A first example of cobalt-catalyzed remote C-H functionalization of 8-aminoquinolines operating through a single electron transfer mechanism

WHITEOAK, Christopher J. <http://orcid.org/0000-0003-1501-5582>, PLANAS, Oriol, COMPANY, Anna and RIBAS, Xavi

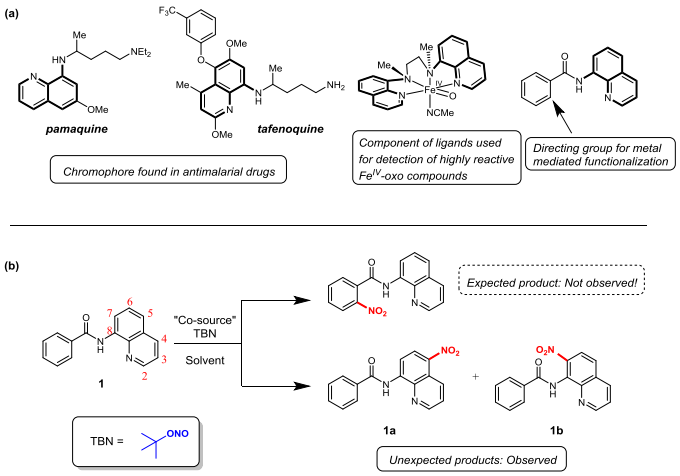
A First Example of Co-Catalyzed Remote C-H Functionalization of 8-aminoquinolines operating through a Single Electron Transfer Mechanism

Christopher J. Whiteoak,*,† Oriol Planas,† Anna Company and Xavi Ribas*

Abstract: The development of new C-H functionalization protocols based on inexpensive cobalt catalysts is currently attracting significant interest. Functionalized 8-aminoquinoline compounds are high-potential building blocks in organic chemistry and pharmaceutical compounds and new facile routes for their preparation would be highly valuable. Recently, copper has been applied as catalyst for the functionalization of 8-aminoquinoline compounds and found to operate through a Single Electron Transfer (SET) mechanism, although requiring elevated reaction temperatures. Herein, we described the first example of a cobalt-catalyzed remote C-H functionalization of 8-aminoquinoline compounds operating through a SET mechanism, exemplified using a practical and mild nitration protocol. The reaction uses inexpensive $Co(NO_3)_2{\cdot}6H_2O$ as catalyst and *tert*-butyl nitrite (TBN) as nitro source. This methodology offers the basis for the facile preparation of many new functionalized 8-aminoquinoline derivatives.

Introduction

The 8-aminoquinoline scaffold is an important motif found in a variety of compounds (Scheme 1a), including pharmaceutical drugs (e.g. the anti-malarial drugs pamaquine and tafenoquine),[1] ligands for coordination chemistry[2] and more recently as a successful directing group for a number of metal-catalyzed transformations.[3] As a result, new methodologies for further functionalization of readily-accessible 8-aminoquinoline compounds are potentially very important developments in organic synthesis. There are many reports of metal-catalyzed C-H functionalization of simple quinolines,[4] whilst in comparison, there are very few concerning C-H functionalization reactions of 8-aminoquinolines. The first reports of C-H functionalization protocols using 8-aminoquinoline as substrate came from Stahl and co-workers, who reported on a Single Electron Transfer (SET) based remote Cu-catalyzed C5 chlorination.[5,6] Since this initial report other Cu-catalyzed functionalizations have been described; remote C5 sulfonylation,[7] C2 alkylation[8] and more recently remote C5 chalcogenation[9,10] and C5 amination.[11] Besides Cu-catalyzed protocols, Fe-catalyzed C4 and C5 allylation,[12] Rh-catalyzed C7 alkenylation[13] and Pd-catalyzed C5/C7 chlorination[6] have also been described, thus expanding the toolbox for preparation of novel 8-aminoquinoline derivatives. Unfortunately though, all of these reports suffer from the requirement of elevated temperatures and/or high catalyst loadings and as a result the development of catalytic protocols which are operative under milder conditions still remains a challenge.



Scheme 1. (a) Examples of compounds containing the 8-aminoquinoline scaffold; arrow indicating the C-H bond selectively activated when using the 8-aminoquinoline directing group. (b) Expected and observed nitration products from this work.

In this work we will demonstrate a new methodology for the functionalization of 8-aminoquinolines using nitration as an example, providing potentially valuable products for further elaboration (*vide infra*) or application. Nitro compounds are key synthons in organic synthesis as a result of their high-potential for further transformation[14] and therefore nitrated derivatives of 8-aminoquinoline compounds may be of significant interest. The classical methodology for nitration is based on a mixed acid H_2SO_4/HNO_3 protocol. Albeit a simple and successful procedure, it suffers from many drawbacks including the use of harsh reaction conditions, poor functional group compatibility, regioselectivity problems and possible over-nitration.[15] As a result of these issues, efforts have been directed towards the development of new nitration protocols.[16] Nitration using mixtures of $Cu(NO_3)_2$ and acetic anhydride has long been known,

Dr. C. J. Whiteoak, O. Planas, Dr. A. Company, Dr. X. Ribas
Grup de Química Bioinspirada, Supramolecular i Catàlisi (QBIS-CAT); Institut de Química Computacional i Catàlisi (IQCC) and Departament de Química
Universitat de Girona
Campus de Montilivi
E-17071 Girona (Catalonia, Spain)
E-mail: christopher.whiteoak@udg.edu and xavi.ribas@udg.edu
Homepage: www.udg.edu/qbis
† These authors contributed equally to this work

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although the requirement for stoichiometric amounts of Cu has limited the application of this procedure.[17] In the search for more favorable protocols, one of the most promising routes that has emerged is the transition-metal catalyzed transformation of aryl halides, triflates and nonaflates reported by Saito and co-workers (Cu-catalyzed)[18] and later Buchwald's methodology (Pd-catalyzed)[19] using nitrite salts as the nitro source. Although solving many of the drawbacks of previous nitration protocols, the main disadvantage of these methodologies is the necessity for a pre-functionalized substrate. Since these early developments and with the advent of directing groups, a number of metal-catalyzed direct C-H nitration protocols have been reported, particularly based on Pd[20] and Cu.[21] Although the field is rapidly developing, selective nitration of C-H bonds still remains a significant challenge.

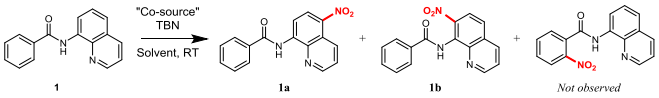
Nitrogen dioxide (NO_2) is an atom economic and therefore highly attractive nitrating agent, but its extreme reactivity (due to its open-shell nature) and toxicity have restricted its use to date. One way of overcoming the issues associated with the handling of NO_2 is to generate it *in-situ*, in a stoichiometric manner. This can be achieved through the use of cheap, commercially available *tert*-butyl nitrite (TBN), which converts into the *tert*-butoxy radical and NO_2 in the presence of air at room temperature.[22,23] Recently there have been a number of reports pertaining to the use of TBN in nitration protocols, although examples using metal catalysts are still rare.[24,25]

The field of Co-catalyzed C-H activation has recently started to receive significant attention as interest in replacing second and third row transition metals with cheaper, more abundant first row transition metals gathers pace.[26] To this end, we have recently become interested in exploiting the potential of Co for the development of new C-H functionalization protocols.[27] We surmised that the use of TBN and Co-catalysis may permit the nitration of the aromatic moiety of **1** (Scheme 1b), using directing group principals. This conversion has been previously successfully realized using Cu as catalyst.[28] As will be described (*vide infra*), this was not the case and instead unexpected nitration of the aminoquinoline directing group was observed (Scheme 1b, products **1a** and **1b**), thus providing a new remote Co-catalyzed protocol for the functionalization of 8-aminoquinoline compounds, which we propose operates through a SET mechanism, alike to that of similar Cu-catalyzed 8-aminoquinoline C-H functionalizations.

Results and Discussion

Initially, nitration of **1** in trifluoroethanol (TFE), using 20 mol% $Co(OAc)_2$ with TBN as nitro source at 100 ^oC was attempted (Table 1, entry 1). To our disappointment none of the expected aromatic nitration product was observed, instead traces of products from nitration of the quinoline directing group at the C5 position (**1a**) were found. The same reaction at room temperature afforded increased yields to 12% of nitration product **1a** and a further unexpected 7-nitration product, **1b**, in

Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	"Co-source"	Conversion (%)[b]	**1a** (%)[b]	**1b** (%)[b]
1[c]	TFE	$Co(OAc)_2$	>99	trace	-
2	TFE	$Co(OAc)_2$	55	12	4
3	$CHCl_3$	$Co(OAc)_2$	38	7	trace
4	Acetic acid	$Co(OAc)_2$	60	36	13
5	DMF	$Co(OAc)_2$	45	-	-
6	Toluene	$Co(OAc)_2$	34	15	6
7	1,4-dioxane	$Co(OAc)_2$	33	18	6
8	EtOAc	$Co(OAc)_2$	44	11	3
9	THF	$Co(OAc)_2$	33	6	2
10	Acetic acid	$Co(acac)_3$	25	13	5
11	Acetic acid	$CoCl_2$	29	19	5
12	Acetic acid	$Co(NO_3)_2{\cdot}6H_2O$	87	65	22
13	Acetic acid	$Co(BF_4)_2{\cdot}6H_2O$	61	44	17
14	Acetic acid	$Co(acac)_2$	40	21	10
15	Acetic acid	$Co(OAc)_2{\cdot}4H_2O$	51	32	13
16	Acetic acid	$CoBr_2$	74	20	7
17	Acetic acid	-	<1	-	-
18[d]	**Acetic acid**	**$Co(NO_3)_2{\cdot}6H_2O$**	**>99**	**74**	**25**
19[e]	Acetic acid	$Co(NO_3)_2{\cdot}6H_2O$	14	9	2
20[f]	Acetic acid	$Co(NO_3)_2{\cdot}6H_2O$	71	46	17

[a] Reaction conditions: **1** (50 mg, 0.2 mmol), cobalt source (0.04 mmol, 20 mol%), TBN (53 µL, 90%, 2.0 equiv., 0.4 mmol), solvent (1.5 mL), RT, 18 h. [b] Conversions and yields calculated from ^1H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c] At 100 ^oC. [d] 4.0 equiv. TBN. [e] No TBN used. [f] 10 mol% $Co(NO_3)_2{\cdot}6H_2O$.

4% yield (Table 1, entry 2). Encouraged by these low but promising yields, the effect of changing the solvent was investigated (Table 1, entries 3-9), whereby it was found that the best results were obtained when acetic acid was used (Table 1, entry 4). Use of acetic acid as solvent furnished an overall yield of the two quinoline nitration products of 49%, in a similar ratio to that observed when using TFE as solvent. Thereafter, the Co-source was optimized (Table 1, entries 10-16), where it was found that $Co(NO_3)_2{\cdot}6H_2O$ was the optimal catalyst (Table 1, entry 12), furnishing a combined yield of 87% of both nitration products and also giving an excellent mass-balance. The use of weakly coordinating anions such as tetrafluoroborate and nitrate appears to be beneficial as these Co-sources provided significantly higher yields of the nitro products than Co-sources with stronger coordinating anions (e.g. Cl, Br, acetate and acetylacetonate). In the absence of a Co-source, no conversion

was observed, highlighting the importance of Co to the conversion (Table 1, entry 17). In the absence of TBN, using $Co(NO_3)_2{\cdot}6H_2O$ as catalyst, 11% of nitrated products was observed, indicating that the nitrate ligand can also act as nitro source (Table 1, entry 19), which is likely as a result of the formation of HNO_3 in situ. Subsequently the effect of increasing the TBN loading to 4.0 equivalents was investigated, which resulted in quantitative conversion and yield of the nitro products (Table 1, entry 18).

To check if 20 mol% of $Co(NO_3)_2{\cdot}6H_2O$ was necessary, the catalyst loading was lowered to 10 mol% and it was found that the combined yield of the nitrated quinolines was reduced (Table 1, entries 12 vs. 20). It should be noted that throughout this study only mono-nitration products have been observed (either 5- *or* 7-nitro-8-aminoquinoline) and that elevated temperatures appear to be highly detrimental to the reaction outcome. After this optimization it was decided that the optimal conditions for further substrate scoping would be 20 mol% $Co(NO_3)_2{\cdot}6H_2O$ and 4.0 equivalents of TBN in acetic acid at room temperature. This optimized protocol is adventitious over traditional nitration procedures as it avoids the use of highly corrosive H_2SO_4 and HNO_3 as reagents.

The optimized nitration protocol was then used with a number of other structurally related substrates (Figure 1, substrates **2**-**5**). In all cases it was not possible to achieve the desired nitration products, thus indicating the necessity for the secondary amide and quinoline in the substrate. Importantly, it was not possible to obtain the nitration product from 8-aminoquinoline, **4**, indicating the importance of the ancillary benzoyl group. The lack of desired product from **4** could be a result of the formation of highly reactive diazonium compounds being formed, which further react and result in a complex mixture of products being observed.

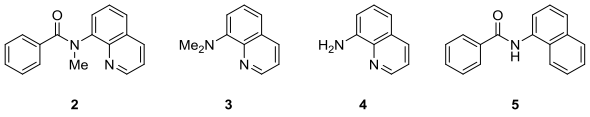
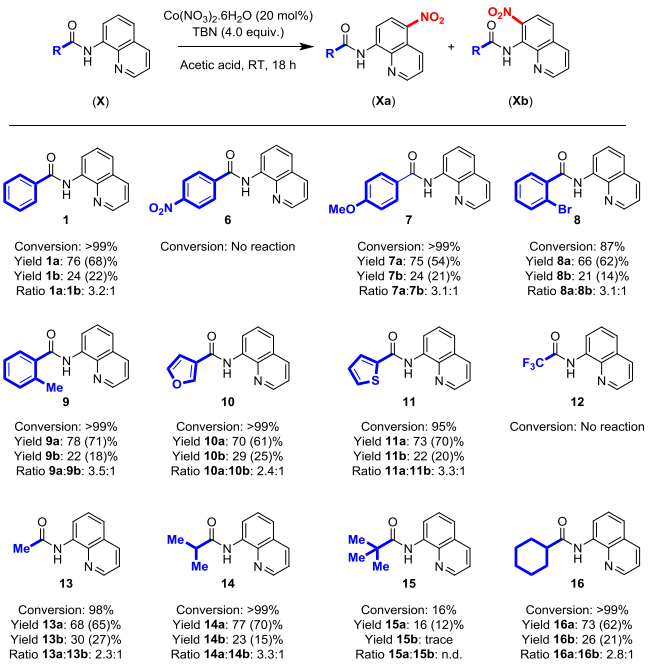


Figure 1. Unsuccessful substrates using the optimized reaction conditions.

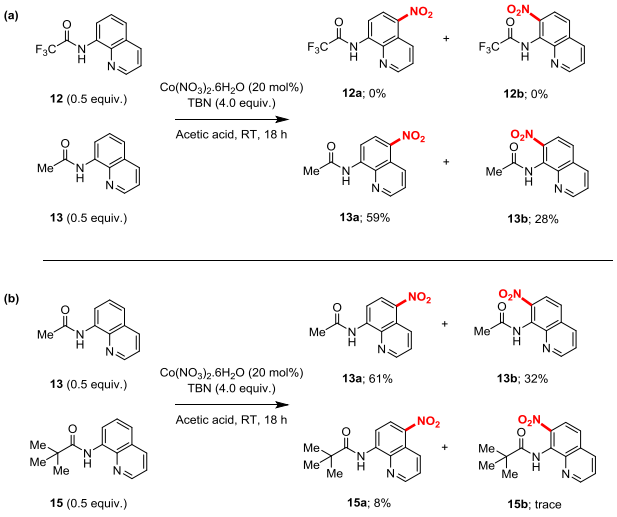
Thereafter, a range of substrates bearing differently substituted ancillary groups were synthesized (Table 2, compounds **6**-**16**). In most cases it was possible to obtain excellent to quantitative overall yields of the nitration products. Confirmation of the structures of the major 5- and minor 7-nitrated products was obtained from X-ray crystal structures of **11b** and **15a** (see Supporting Information, Figures S140-S142). There are however several notable exceptions where the reaction was quenched; if a *p*-nitro group was included on the benzoyl ancillary (**6**) or if the ancillary group contains a trifluoromethyl group (**12**), no conversion was observed. These results suggest that ancillary groups containing strong electron-withdrawing moieties are unsuitable for use in the nitration reaction.

To investigate whether the strongly electron withdrawing ancillary groups were unreactive or poisoning the catalyst, competitive reactions were performed (Scheme 2). In a single

Table 2. Screening of different ancillary groups.[a,b,c]



[a] Reaction conditions: substrate (0.5 mmol), $Co(NO_3)_2{\cdot}6H_2O$ (29.1 mg, 0.1 mmol, 20 mol%), TBN (267 µL, 90%, 4.0 equiv., 2.0 mmol), acetic acid (3.5 mL), RT, 18 h. [b] Conversions and yields calculated from ^{1}H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yields in parenthesis.

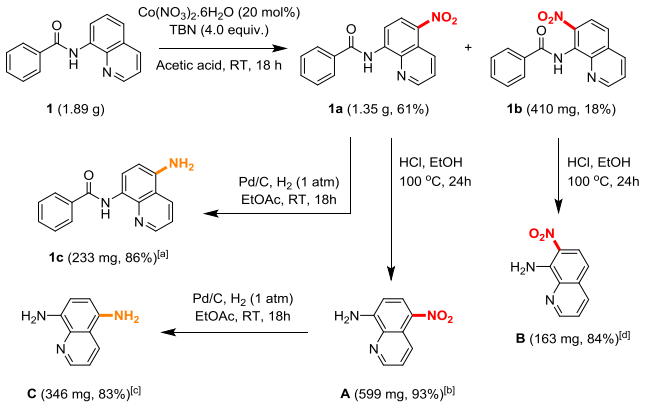


Scheme 2. Reactions performed to investigate the nature of the inactivity/poor activity of substrates **12** (a) and **15** (b). Yields calculated from ^{1}H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard and are based on conversion of corresponding substrate. Reaction conditions: substrate (0.5 mmol; 0.25 mmol of each substrate), $Co(NO_3)_2{\cdot}6H_2O$ (29.1 mg, 0.1 mmol, 20 mol%), TBN (267 µL, 90%, 4.0 equiv., 2.0 mmol), acetic acid (3.5 mL), RT, 18 h.

reaction vial trifluoromethyl (**12**) and methyl (**13**) containing substrates were reacted at the same time and it was found that the conversion of **13** proceeded in similar yield to in the absence of **12** (Scheme 2a). This result indicates that **12** did not convert due to it being unreactive rather than poisoning the catalyst.

In a similar manner, the reason why the substrate containing the *tert*-butyl group (**15**), which afforded significantly reduced nitration products, was investigated. Again, the related substrate bearing the methyl containing ancillary was used for the competition and little inhibition of the formation of the nitration products of **13** was observed (Scheme 2b). We therefore propose that the *tert*-butyl group is preventing the Co from coordinating to the amide through steric effects; indeed, the less sterically demanding isopropyl containing substrate (**14**) can be successfully converted (Table 2). From the results obtained in this study it was decided to continue using the benzoyl ancillary group for future studies as a result of the high yields, low cost and easy installation/cleavage (*vide infra)*.

After ancillary group optimization, the potential for the reaction protocol to be transferred to gram-scale and upgrading of the nitrated products was investigated (Scheme 3). We were pleased to find that when starting from 1.89 g of **1** it was possible to obtain attractive isolated yields of product **1a** (1.35 g, 61 %) and also a sufficient amount of product **1b** (410 mg, 18 %) to perform the upgrading experiments. The gram-scale experiments also led us to find a new facile route for isolation of the products, as it was found that **1a** is significantly less soluble in ethanol than **1b**, permitting easy separation (see Supporting Information for details).

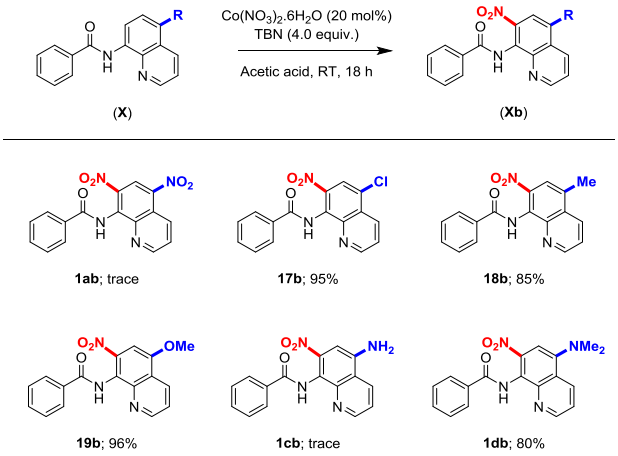


Scheme 3. Gram-scale nitration reaction and subsequent upgrading of nitrated products obtained; Isolated yields reported. Reaction conditions for gram-scale nitration reaction: **1** (1.89 g, 7.6 mmol), $Co(NO_3)_2{\cdot}6H_2O$ (443 mg, 1.5 mmol, 20 mol%), TBN (4.1 mL, 90%, 4.0 equiv., 30.4 mmol), acetic acid (50 mL), RT, 18 h. [a] Isolated yield starting from 300 mg of **1a**. [b] Isolated yield starting from 1.0 g of **1a**. [c] Isolated yield starting from 500 mg of **A**. [d] Isolated yield starting from 320 mg of **1b**.

With analytically pure samples in-hand, reactions targeting the removal of the ancillary group and reduction of the nitro groups to amines were attempted (Scheme 3). Reduction of **1a** using Pd/C and H_2 (1 atm) results in selective formation of **1c** in 86% isolated yield, whereby the amide remains unaffected. The (benza)amide ancillary groups of both **1a** and **1b** can be easily removed by heating the compounds in boiling acidic ethanol to furnish the desired 5-nitro-8-aminoquinoline (**A**) and 7-nitro-8-aminoquinoline (**B**), respectively, in excellent yields. The nitro-8-aminoquinolines can then be easily converted into the corresponding diamines in excellent yield as exemplified by the conversion of **A** to 5,8-diaminoquinoline (**C**) using Pd/C and H_2 (1 atm). These diamines may in the future find a wide range of applications, given that their ease of synthesis should make them relatively cheap synthetic precursors for increasing molecular complexity, compared with other substituted 8-aminoquinolines.

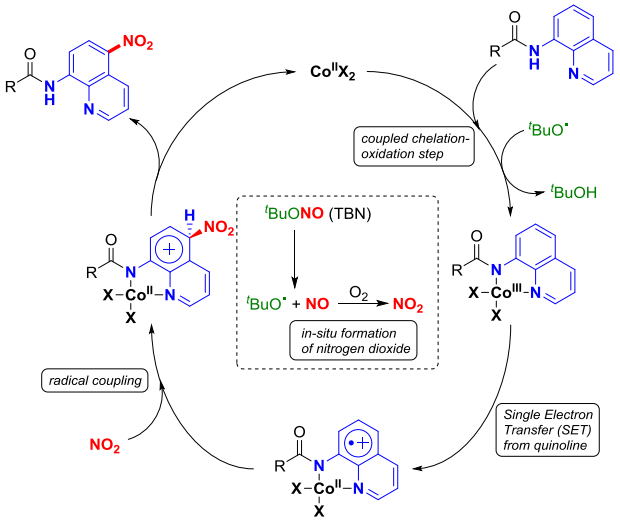
There are currently few inexpensive derivatives of the 8-aminoquinoline scaffold commercially available. To further study the versatility of our Co-catalyzed methodology, 5-substituted-8-nitroquinolines were prepared through Skraup reactions,[29] and were subsequently reduced using Pd/C and H_2, before addition of the ancillary benzoyl group (see Supporting Information for details of the preparation of **17**, **18**, and **19**). Substrates **1a** and **1c** were prepared during this work (Scheme 3). Applying the optimized reaction conditions to these substrates furnished **17b**, **18b** and **19b** in good to excellent isolated yields, with selective formation of the 7-nitro products (Table 3). In line with the exclusive mono-nitration observed previously (Table 2), when the benzoyl ancillary group contained a nitro substituent, it was not possible to convert **1a**, with only trace amounts of product obtained. The amine containing substrate, **1c**, derived from **1a,** also failed to give the desired product, suggesting interference of the primary amine in the catalysis. When this substrate was dimethylated at the amine (**1d**), it was possible to obtain the nitrated product **1db** in an 80% isolated yield. This result indicates that the amine of **1c** should be pre-functionalized before further nitration is attempted. Compound **1db** contains amine, nitro and amide functionalities which can be derivatized independently making it an excellent candidate for further upgrading.

Table 3. Screening of different 8-aminoquinoline scaffolds.[a,b,c]

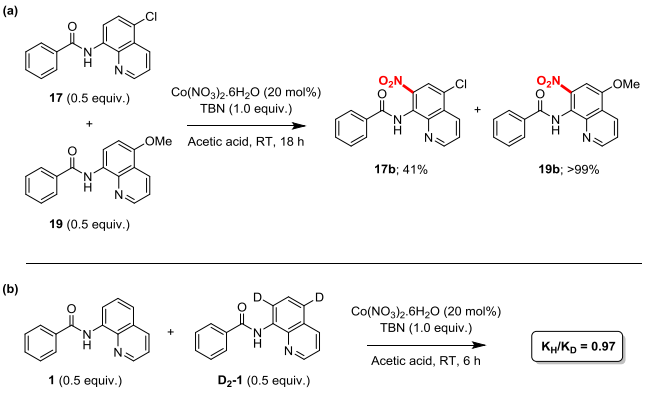


[a] Reaction conditions: substrate (0.5 mmol), $Co(NO_3)_2{\cdot}6H_2O$ (29.1 mg, 0.1 mmol, 20 mol%), TBN (267 µL, 90%, 4.0 equiv., 2.0 mmol), acetic acid (3.5 mL), RT, 18 h. [b] Isolated yields reported. [c] Selectivity >99% in all cases.

Taking into account all the observations during this study, the Single Electron Transfer (SET) based mechanism depicted in Scheme 4 is proposed. Initially Co(II) coordinates to the substrate, and is oxidized to Co(III) by the *tert*-butoxy radical generated through the decomposition of TBN with O_2. The resulting Co(III) species is a strong oxidizing species in acid media[30,31] and as a result a SET from the quinoline occurs to yield a cationic quinoline radical and Co(II). Subsequently, NO_2, generated *in-situ* from TBN, reacts with the quinoline radical and a concerted proton transfer/demetallation step provides the nitration product and Co(II)X_2. This proposed mechanism is similar to the Cu(II)-catalyzed chlorination of 8-aminoquinolines reported by Stahl and co-workers, in that the key intermediate is a cationic quinoline radical species.[5] To the best of our knowledge this work represents the first example of a SET remote functionalization of 8-aminoquinoline using Co. The absence of activity when strong electron-withdrawing groups are present in the substrate structure (**1a**, **6** and **12**) further indicates the plausibility of the proposed cationic quinoline radical species. To further highlight this effect a competitive reaction between **17** and **19** was performed (Scheme 5a), where it was observed that **19b** was obtained in >99% yield and **17b** in 41%, with respect to the individual starting substrates, confirming the preference for substrates containing electron-donating substituents as would be expected for the proposed SET mechanism. Furthermore, a Kinetic Isotope Experiment (KIE) revealed (Scheme 5b) a k_H/k_D value of 0.97, indicating that the rate limiting step is not a C-H activation and adding further evidence for the proposed mechanism.



Scheme 4. Proposed mechanism for the nitration reaction at C5.



Scheme 5. (a) Competition reactions performed to investigate relative reactivity of substrates **17** and **19**. Yields calculated from ^{1}H NMR of crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard and are based on conversion of corresponding substrate. Reaction conditions: substrate (0.5 mmol; 0.25 mmol of each substrate), $Co(NO_3)_2{\cdot}6H_2O$ (29.1 mg, 0.1 mmol, 20 mol%), TBN (267 µL, 90%, 4.0 equiv., 2.0 mmol), acetic acid (3.5 mL), RT, 18 h. (b) Summary of Kinetic Isotope Experiment (KIE); for further details see Supporting Information.

Conclusions

In conclusion, a new practical room-temperature Co-catalyzed remote nitration protocol for the preparation of 5- and 7-nitro-8-aminoquinolines using easily installable and removable ancillary groups has been developed. The protocol is proposed to operate through a previously unreported remote C-H functionalization route based on a SET mechanism for the described 8-aminoquinoline substrates. This new methodology is intended to inspire further work into the development of new facile and mild catalytic routes for the preparation of newly functionalized 8-aminoquinoline compounds. Indeed, we are now working towards the installation of other functional groups using this radical-based protocol and also the application of the products obtained in this study, in particular the utilization of differently substituted 8-aminoquinolines as directing groups in C-H activation protocols.

Experimental Section

General procedure for cobalt-catalyzed nitration reaction: a 10 mL vial was charged with 0.5 mmol of substrate, $Co(NO_3)_2{\cdot}6H_2O$ (29.1 mg, 20 mol%, 0.1 mmol), *tert*-butyl nitrite (TBN) (267 µL, 90%, 4.0 equiv., 2.0 mmol) and 3.5 mL of acetic acid. The vial was sealed and the reaction stirred at room temperature for 18 hours. After this period the reaction mixture was diluted with ethyl acetate (30 mL) and extracted using brine (20 mL). The aqueous layer was then extracted with ethyl acetate (2 x 30 mL), the organic layers combined, dried over magnesium sulfate and the solvent removed under reduced pressure. The crude reaction mixture was purified by column chromatography, using dichloromethane as eluent unless stated, providing analytically pure nitrated products.

Full characterization data obtained (including original ^{1}H, ^{13}C $\{^{1}H\}$ and COSY NMR spectra for all products and new compounds) can be found in the Supporting Information. Crystallographic data for compounds **11b** (CCDC-1438116), **13b** (CCDC-1438117) and **15a** (CCDC-1438118) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: cobalt • 8-aminoquinolines • C-H functionalization • nitrogen oxides • nitration • homogeneous catalysis

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Additional Author information for the electronic version of the article.

Christopher J. Whiteoak: 0000-0003-1501-5582
Oriol Planas: 0000-0003-2038-2678
Anna Company: 0000-0003-4845-4418
Xavi Ribas: 0000-0002-2850-4409