

Bio-Inspired Primary Amine α -C-H Functionalization

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The selective manipulation of complex amine architectures has received great attention in recent years with widespread applications including *inter alia* drug discovery. Inspired by an enzymatic copper amine oxidase process, a synthetic quinone co-factor mediated general platform for the construction of α -fully substituted primary amines from abundant α -branched primary amine starting materials is described. This procedure pivots on the efficient generation of reactive ketimine intermediates *in situ* which are primed to react with carbon-centered nucleophiles such as organomagnesium and organolithium reagents, and TMSCN. Extension to reverse polarity photoredox catalysis enables reactivity with electrophiles. Subsequent oxidative hydrolysis releases the unprotected α -fully substituted primary amine product. This efficient, broadly applicable and scalable amine-to-amine synthetic platform was successfully applied to library and API synthesis and in the late stage functionalization of drug molecules.

C(sp³)-H functionalization has come to the forefront of modern synthetic methodology development due to burgeoning applications in late stage modification of complex biologically relevant molecules, the construction of challenging building blocks, and in natural product synthesis.¹⁻² The persistent need from drug discovery programs for elaborate amine containing architectures has led to pioneering developments in the C(sp³)-H functionalization of amines. Elegant use of transition metal catalysis, often in conjunction with a directing group strategy, has enabled the selective β ,³⁻⁸ γ ,⁹⁻¹² δ ,¹³⁻¹⁵ and remote¹⁶ C(sp³)-H functionalizations of amines through bespoke and meticulously tailored catalyst and/or reaction systems (Scheme 1A). To date, the α -functionalization of amines has only been achieved using mono-branched primary,¹⁷⁻¹⁸ protected secondary^{2,19-23} and tertiary²⁴⁻²⁵ amines. Presently, there is no general practical protocol for unactivated/non-directed systems to construct α -fully substituted primary amines *via* C-H functionalization. In a continuation of our programme on modular and selective amine synthesis,

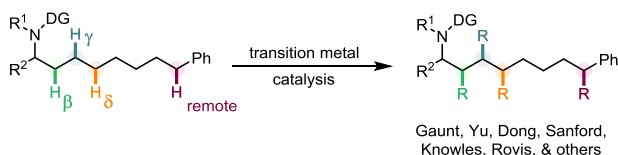
we were attracted to the challenge of developing a new amine-to-amine α -functionalization platform to readily access these important fully-substituted amine scaffolds. Reducing this concept to practice and developing a practical protocol for its general application would find widespread use throughout the chemical industries owing to the abundance of α -branched amines as feedstock chemicals, building blocks for library synthesis, and branch-point intermediates in drug discovery programs.

In search of a robust amine-to-amine α -functionalization platform, we were inspired by an enzymatic copper amine oxidase process as a potentially viable reaction model. Copper amine oxidases (CuAOs)²⁶ are a family of metalloenzymes which selectively catalyze the oxidation of α -branched primary amines into aldehydes (Scheme 1B, R₂ = H) using molecular oxygen through the combination of a quinone-based cofactor and a Cu^{II} species. The mechanism of this transformation involves the condensation of a quinone co-factor with the primary amine substrate and a subsequent formal [1,5] H-shift from the α -position of the amine to generate a reactive imine which is then hydrolyzed to afford the aldehyde product. Aligned to this enzymatic process we hypothesized that, if we could intercept this reactive imine intermediate with appropriate nucleophiles for efficient carbon-carbon bond formation, a new synthetic platform for the generation of α -fully substituted primary amines could be realized.

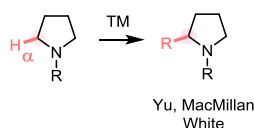
We envisaged that the addition of a synthetic quinone co-factor²⁷⁻²⁸ to an α,α -disubstituted primary amine would give intermediate (I), which would lead to an *in situ* rearrangement mimicking the CuAO system (Scheme 2A), creating a reactive intermediary ketimine structure (II). C-C bond formation *via* nucleophilic interception of this intermediate and subsequent oxidation of the quinone would release the synthetic co-factor, creating an α -fully substituted primary amine, in a one-pot procedure.

A Amine C(sp³)-H functionalization in context

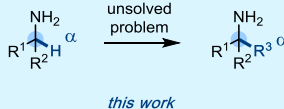
(i) β,γ,δ -functionalization of amine substrates: several approaches



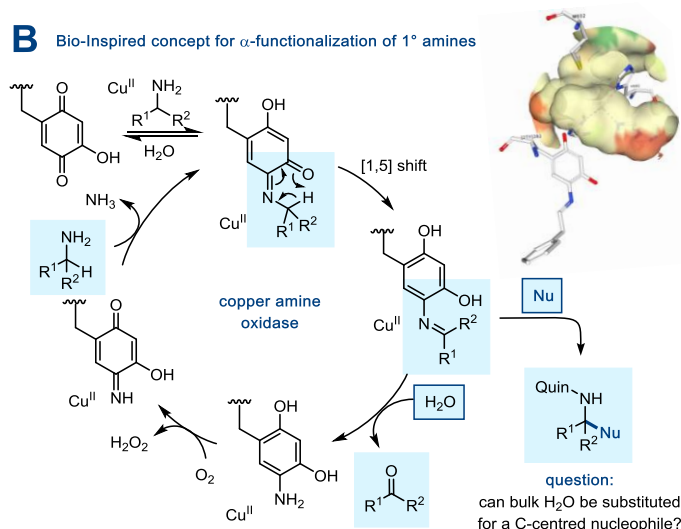
(ii) α -functionalization of 2° & 3° amines: few examples



(iii) α -functionalization of α,α -disubstituted 1° amines: unexplored

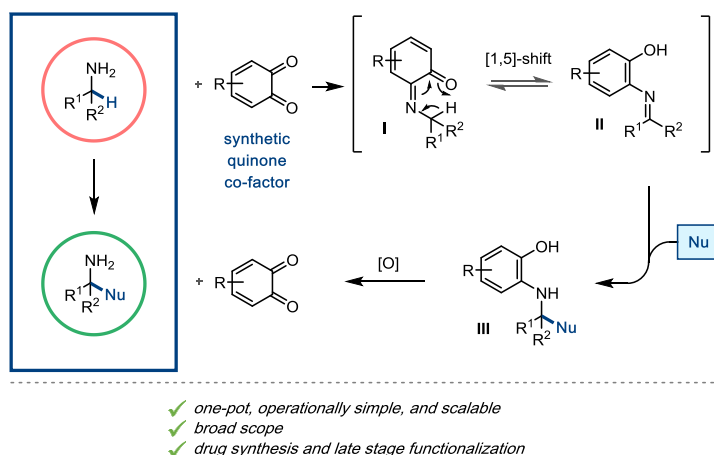


B Bio-Inspired concept for α -functionalization of 1° amines

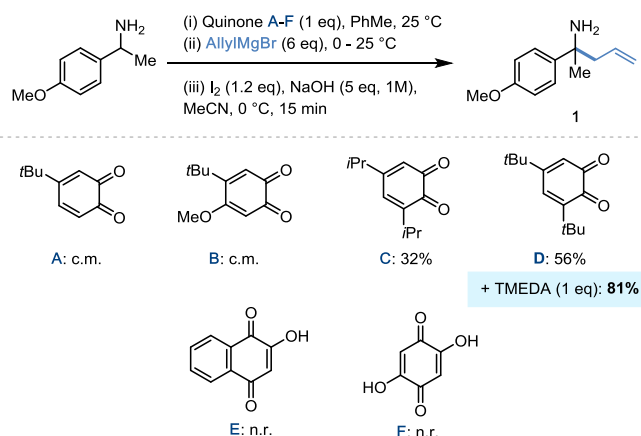


Scheme 1 | Bio-inspired C-H functionalization of primary amines. (A). C-H functionalization of alkyl amines. DG = Directing group. TM = Transition metal (B). Mechanism of action of copper amine oxidases and imine intermediate of copper amine oxidases from *arthrobacter globiformis* (2CWV, Protein Data Bank)

A Reaction design - biology to chemistry



B Concept development - realization and optimization



Scheme 2 | Reaction design and development (A). Quinone mediated α -functionalization platform. **(B)** Reaction optimization via quinone variation. c.m. = complex mixture of products. n.r. = no reaction.

In order to explore the proposed reaction design, a selection of substituted quinones was studied in the allylation of α -methyl-*p*-methoxybenzylamine as a model system (Scheme 2B). We identified toluene as the preferred reaction solvent and following condensation of the quinone (**A-D**) and amine, sequential addition of excess allyl Grignard reagent was required for full conversion. A simple, oxidative hydrolytic work-up using iodine and NaOH (1M) was sufficient to detach the hydroxyarene from the desired α -allylated 1°-amine product **5**.²⁹ Following this sequential procedure, whereas quinones **A** & **B** led to complex product mixtures (for full optimization details see supporting information), quinones **C** & **D** did provide access to the α -allylated product **5** in good yields over the three-stage, one-pot sequence. Pleasingly, the inclusion of TMEDA (1 eq) in the nucleophilic alkylation step resulted in a significant increase in the product yield (81%). Quinones **E** & **F** were found to be ineffective in this protocol due to their poor solubility in the solvent medium and solvent exchange provided no improvement in comparison to quinone **D**.

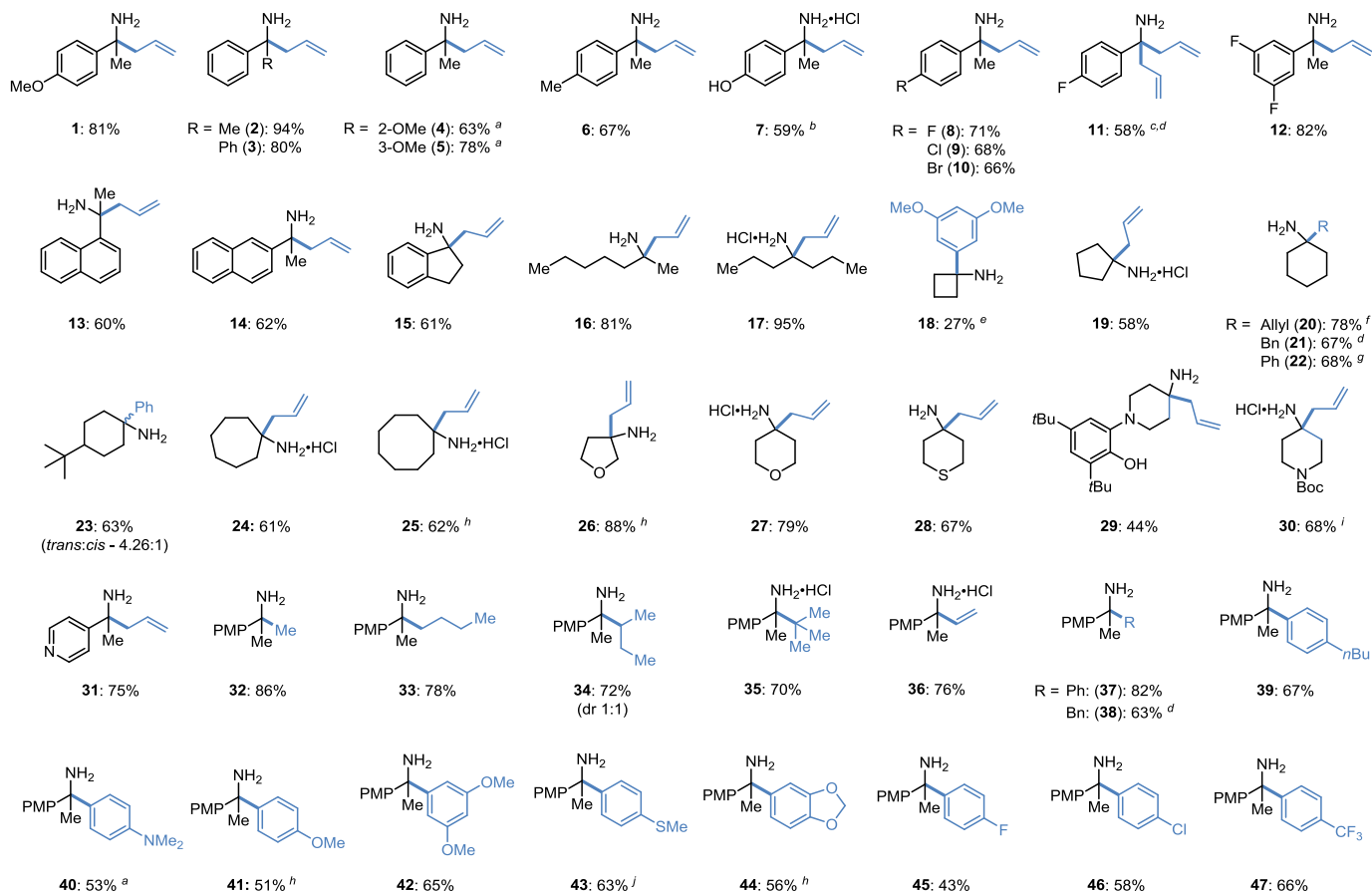
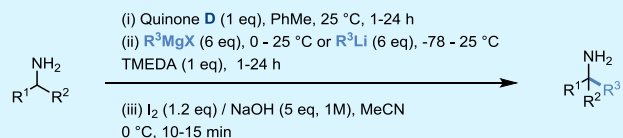
With an efficient protocol established, we sought to develop this reaction concept into a robust platform for the α -functionalization of a variety of α,α -disubstituted primary amine substrates. We began our investigation using the model allylation procedure described above with a wide range of α -substituted benzylamine structures (Scheme 3A, **1-14**, 58-94%). Pleasingly, the use of the unsubstituted aryl ring (**2**, 94%) gave excellent yields of the α -functionalized amine, and biaryl structure (**3**, 80%) also proceeded efficiently in the reaction. The chemistry was tolerant of substitution at *ortho* and *meta* with alkoxy groups (**3-5**, 63-81%). Alkyl (**6**), phenol (**7**) and halogen (**8-10**) functional groups were also shown to possess efficient reactivity manifesting a wide selection of electronic tolerance. The biologically relevant 1-indanamine scaffold (early on-set Parkinson's treatment) was shown to partake in this chemistry in good yield (**15**, 61%). The transition from benzylic to aliphatic amines was achieved with remarkable success, with excellent yields on branched aminoheptane derivatives (**16-17**, 81-95%). Cyclic systems were shown to be effective substrates for the allylation platform (**18-30**, 27-88%), with larger ring and heterocyclic systems achieving good to excellent yields, and even challenging cyclobutane units affording α -functionalized products (**18**). The cyclohexylamine structure was also amenable to reaction with benzyl Grignard and phenyllithium reagents (**21-22**, 67-78%). Pleasingly heteroaryl substituted amine (**31**, 75%) granted access to the α -functionalized product effectively. From this standpoint it was of interest to study the effects of diverse organometallic reagents using 1-(4-methoxyphenyl)ethan-1-amine as a model α -disubstituted amine. Initial studies using aliphatic organomagnesium reagents were disappointing (with and without TMEDA additive). Despite this, a survey of organometallic alternatives identified simple aliphatic organolithium reagents as effective coupling partners in this pro-

cedure. To this end, methyl (**32**, 86%), *n*-butyl (**33**, 78%), *s*-butyl (**34**, 72%), and *t*-butyl (**35**, 70%) alkyl groups were installed using their corresponding organolithium with good to excellent success. The *tert*-butylation strongly highlights that the steric profile of this methodology can be exceptionally broad in the construction of neighboring quaternary centers. We were pleased to find that the general protocol was effectively applied to aryllithiums with a broad electronic profile (**37**, **39-47**, 43-82%), ranging from NMe₂ (**40**, 53%) to CF₃ (**47**, 66%) with electron neutral arenes functioning most efficiently (**37** & **39**, 67-82%).

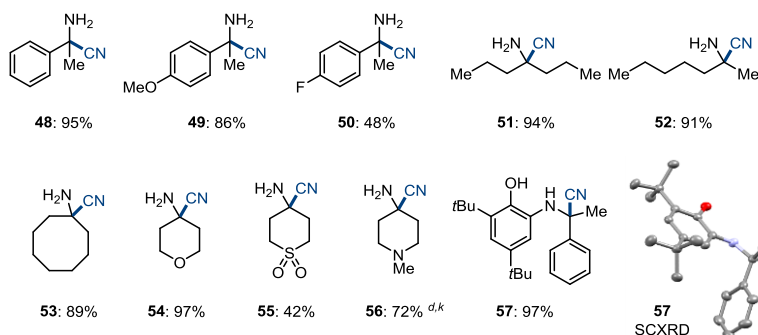
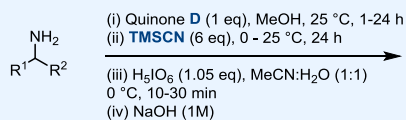
Following the success of the organometallic studies, we were intrigued to identify other nucleophilic species that could intercept the reactive imine. Due to the versatility of nitrile substituents, which for example, can be transformed into a multitude of different functional groups, we decided to investigate the incorporation of a nitrile group at the α position of primary amines. Pleasingly, we found that the use of TMSCN as a nucleophilic source of cyanide in conjunction with a solvent exchange to MeOH in the initial ketimine forming step, led to near quantitative addition to the imine (Scheme 3B). Despite this, the oxidation conditions used previously were ineffective, however orthoperiodic acid (H₅IO₆) was identified as an excellent replacement. This modified protocol allowed, after a basic work-up, the clean isolation of the α -aminonitrile product in 95% yield (**48**). We then expanded the scope of this methodology to electron rich (**49**, 86%) and electron deficient (**50**, 48%) arenes, as well as linear (**51-52**, 91-94%) and cyclic (**53-56**, 42-97%) with excellent yields for the one-pot multi-step process. Over the course of establishing the scope, we also isolated and fully characterized the α -aminonitrile addition intermediate via single crystal X-ray analysis (**57**, 97%), this supporting our proposed reaction pathway.

Recently our group and others have demonstrated that photoredox catalysis can reverse the polarity of an imine moiety to enable new reactivity. Proton coupled electron transfer (PCET) reduction of an imine can generate a nucleophilic α -amino radical which can be intercepted by electrophiles.³⁰ We recognized that applying this concept to the quinone-generated ketimine intermediate, could expand the capability of the synthetic platform (Scheme 3C). Indeed, when the ketimine intermediate was treated with a photocatalyst ([Ir(dF(CF₃)ppy)₂(dtbpy)]PF₆, [Ir]), the commercial Hantzsch ester (HE), an electrophilic radical acceptor (*tert*-butyl 2-((phenylsulfonyl)methyl)acrylate) in DMSO and irradiated with blue light, we were delighted to observe α -allylated product in moderate to good yields for the overall process with a challenging photocatalytic step (**58-62**, 30-43%). We also demonstrated that the use of the ethyl derivative of the allyl sulfone coupling partner led to an *in situ* lactamization on addition of NaOH, affording a highly decorated γ -lactam containing a quaternary center and reactive functional groups for orthogonal functionalization.

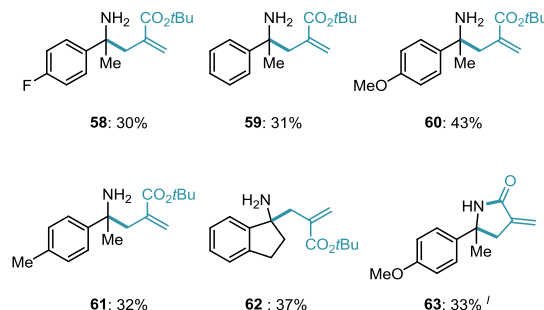
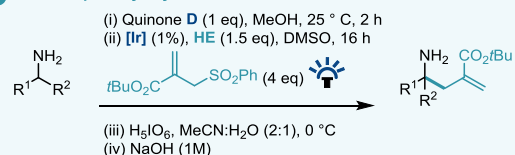
A Organometallic addition



B Cyanide addition

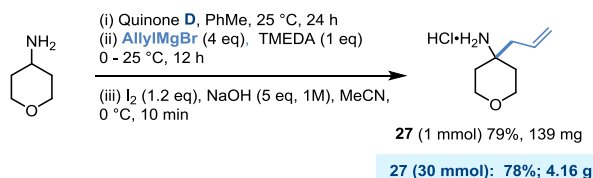


C Reverse polarity allylation

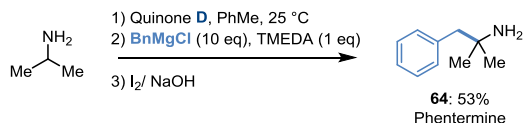


Scheme 3 | Substrate scope for primary amine α -functionalization. (A): α -functionalization using organometallics. (B): α -cyanation of amines. (C): α -allylation via reverse polarity photoredox catalysis. ^a: 3 eq oxidant used. ^b: THF:PhMe (5:1) used as solvent for step (i). ^c: 2-amino-2-(4-fluorophenyl)acetonitrile used as starting material and step (i) carried out at 80 °C. ^d: 10 eq coupling partner used. ^e: DCE used as solvent for step (i). ^f: isolated as HCl salt. ^g: isolated as benzoylated product. ^h: 2 eq oxidant used. ⁱ: pyrrolidine (1.2 eq) added. ^j: 5 eq oxidant used. ^k: oxidation (1 h). ^l: ethyl 2-((phenylsulfonyl)methyl)acrylate used as coupling partner.

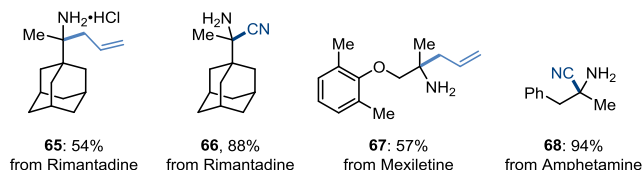
A Gram-scale synthesis



B Drug synthesis



C Late stage functionalization



Scheme 4 | Concept application. (A) Gram-scale synthesis. (B) Drug synthesis. (C) Late stage functionalization. Reaction conditions for late stage functionalization are identical to those in Scheme 3.

We sought to substantiate the synthetic viability of this reaction methodology on gram scale. To this end, we performed the α -allylation chemistry with 30 mmol of 4-aminopyran with 4 eq coupling partner (Scheme 4A). Pleasingly, the reaction performed equably, affording over 4 g of α -functionalized product. Furthermore, the utility of this methodology was also highlighted in the one-step synthesis of the anorectic drug Phentermine in 53% yield, where previous reports require multiple steps (Scheme 4B). A prominent advantage of this mild protocol is the potential application to late stage functionalization projects for *inter alia* drug discovery. To demonstrate this, we were pleased to obtain α -allylated (**65**, 54%) and α -cyanated (**66**, 88%) derivatives of Rimantadine, an α -allylated derivative of Mexiletine (**67**, 57%) and α -cyanated Amphetamine analogue (**68**, 94%) in good to excellent yields (Scheme 4C).

In conclusion, we have conceived and developed a synthetic platform for the α -functionalization of primary amines. This methodology has enabled the challenging construction of α -fully-substituted primary amines through an enzyme-inspired quinone-mediated one-pot synthetic protocol. We have demonstrated that this chemistry is amenable to α -allylation, α -alkylation, α -arylation, α -cyanation and photocatalytic reverse polarity α -allylation methodologies. These techniques have been shown to take place with a wide scope of 68 examples including the one-step synthesis of Phentermine and in the late stage functionalization of API's. We believe that this broadly applicable α -functionalization platform of primary amines will find widespread application in complex amine architecture synthesis, and in the late stage diversification of biologically relevant primary amine libraries, this directly impacting the pharmaceutical and biomedical sciences.

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Supplementary Information is linked to the online version of the paper at.

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Author Contributions D.J.D. conceived and directed the project. D.V., A.L.F.A., and J. A. L. designed the experiments. D.V., A.L.F.A., J.A.L. and A.d.G. performed and analyzed the experiments. D.V., J.A.L., A.L.F.A., and D.J.D. prepared the manuscript.

Author Information Metrical parameters for the structure of **57** are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference number CCDC:1851038. Reprints and permissions information is available at. The authors declare no competing financial interest. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to D.J.D. (darren.dixon@chem.ox.ac.uk)

METHODS

A: Organometallic addition: To a stirred solution of 3,5-di-*tert*-butyl-*o*-benzoquinone **D** (1 eq) in toluene (0.2 M), was added slowly a solution of relevant amine (1 eq) in toluene (0.2 M) dropwise over 5 min under argon atmosphere. The deep green coloured solution was stirred at room temperature for 2 h. After completion as indicated by TLC (*Note: colour changes from deep green to dark violet*), the reaction mixture was cooled to 0 °C, and was added sequentially TMEDA (1.0 eq) and organometallic reagent (6-10 eq, see supporting information for preparation if appropriate) and maintained at 0°C for 1 h. The reaction temperature was gradually allowed to return to 25 °C and stirring was maintained until TLC analysis showed complete conversion. The reaction mixture was then cooled to 0 °C and aqueous NaOH (1M, 5 eq) was carefully added dropwise to quench the remaining organometallics. To the resulting heterogeneous mixture was added MeCN (0.05 M) and iodine granules (1.2 eq) and stirred vigorously for 10 min under argon atmosphere (appearance of brown colour denotes reformation of quinone). After completion, the reaction mixture was extracted with MeCN (3x). The combined organic layers were washed with aqueous saturated sodium thiosulfate (1x), brine (2x) respectively, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. **P1:** The crude residue was purified by column chromatography on silica gel to give free amine product. **P2:** Alternative purification method used in some cases, especially for volatile, low boiling amines. The combined organics were washed with aqueous HCl (2M) and the organics extracted with HCl (2M, 2x). The combined aqueous phases were washed with hexane and concentrated *in vacuo* to give amine product as hydrochloride salt (see supporting information for further details).

B: Cyanide addition: To a stirred solution of 3,5-di-*tert*-butyl-*o*-benzoquinone **D** (1 eq) in MeOH (0.2 M), was added slowly a solution of amine (1 eq) in MeOH (0.2 M) dropwise over 5 min and the resulting mixture was stirred for 1 h at 25 °C. After completion as indicated by TLC, the reaction mixture was then cooled to 0°C and trimethylsilyl cyanide (6 eq) was added. The resulting mixture was gradually allowed to return to 25 °C and allowed to stir until TLC analysis showed complete conversion. The reaction mixture was concentrated *in vacuo* using bath temperature below 25 °C (*Caution: high bath temperature causes decomposition of addition product*). The resulting crude residue was dissolved in MeCN:H₂O (1:1) (0.07 M) and cooled to 0 °C. To the resulting mixture was added orthoperiodic acid (1.05 eq) and stirred vigorously for 10 min (appearance of brown colour denotes reformation of quinone). After this time, the reaction mixture was concentrated. The resulting aqueous acidic phase was washed with Et₂O:Hexane (10:1) (2x) and the aqueous phase was then concentrated *in vacuo*. The resulting residue was basified with NaOH (1M) and extracted with CHCl₃ (3x). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give free primary amine product (two cases require further silica gel (Et₃N neutralised) column chromatography).

C: Reverse polarity allylation: To a vial under a stream of N₂ was equipped a micro-stirrer charged 3,5-di-*tert*-butyl-*o*-benzoquinone **D** (1 eq), anhydrous MeOH (0.5 M), and amine (1 eq). The nitrogen line was removed and the reaction mixture allowed to stir for 2 h. The solvent was then removed under a nitrogen stream. To the residue, was added anhydrous DMSO (1 M), followed by [Ir{(dF(CF₃)ppy)₂(dtbpy)}]PF₆ ([Ir], 1 mol%), diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (HE, 1.5 eq) and *tert*-butyl 2-((phenylsulfonyl)methyl)acrylate (4 eq). The reaction mixture was then degassed with N₂ for 10 min. The flask was sealed and allowed to stir for 20 h under blue light irradiation. After this time the reaction mixture was cooled to 0 °C, and MeCN (0.5 M), water (1 M) and orthoperiodic acid (1.1 eq) were added. The resulting mixture went instantly deep brown to signal reformation of 3,5-di-*tert*-butyl-*o*-benzoquinone and was then allowed to stir at 0 °C for 30 min. The reaction mixture was poured into a separating funnel containing water and Et₂O. The aqueous phase was extracted, and the organic phase re-extracted with water (4x). To the combined aqueous phases was added NaOH (1M). The aqueous phase was then extracted with EtOAc:MeCN (1:1, 5x). The combined organics were then washed with NaOH (1M, 5x) and the organics were dried over MgSO₄ and concentrated *in vacuo*. The crude residue was then purified *via* silica gel column chromatography to give the desired primary amine product.