 °C. No gas output was observed during the addition of the 4-(trifluoromethyl)aniline **42**.

tert-Butyl nitrite addition: *tert*-butyl nitrite (4.92 mL, 37.2 mmol) was then added dropwise with a syringe pump over 10 minutes to the previous reaction mixture under nitrogen at 40°C and a third calibration was performed (Cp = 2170 J/[Kg.K]) after 19 hours. The RC 1 instrument indicated a total heat output of 10.4 kJ and a predicted adiabatic temperature rise of 81°C.

Work-up / isolation: The slurry was then stirred for 17 hours at 40°C under nitrogen before being cooled down to 20 °C. 6-Methoxy-2-(4-(trifluoromethyl)phenyl)quinoline *N*-oxide **44** precipitated spontaneously during the course of the reaction and was isolated by filtration to give a beige solid (3.88 g, 12.15 mmol, 39% yield).

General Procedure for the substrate scope using optimised reaction conditions (Table 5): To a glass tube containing the aniline (1.0 equiv) and the *N*-oxide heterocycle (2.0 equiv) [L-ascorbic acid **35** (1.0 mol%) when required] under a nitrogen atmosphere was added degassed acetonitrile (10 volumes), followed by *tert*-butyl nitrite (1.2 equiv.) and the reaction mixture was stirred for 17 hours at 40 °C. The reaction mixture was then evaporated to dryness and the crude product was purified by silica gel chromatography eluting with either heptane/ethyl acetate or CH_2Cl_2/MeOH mixtures to yield the target compound.

2-(4-(Ethoxycarbonyl)phenyl)-6-methoxyquinoline *N*-oxide (57): Beige solid (252 mg, 52% yield without L-ascorbic acid **35**; 244 mg, 50% yield with L-ascorbic acid **35**), Mp 201–204 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.76 (d, 1H, *J* = 9.5 Hz), 8.18 (d, 2H, *J* = 8.4 Hz), 8.05 (d, 2H, *J* = 8.5 Hz), 7.68 (d, 1H, *J* = 8.5 Hz), 7.48 (d, 1H, *J* = 8.8 Hz), 7.42 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.14 (d, 1H, *J* = 2.5 Hz), 4.43 (q, 2H, *J* = 7.1 Hz), 3.97 (s, 3H), 1.43 (t, 3H, *J* = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2 (C_{IV}), 159.6 (C_{IV}), 142.4 (C_{IV}), 137.9 (C_{IV}), 137.8 (C_{IV}), 131.3 (C_{IV}), 131.0 (C_{IV}), 129.6, 129.4, 124.6, 123.6, 122.9, 122.1, 106.0, 61.2, 55.8, 14.3 ppm. HRMS (ESI^+): calculated for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1232, found 324.1230.

2-(4-(*tert*-Butyl)phenyl)quinoline *N*-oxide (**58**)**:** Red solid (255 mg, 55% yield without L-ascorbic acid **35**; 238 mg, 51% yield with L-ascorbic acid **35**), Mp 156–160 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, 1H, *J* = 8.5 Hz), 7.95 Hz (d, 2H, *J* = 8.1 Hz), 7.84 (d, 1H, *J* = 8.1 Hz), 7.77-7.75 (m, 1H), 7.72 (d, 1H, *J* = 8.8 Hz), 7.62-7.59 (m, 1H), 7.55-7.50 (m, 3H), 1.37 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8

(C_{IV}), 145.1 (C_{IV}), 142.3 (C_{IV}), 130.5, 129.5, 129.4, 128.3, 128.0, 125.4, 125.3, 125.3, 123.3, 120.3, 34.9 (C_{IV}), 31.3 ppm. HRMS (ESI^+): calculated for $C_{19}H_{20}NO$ $[M + H]^+$ 278.1539, found 278.1544.

2-(4-((*N*-Boc)aminomethyl)phenyl)-8-methylquinoline *N*-oxide (59): Orange solid (107 mg, 44% yield without L-ascorbic acid **35**; 236 mg, 58% yield with L-ascorbic acid **35**), Mp 119–123 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 2H, *J* = 8.2 Hz), 7.65 (d, 2H, *J* = 9.0 Hz), 7.44-7.41 (m, 4H), 7.37 (d, 1H, *J* = 8.6 Hz), 4.91 (bs, 1H), 4.38 (d, 2H, *J* = 5.7 Hz), 3.20 (s, 3H), 1.47 (s, 9H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.9 (C_{IV}), 146.1 (C_{IV}), 142.1 (C_{IV}), 140.2 (C_{IV}), 134.1 (C_{IV}), 133.8, 133.2 (C_{IV}), 131.7, 129.7, 127.9, 127.4, 126.8, 125.6 (C_{IV}), 123.0, 79.6 (C_{IV}), 44.5, 28.4, 25.6 ppm. HRMS (ESI^+): calculated for $C_{22}H_{25}N_2O_3$ $[M + H]^+$ 365.1860, found 365.1875.

2-(4-Bromophenyl)-3-methylquinoline *N*-oxide (60): Beige solid (235 mg, 52% yield without L-ascorbic acid **35**; 233 mg, 51% yield with L-ascorbic acid **35**), Mp 140–143 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.71 (d, 1H, *J* = 8.5 Hz), 7.81 (d, 1H, *J* = 7.6 Hz), 7.73-7.60 (m, 5H), 7.32 (d, 2H, *J* = 8.6 Hz), 2.24 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.1 (C_{IV}), 140.4 (C_{IV}), 132.2, 132.0 (C_{IV}), 131.0 (C_{IV}), 130.8, 129.8, 129.3 (C_{IV}), 128.8, 127.3, 126.0, 123.3 (C_{IV}), 120.2, 20.6 ppm. HRMS (ESI^+): calculated for $C_{16}H_{13}{}^{79}BrNO$ $[M + H]^+$ 314.0175, found 314.0188.

6-Methoxy-2-(4-chlorophenyl)quinoline *N*-oxide (61): Beige solid (294 mg, 53% yield without L-ascorbic acid **35**; 286 mg, 51% yield with L-ascorbic acid **35**), Mp 140–143 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, 1H, *J* = 9.6 Hz), 7.94 (d, 2H, *J* = 8.6 Hz), 7.68 (d, 1H, *J* = 8.6 Hz), 7.51 (d, 2H, *J* = 8.5 Hz), 7.47 (d, 1H, *J* = 8.8 Hz), 7.44 (dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.13 (d, 1H, *J* = 2.7 Hz), 3.97 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4 (C_{IV}), 142.1(C_{IV}), 137.8 (C_{IV}), 135.2 (C_{IV}), 131.9 (C_{IV}), 131.0 (C_{IV}), 130.9, 128.5, 124.4, 123.4, 122.7, 122.0, 105.9, 55.7 ppm. HRMS (ESI^+): Calculated for $C_{16}H_{13}{}^{35}ClNO_2$ $[M + H]^+$ 286.0629, found 286.0633.

4-(Methoxycarbonyl)-2-phenylquinoline *N*-oxide (**62**)**:** Orange solid (251 mg, 70% yield without L-ascorbic acid **35**; 351 mg, 65% yield with L-ascorbic acid **35**), Mp 112–117 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.05 (dd, 1H, J_1 = 8.3 Hz, J_2 = 1.0 Hz), 8.87 (dd, 1H, J_1 = 8.6 Hz, J_2 = 1.0 Hz), 8.24 (s, 1H), 7.96 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.5 Hz), 7.80 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz), 7.74 (ddd, 1H, J_1 = 8.3 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz), 7.57-7.46 (m, 3H), 4.02 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4 (C_{IV}),144.1 (C_{IV}), 143.1 (C_{IV}), 132.8 (C_{IV}), 130.6, 129.9, 129.7, 129.5, 128.5, 127.3 (C_{IV}),

126.8, 126.7, 122.4 (C_{IV}), 120.3, 52.6 ppm. HRMS (ESI^+): calculated for $C_{17}H_{14}NO_3$ $[M + H]^+$ 280.0968, found 280.0976.

2-(2-Chloro-6-methoxypyridin-3-yl)-quinoxaline *N*-oxide (**63**)**:** Brown solid (58 mg, 15% yield without L-ascorbic acid **35**; 117 mg, 22% yield with L-ascorbic acid **35**), Mp 174–180 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H), 8.65 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 8.3 Hz), 7.89-7.76 (m, 3H), 6.87 (d, 1H, *J* = 8.9 Hz), 4.03 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5 (C_{IV}), 148.0 (C_{IV}), 147.9, 145.0 (C_{IV}), 142.5, 137.4 (C_{IV}), 136.9 (C_{IV}), 131.7, 130.5, 130.2, 119.3, 117.9 (C_{IV}), 109.8, 54.5 ppm. HRMS (ESI^+): calculated for $C_{14}H_{11}{}^{35}ClN_3O_2$ $[M + H]^+$ 288.0534, found 288.0544.

2-(6-Acetamidopyridin-3-yl)quinoxaline *N*-oxide (**64**): White solid (201 mg, 43% yield without L-ascorbic acid **35**; 99 mg, 43% yield with L-ascorbic acid **35**), Mp 245–250 °C. ^1H NMR (DMSO-d_6, 400 MHz): δ 10.81 (s, 1H), 9.18 (s, 1H), 9.08 (d, 1H, *J* = 2.0 Hz), 8.56-8.53 (m, 2H), 8.26 (d, 1H, *J* = 8.8 Hz), 8.17 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1.4 Hz), 7.96-7.88 (m, 2H), 2.16 (s, 3H) ppm. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 170.2 (C_{IV}), 153.3 (C_{IV}), 149.3, 148.0, 144.4 (C_{IV}), 139.6, 137.1 (C_{IV}), 136.7 (C_{IV}), 132.0, 131.2, 130.3, 121.7 (C_{IV}), 119.2, 112.7, 24.5 ppm. HRMS (ESI^+): calculated for $C_{15}H_{13}N_4O_2$ $[M + H]^+$ 281.1033, found 281.1034.

2-(5-(Methoxycarbonyl)pyridin-3-yl)quinoline *N*-oxide (**65**)**:** White solid (162 mg, 35% yield without L-ascorbic acid **35**; 158 mg, 34% yield with L-ascorbic acid **35**), Mp 180–183 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.34 (d, 1H, *J* = 1.9 Hz), 9.30 (d, 1H, *J* = 1.4 Hz), 9.04 (s, 1H), 8.84 (d, 1H, *J* = 8.8 Hz), 7.92 (d, 1H, *J* = 8.1 Hz), 7.85-7.80 (m, 2H), 7.72-7.68 (m, 1H), 7.56 (d, 1H, *J* = 8.6 Hz), 3.99 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.4 (C_{IV}), 153.5, 151.2, 142.3 (C_{IV}), 141.1 (C_{IV}), 138.1, 131.1, 130.1, 129.6, 129.2, 128.2, 125.6, 122.4, 120.2, 52.6 ppm. One quaternary carbon peak is missing. HRMS (ESI^+): calculated for $C_{16}H_{13}N_2O_3$ $[M + H]^+$ 281.0921, found 281.0923.

Synthesis of 4-(methoxycarbonyl)quinoline *N*-oxide (56): To a solution of methyl quinoline-4-carboxylate **66** (1.94 g, 10.36 mmol) in 2 MeTHF (100 mL) at room temperature under air was added portionwise *m*-CPBA (1.967 g, 11.40 mmol). The resulting solution was stirred for 24 hours at room temperature and the solvent was removed under reduced pressure. The crude product was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ and the organic layer was dried over anhy-

drous Na_2SO_4 before being concentrated in vacuo. The crude product was then purified by silica gel chromatography eluting with dichloromethane/acetone to give 4-(methoxycarbonyl)-quinoline *N*-oxide **56** (1.40 g, 6.89 mmol, 67% yield) as a white solid.

4-(Methoxycarbonyl)quinoline *N*-oxide (56): White solid (1.40 g, 67% yield), Mp 152–153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07 (dd, 1H, J_1 = 8.1 Hz, J_2 = 1.5 Hz), 8.78 (dd, 1H, J_1 = 8.2 Hz, J_2 = 1.5 Hz), 8.55 (d, 1H, J = 6.4 Hz), 8.01 (d, 1H, J = 6.4 Hz), 7.82 7.70 (m, 2H), 4.02 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.1 (C_{IV}), 142.3 (C_{IV}), 134.4, 130.4, 130.2, 128.4 (C_{IV}), 126.8, 124.4, 123.0 (C_{IV}), 119.8, 52.6 ppm. HRMS (ESI$^+$): Calculated for $C_{11}H_{10}NO_3$ $[M + H]^+$ 204.0655, found 204.0653

Synthesis of 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (69): To a stirred solution of DABAL-Me_3 **67** (193 mg, 0.75 mmol) in anhydrous THF at room temperature under nitrogen was added (*S*)-α-ethylbenzylamine **68** (0.108 mL, 0.75 mmol) and the resulting solution was stirred at 40°C for 1 hour. To this mixture 4-(methoxycarbonyl)-2-phenylquinoline *N*-oxide **62** (140 mg, 0.50 mmol) was added and the reaction was stirred at reflux for 22 hours. The reaction mixture was cooled to ambient temperature and quenched with aqueous HCl (2 M) dropwise and was extracted with ethyl acetate. The organic phase was separated and evaporated to dryness under reduced pressure. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)-quinoline *N*-oxide **69** (162 mg, 0.42 mmol, 85 % yield) as an off-white solid.

2-Phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (69): Off-white solid (162 mg, 85% yield), Mp 90–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.03 (d, 1H, J = 8.3 Hz), 8.32 (d, 1H, J = 8.8 Hz), 7.76 (d, 1H, J = 8.1 Hz), 7.69 (d, 2H, J = 7.5 Hz), 7.50 (d, 2H, J = 7.1 Hz), 7.40-7.21 (m, 9H), 5.15 (q, 1H, J = 7.8 Hz), 2.20-2.00 (m, 2H), 1.07 (t, 3H, J = 7.4 Hz) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.6 (C_{IV}), 143.6 (C_{IV}), 142.5 (C_{IV}), 141.1 (C_{IV}), 133.9 (C_{IV}), 131.7 (C_{IV}), 130.6, 130.2, 129.6, 129.0, 128.7, 128.2, 127.4, 127.1, 125.9, 125.6 (C_{IV}), 121.1, 119.5, 56.2, 29.7, 11.5 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{23}N_2O_2$ $[M + H]^+$ 383.1754, found 383.1761

Synthesis of 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline (70): 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline *N*-oxide (**69**) (147 mg, 0.38 mmol,), Johnson Matthey 5% rhodium on charcoal type 20A paste, 60% wet (99 mg, 0.02 mmol) and THF (3.5 mL) were added to a hydrogenation reactor which was purged 3 times with 5 bar of nitrogen and then 3 times with 3 bar of hydrogen. The reaction was then stirred at room temperature under 3 bar of hydrogen for 2 hours and was stopped by flushing the hydrogenation reactor with nitrogen. The reaction mixture was then filtered through a plug of Celite to remove the catalyst and the filtrate was evaporated in vacuo. The crude product was then purified by silica gel chromatography eluting with heptane/ethyl acetate to give 2-phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline (**70**) (131 mg, 0.36 mmol, 93 % yield) as a stable white foam.

2-Phenyl-4-(carboxy-(*S*)-α-ethylbenzylamine)quinoline (70): Off-white solid (162 mg, 85% yield), Mp 140–150 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.25 (d, 1H, *J* = 8.5 Hz), 8.30 (d, 2H, *J* = 6.9 Hz), 8.13 (d, 1H, *J* = 8.1 Hz), 8.08 (s, 1H), 8.02 (dd, 1H, J_1 = 8.6 Hz, J_2 = 0.8 Hz), 7.82 (dd, 1H, J_1 = 7.1 Hz, J_2 = 0.5 Hz), 7.63-7.54 (m, 4H), 7.46 (d, 2H, *J* = 7.1 Hz), 7.38 (d, 2H, *J* = 7.6 Hz), 7.28 (at, 1H, *J* = 7.3 Hz), 5.06 (q,1H, *J* = 6.6 Hz), 1.91-1.79 (m, 2H), 0.98 (t, 3H, *J* = 7.4 Hz) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 166.7 (C_{IV}), 156.3 (C_{IV}), 148.4 (C_{IV}), 143.9 (C_{IV}), 143.8 (C_{IV}), 138.8 (C_{IV}), 130.6, 130.3, 130.0, 129.4, 128.8, 127.8, 127.6, 127.3, 127.0, 125.6, 123.9 (C_{IV}), 116.9, 55.5, 29.7, 11.7 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{23}N_2O$ $[M + H]^+$ 367.1805, found 367.1806

NOTE

The results of reactions in the presence of ascorbic acid (Tables 1, 2, 3 and 5) were previously presented in this journal (Colleville, A. P.; Horan, R. A. J.; Olazabal, S.; Tomkinson, N. C. O. *Org. Process Res. Dev.*, 2015, 19, 1434–1434). This paper was retracted by the authors immediately after online publication when control reactions revealed that the presence of ascorbic acid had little or no impact on the outcome of the reaction.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}HNMR, ^{13}C NMR, OPLS, DoE, calorimetry and DSC data.

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