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ARTICLE

Amide α-C–H Oxidative Coupling Reactions Enabled by Base-Promoted Halogen Transfer

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A base-promoted protocol for the direct oxidative coupling of amide α-C–H bonds with common *O*-, *S*-, and *N*-pronucleophiles is described. This process operates *via* a synergistic deprotonation, halogenation, and substitution sequence that is enabled by the use of mild bases with inexpensive 2-bromothiophenes as halogen oxidants. This strategy overcomes longstanding challenges associated with conventional two-step amide enolate formation/halogenation sequences that are generally ineffective. Furthermore, this route to α-substituted amides serves as a streamlined and modular alternative to traditional multistep syntheses that require preassembly of an α-functionalized carboxylic acid before amide coupling.

Introduction

Amides are one of the most common functional groups present in medicinal, agrochemical, and polymeric compounds, with many containing an α-heteroatom substituent (Figure 1a).[1,2] The ubiquitous value of α-functionalized amides is derived from their structural similarity to α-amino acids and peptides, as well as the α-substituent's ability to tailor specific properties (*e.g.*, conformational, H-bonding, and substrate binding effects).[3] While amides are typically prepared using highly developed amine-carboxylic acid coupling protocols, there are few methods to transform α-C–H bonds into heteroatom substituents after amide bond formation.[4,5] Therefore, if a desired α-substituted amide does not map onto an already available α-functionalized carboxylic acid, then an acid α-halogenation, substitution, and amidation sequence is typically employed.[6] Alternatively, preassembled α-haloamides can be used for selective coupling reactions while amides with preinstalled N-oxidants can undergo α-substitution en route to secondary amides.[7,8] These multistep routes underscore the need for a direct amide α-C–H functionalization protocol as an efficient and modular means to vary the α-substituent. Such a capability could improve the cost of large-scale amide product syntheses and be used to diversify amide substructures in complex molecules. To this end, we herein describe a base-promoted method for the α-oxidative coupling of amides with heteroatom-based pronucleophiles.

The potential utility of direct amide α-C–H oxidative coupling reactions has motivated significant work over the past decade. An attractive mode of amide α-C–H activation is deprotonation for subsequent reaction with an electrophile.[9] This strategy, however, has not provided a general solution for α-coupling reactions due to the low acidity of most amides and the need for electrophilic O/N/S-reagents.[10,11] These inherent challenges led Maulide and coworkers to develop an innovative electrophilic amide activation strategy

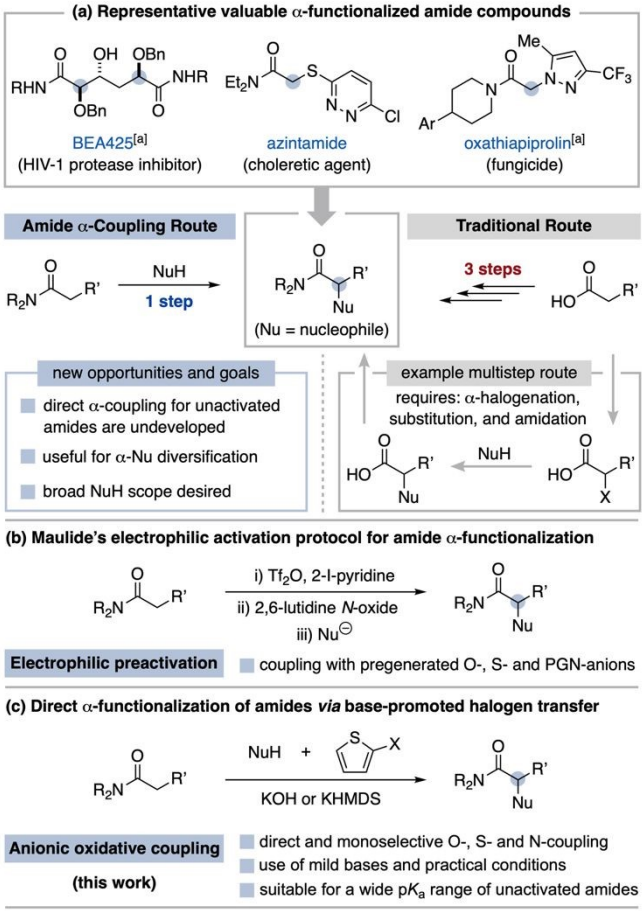

Figure 1. Background and methods for direct amide α-functionalization. PG = Protecting group. [a] See ref 2 for structures.

using triflic anhydride (Tf_2O), 2-iodopyridine, and 2,6-lutidine *N*-oxide to form α-OTf amide intermediates that subsequently react with pregenerated anionic nucleophiles (*e.g*, alkoxides and sulfonyl-protected amine anions, Figure 1b).[12] More broadly, Tf_2O-based amide activation can be used to introduce a variety of other α-substituents (*e.g.*, halogens, azides, and aryl groups).[5,13] As an alternative to multistep electrophilic activation strategies, we sought

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to use a base-promoted halogen transfer (X-transfer) approach to overcome the traditional challenges of a deprotonative amide activation. This led us to develop a direct amide α-coupling protocol for diverse *O*-, *S*-, and *N*-pronucleophiles using practical bases and 2-halothiophene oxidants (Figure 1c).

The introduction of nucleophiles to amide α-positions could be envisioned using a three-step deprotonation, halogenation, and substitution sequence. In theory, this approach would require the use of a strong base (*e.g.*, LDA, p$K_{a'}$ >40 in DMSO) at low temperatures with a subsequent electrophilic halogen quench.[9,14] However, in practice, full amide deprotonation is difficult, and the reaction typically leads to overoxidation and/or enolate-derived side products (Figure 2a).[15] For these reasons, deprotonative α-halogenation of *N,N*-dialkylamides is generally limited to α-aryl amides, acetamides, and lactams and is undeveloped for more common amide substructures (*e.g.*, where R and R' are alkyl in Figure 2a).[15-17] Given such limitations, we sought to develop an effective α-oxidative coupling method that is applicable to weakly acidic *N,N*-dialkylamide substrates.

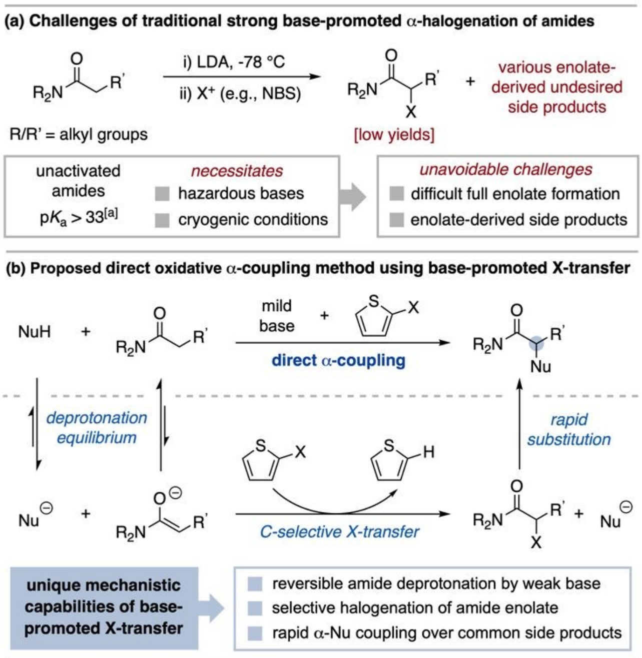

Figure 2. The (a) challenges of a traditional deprotonative amide α-halogenation protocol and (b) a solution using base-promoted X-transfer. [a] see ref 14 for pK_a values in DMSO.

Our group has recently reported aryl (Ar-H) and benzylic ($Ar\text{-}CH_3$) C–H etherification protocols enabled by base-promoted halogen transfer (X-transfer) chemistry using 2-halothiophenes as halogen oxidants.[18] This methodology is distinct from traditional metalation protocols in that deprotonation, halogenation, and substitution steps are compatible and occur concurrently *in situ*. Thus, mild bases can be used to generate low concentrations of carbanionic intermediates that undergo *in situ* halogenation and substitution for an overall exergonic transformation.[19] We hypothesized that if X-transfer from 2-halothiophenes to carbanionic species is a general phenomenon, this mechanistic scenario would be well suited to address the challenges associated with amide α-halogenation/substitution sequences.[20]

An outline of this proposal is shown in Figure 2b, where the initial deprotonation equilibrium generates a large concentration of heteroatomic nucleophilic anion (*e.g.*, an alkoxide) and a low concentration of amide enolate.[14] Selective X-transfer to the enolate would generate an α-haloamide for rapid and selective substitution with the nucleophilic anion. Successful implementation of this strategy would necessitate: (a) the use of mild bases to prevent nucleophilic acyl–NR_2 displacement (*e.g.*, esterification),[21] (b) halogenation of the enolate to be faster than enolate-derived side processes (*e.g.*, Claisen-type reactions),[15,22] and (c) deprotonative halogenation of the starting amide to be faster than the α-functionalized product. A method that meets these requirements would thus enable the direct α-C–H coupling of unactivated amides using practical reagents and conditions.

Results and Discussion

We initially developed the proposed method for the coupling of morpholine-derived amide **1** with benzyl alcohol (**2**) as a model reaction. We found that KOH with 18-crown-6 additive (2.3 eq of each) in DME promotes direct α-etherification using a variety of simple 2-halothiophenes, including 2,5-dibromothiophene (**XTR 1**, where XTR = X-transfer reagent), which gives an optimal 89% yield (Figure 3a).[23] It is noteworthy that the more base-compatible but less available 2-halobenzothiophene oxidants that our lab has developed are not required for this protocol.[18] Use of traditional electrophilic halogen sources (*e.g.*, NBS) results in 0% yield due to their incompatibility with basic conditions and competitive benzyl alcohol oxidation to benzaldehyde as a common side product.[24] These observations illustrate the unique chemoselectivity and efficacy of 2-halothiophene oxidants for amide α-oxidation. Furthermore, KOH is not only an attractive base for this protocol, but we observed that stronger bases (*i.e.*, KO-*t*-Bu or LDA) do not perform well, likely due to the aforementioned side processes associated with amide deprotonation. The use of 18-crown-6 in at least 0.5 eq is required for high yields, while shorter reaction times or the use of less base and **XTR 1** gives reduced yields. Additional condition variation details are shown in the Supplementary Information.

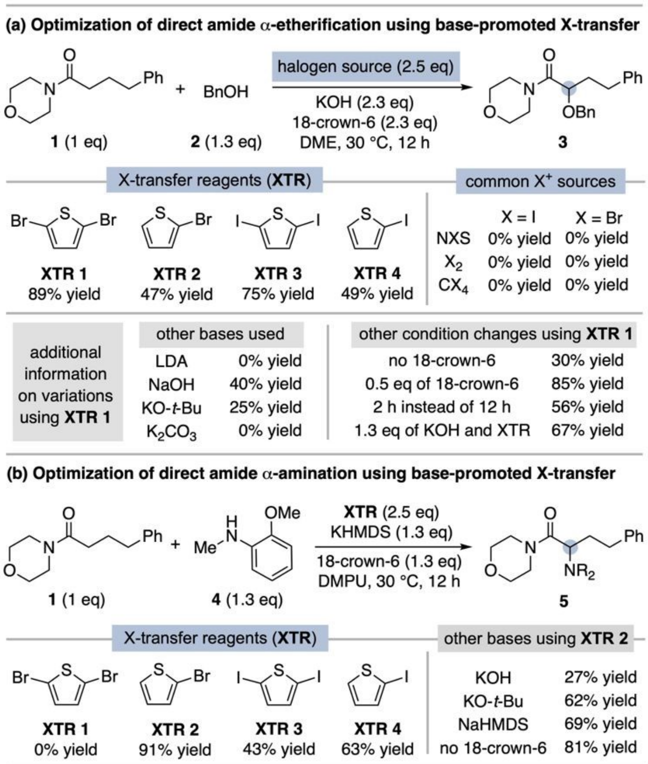

Figure 3. Optimization of amide α-C–H coupling with (a) alcohols and (b) amines. Yields determined by ^1H NMR spectroscopy.

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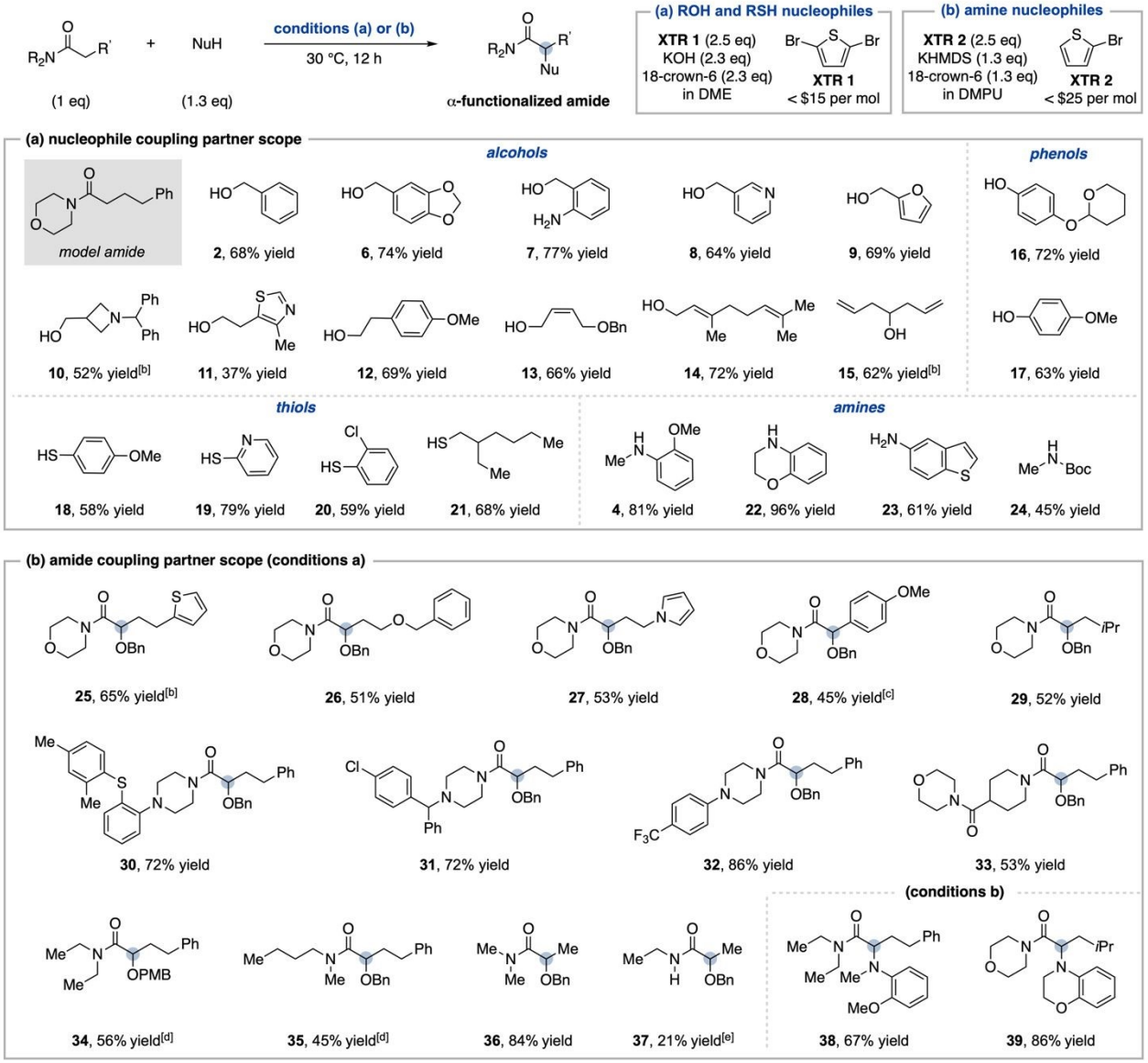
Chart 1. Substrate scope for the α-functionalization of amides.[a]



[a] Isolated yields from 1 mmol scale reactions. [b] 0.5 eq 18-crown-6. [c] 1 eq KOH/18-crown-6. [d] 2.3 eq nucleophile and 3.3 eq KOH/18-crown-6. [e] 3.3 eq KOH/18-crown-6.

We next sought to extend this protocol to unprotected amine coupling partners, which are undeveloped for α-amide coupling reactions and represent an important target due to their similarity to peptide substructures.[1] We initially studied a secondary aniline coupling partner which necessitated a switch to KHMDS as base (1 M in THF commercial solution) and DMPU as solvent for optimal yields.[25] We speculate that the stronger base and more polar solvent are required for deprotonation of the less acidic aniline, with a full condition variation table provided in the Supplementary Information.[14] Thus, we found that the coupling of 2-methoxy-*N*-methylaniline (**4**) with amide **1** occurs in 91% yield using 2-bromothiophene (**XTR 2**) as the oxidant. We speculate the better performance of **XTR 2** over **XTR 1** is due to the greater base stability of a monobromothiophene over a dibromothiophene.[26] The use of iodothiophene oxidants (**XTR 3** and **4**) or weaker bases (*e.g.*, KOH or NaHMDS) gives reduced but moderate yields.

Chart 1a provides a representative pronucleophile scope for the α-coupling of model amide **1** using the optimized reaction conditions and inexpensive 2-bromothiophene oxidants (**XTR 1** and **2**).[27] We used stoichiometric 18-crown-6 additive in the scope development for overall generality purposes, with a thorough discussion of its impact on yields for each pronucleophile class documented in the Supplementary Information. Benzyl alcohols, including pyridyl and furfuryl variants, undergo coupling in good yield (**2, 6**-**9**). A benzyl alcohol that contains an unprotected aniline selectively reacts from the alcohol (**7**). Primary and secondary aliphatic alcohols are also effective coupling partners (**10**-**15**). A moderate yield for a thiazole-containing alcohol (**11**) is notable given the presence of acidic benzylic and aryl C–H bonds that could undergo competing deprotonative halogenation.[18,28] *E*- and *Z*-Allylic alcohols (**13** and **14**) and terminal alkenes (**15**) are well tolerated and do not undergo alkene isomerization.[29] This method is further suitable for more acidic (thio)phenol substrates, as illustrated with *p*-OMe variants (**17**, **18**), and the tolerance of acetal (**16**) and chloro (**20**) substituents, and 2-thiopyridine (**19**). Alkylthiols likewise couple in good yield (**21**). The amine coupling conditions are suitable for primary and secondary

anilines (**4, 23**), including cyclic variants (**22**). No competing X-transfer to the 2-position is observed on the benzothiophene-based aniline substrate **23**. We also found that Boc-protected amines can couple in moderate yields (**24**), which provides an attractive route to simple α-alkylamino amides. Tertiary alcohols and electron-deficient phenols provide low to moderate yields under these conditions, while sterically hindered phenols give no product; these limitations are documented in the Supplementary Information.

Chart 1b illustrates the generality of this method for diverse amides using BnOH (**2**) as a coupling partner. We first showed that the alkyl chain of morpholine-based amides can be varied to include other aryl groups or heteroatom functionality. For example, a thiophene (**25**) in place of the phenyl group does not undergo competing X-transfer. Benzyl ether (**26**) and pyrrole (**27**) groups are also tolerated. An α-aryl amide (**28**), which is more acidic and thus prone to overoxidation, led to moderate yield of the α-ether. A leucine derivative was also shown to perform well in the α-etherification (**29**) and α-amination conditions (**39**).

The identity of the cyclic amino group on the amide was changed to study those with diverse functionality, including derivatives of vortioxetine (**30**) and chlorcyclizine (**31**), and a piperazine derivative (**32**), which provide good yields without competing reactivity of benzylic C–H bonds or aryl functional groups. We also observe good site-selectivity on diamide substrate **33** for the secondary α-amide position over a less acidic tertiary α-C–H bond. We next investigated various acyclic $–NR_2$ groups on the amide, which can substantially impact the ease of α-C–H deprotonation. For example, amides with larger acyclic dialkylamino groups (*e.g.*, *N*,*N*-diethylamides) are more difficult to deprotonate than cyclic $–NR_2$ groups due to unfavorable steric interactions upon enolate generation, which explains the lack of α-functionalization protocols for these amide types.[9,30] This protocol overcomes this challenge through the use of additional base and pronucleophile for an *N,N*-diethylamide substrate (**34**, 56% yield), thus illustrating a wide pK_a latitude for this method. Other acyclic *N,N*-dialkylamides undergo etherification in modest to high yields (**35** and **36)**, while secondary *N*-alkyl amides with a free N–H group were found to give low but appreciable yields (**37**, 21% yield). Acyclic *N,N*-dialkylamides also undergo α-amination in good yields (**38**), illustrating the generality of this substrate class. We note that sterically hindered amides (*e.g.*, *N*,*N*-diisopropylamides) give low yields while amides containing additional acidic functional groups (e.g., ketones and carboxylic acids) are ineffective substrates, as documented in the Supplementary Information. On a related note, the optimized conditions are not immediately applicable for α-substitution of other carbonyl groups, such as esters and ketones, which we anticipate will require alternative base and oxidant combinations for productive reactivity.

Although the general conditions employ stoichiometric 18-crown-6, we sought to illustrate that this additive could be lowered to substoichiometric quantities for improved practicality (Figure 4). The coupling of amide **1** with BnOH (**2**) was thus conducted on a 5-gram scale using 0.5 eq of 18-crown-6 (66% yield, comparable to 68% when 2.3 eq 18-crown-6 used in Chart 1a). We therefore anticipate this method will be suitable for preparative scale applications, especially given that it employs only inexpensive reagents.[31]

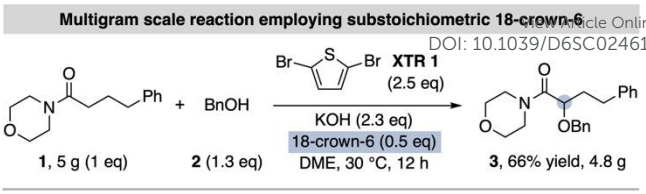


Figure 4. Reaction scaleup using substoichiometric 18-crown-6 additive.

We next conducted a series of control experiments to better understand how this method leads to high α-oxidative coupling yields. A time profile of the model reaction illustrates that product formation (**3**) coincides with generation of 2-bromothiophene as a byproduct, which is consistent with an operative X-transfer oxidation process (Figure 5a). We did not observe the postulated α-bromo amide intermediate during the course of this time study, likely due to its propensity for rapid substitution. The high yield of this reaction depends on the selective oxidation of the starting amide over the α-functionalized product. This selectivity was probed by subjecting the α-ether product **3** to the reaction conditions where it underwent slow oxidation to an allyl diether compound **40** (Figure 5b). This result shows that the starting amide undergoes α-oxidation substantially faster than the α-functionalized product; we also note that the overoxidized product **40** is not observed during the time course study in Figure 5a. The success of this α-coupling protocol starkly contrasts the ineffectiveness of a traditional two-step α-deprotonation/halogenation approach. This distinction is illustrated in Figure 5c for model amide **1**, where the use of common lithium amide bases and halogen electrophiles give low α-halogenation (**41**) yields along with enolate side products and significant starting material remaining.[16,32] These results emphasize that a critical feature of this X-transfer promoted α-coupling protocol is the merger of uphill deprotonation with a tandem *in situ* halogenation/substitution sequence. Although we have not directly observed α-bromo intermediates, subjection of α-tertiary amide **42** to the reaction conditions led to acrylamide **43** in 40% yield, which is consistent with generation of α-bromo amide **44** that is more prone to elimination over substitution (Figure 5d).[33]

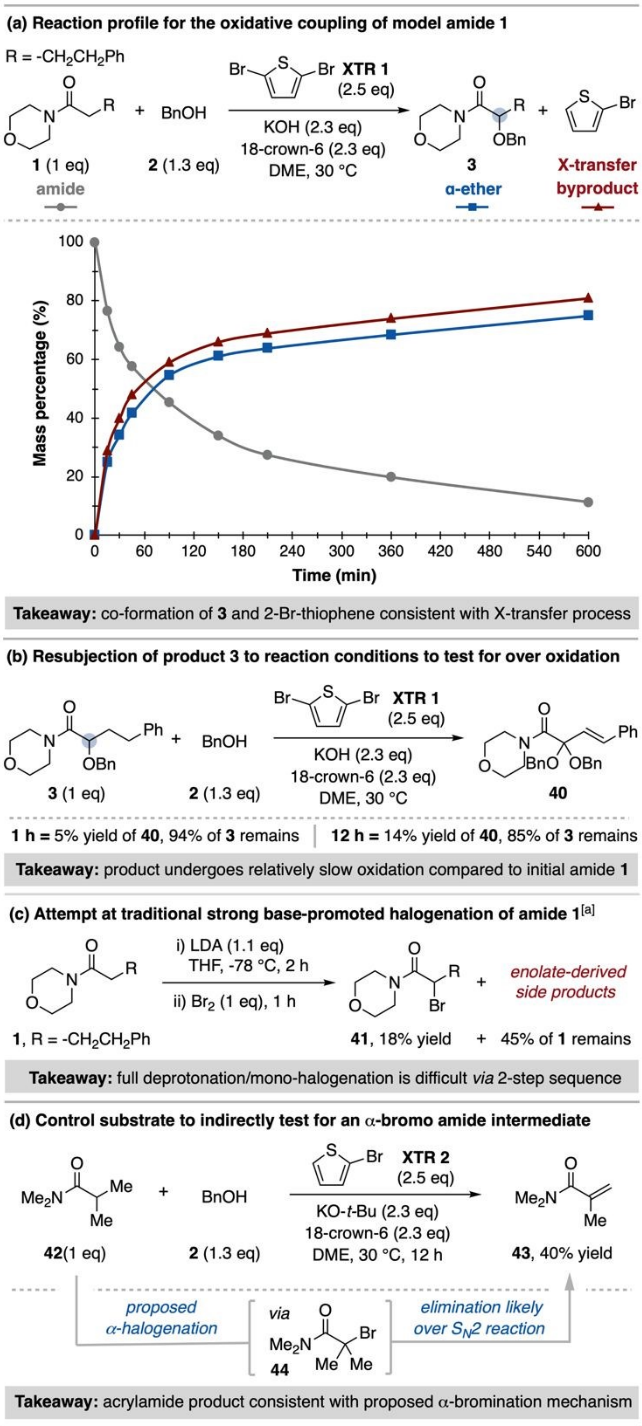


Figure 5. Reaction profile and control studies that illustrate the necessity of merging deprotonation, halogenation and substitution for direct amide α-substitution. Yields determined by ^{1}H NMR spectroscopy. [a] Conditions representative of various bases/halogen sources investigated; see Supplementary Information for additional experiments.

To expand the utility of this methodology, we hypothesized that other valuable α-oxidized amides could be formed from the postulated α-bromo intermediates. We reasoned α-hydroxy and α-oxo amides could be synthesized *via* KOH acting as the base and nucleophile, with the oxidation state controlled by KOH equivalents and the identity of X-transfer reagent (Figure 6). These transformations would be valuable as the α-hydroxy or -oxo groups could serve as synthetic handles to diversify preassembled amides, in addition to these substructures' prevalence in natural products and pharmaceuticals.[34] Using α-phenyl amide **45** as a model substrate, excess base and 18-crown-6 led to the α-oxo amide **46** in 72% yield.[35] Alternatively, use of less base and 2-bromo-3-phenylbenzothiophene (**XTR 5**) selectively forms α-hydroxy amide **47** in 81% yield. We speculate that the larger **XTR 5** is less likely to oxidize the tertiary α-hydroxy amide than simple 2-bromothiophenes.[36]

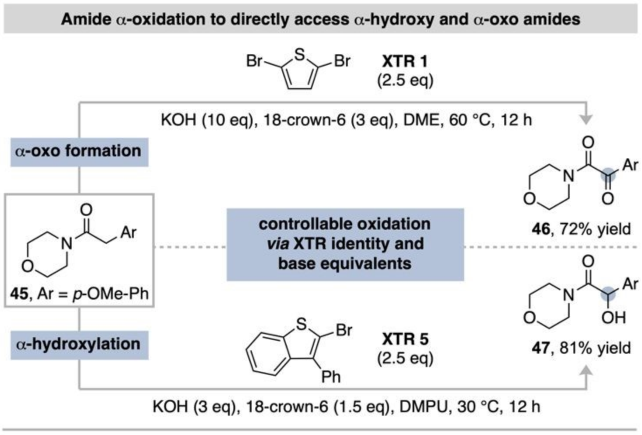


Figure 6. Utility of base-promoted X-transfer for controllable access to α-hydroxy and α-oxo amide oxidation products. Isolated yields shown.

Conclusions

In summary, uphill amide deprotonation in the presence of 2-bromothiophenes enables selective α-oxidative coupling with a broad range of common *O*-, *S*-, and *N*-pronucleophiles. This addresses the longstanding challenges associated with traditional amide α-halogenation and enolate chemistry to provide a practical, streamlined, and modular route to valuable α-substituted amides. We anticipate that this approach, given the appropriate reagent identification, could be used to overcome similar limitations for a wide variety of weakly acidic functional groups.

Conflicts of interest

There are no conflicts to declare.

Author contributions

All authors contributed to the conceptualization, analysis and writing of this project. F. E. K. was responsible for the methodology and J. S. B. was responsible for project administration and supervision.

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Data Availability Statement

The data supporting this article have been included as part of the Supplementary Information. This includes all experimental procedures and characterization data (e.g., NMR spectra, IR data, mass spectrometry data, and melting point analysis) for new compounds.