Diverting Radical-Anionic C-H Amidation to a C-N/C-O Cascade for the Construction of Hydroxyisoindolines from Unprotected Amides

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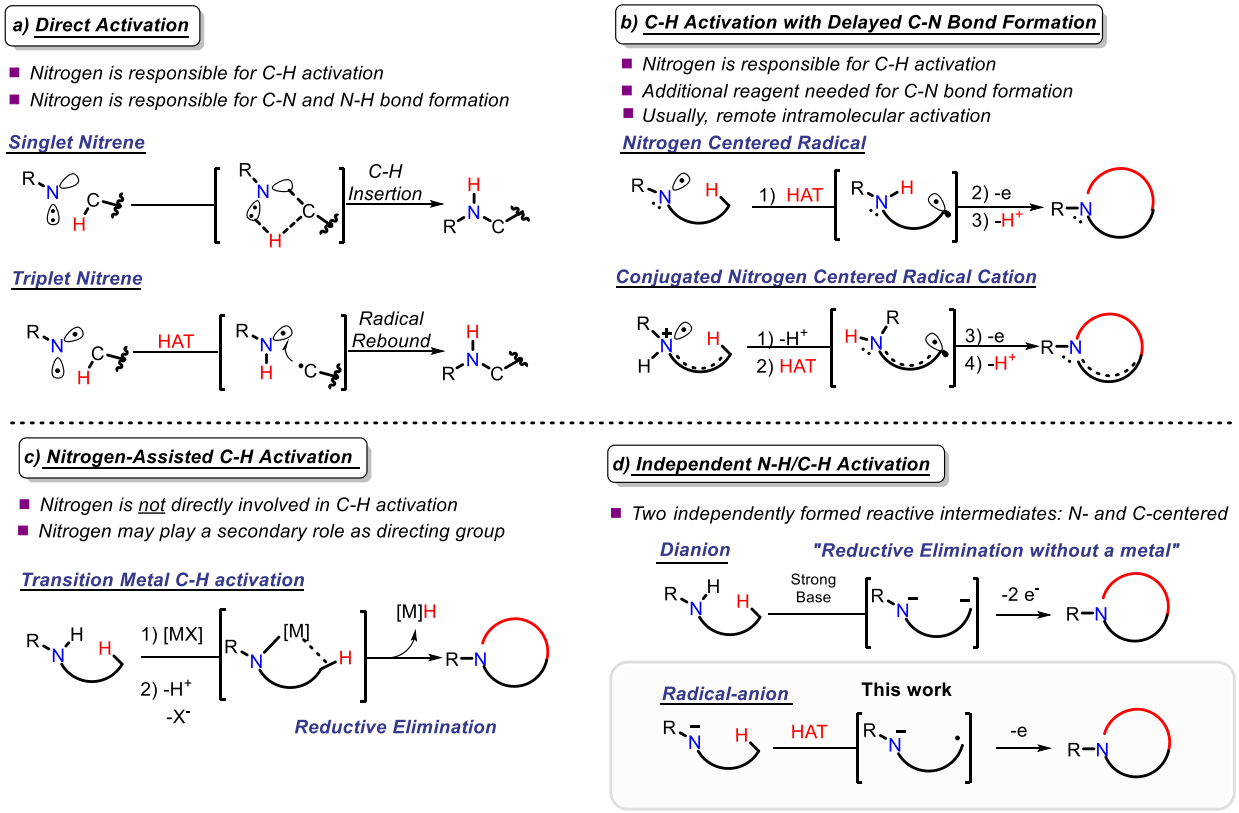
Abstract:

An intramolecular C(sp^3)-H amidation proceeds in the presence of *t*-BuOK, molecular oxygen, and DMF. The success of this reaction hinges on the deprotonation of a mildly acidic N-H bond and selective radical activation of a benzylic C(sp^3)-H bond towards hydrogen atom transfer (HAT). DFT calculations suggest a thermodynamically favorable sequence of steps mediated by the generation of a radical-anion intermediate. As this intermediate starts to form a two-centered/three-electron (*2c,3e)* C-N bond, the extra electron is "ejected" into the π*-orbital of the aromatic core. The resulting cyclic radical-anion is readily oxidized by molecular oxygen to forge the C-N bond of the product. The transformation of a relatively weak reductant into a stronger reductant (i.e., "reductant upconversion") allows one to use mild oxidants such as molecular oxygen. In contrast, the second stage of NH/CH activation forms a highly stabilized radical-anion intermediate incapable of electron transfer to molecular oxygen. Hence, the oxidation is impossible and an alternative reaction path opens via coupling between the radical anion intermediate and either superoxide or hydroperoxide radical. The hydroperoxide intermediate transforms into the final hydroxyisoindoline products under basic conditions. The use of TEMPO as an additive was found to activate less reactive amides. The combination of experimental and computational data outlines a conceptually new mechanism for the conversion of unprotected amides into hydroxyisoindolines proceeding as a sequence of C-H amidation and C-H oxidation.

Introduction

Due to their abundance, the C(sp^3)-H bonds offer an excellent starting point for the functionalization of organic compounds.[1] However, the productive use of C-H bonds is complicated due to the difficulties associated with their selective activation.[2] These challenges prompt chemists to search for the new approaches for utilizing the C-H bonds as a reactive organic functionality.[3]

C-H amination couples C-H activation with the concomitant formation of a C-N bond and opens new avenues to the synthesis of nitrogen-containing organic compounds.[4] This approach has evolved into a versatile group of reactions that overcome the challenges faced with C-H activation and C-N bond formation. We suggest that, depending upon nitrogen's participation in C-H activation and C-N bond formation, one can broadly classify C-H amination reactions within the following four approaches: a) C-H activation directly coupled with C-N formation (direct activation), b) C-H activation with delayed C-N bond formation, c) N-assisted C-H activation, and d) independent C-H/N-H activation (Scheme 1).



Scheme 1. Selected examples for the four approaches to C-N bond formation via C-H activation. All carbons are tetravalent, the non-participating C-H bonds omitted for clarity.

In direct activation (Scheme 1a), nitrogen is responsible for the activation of C-H bonds and the formation of ***both*** the C-N and the N-H bonds. This mode of activation can be achieved if N has two non-bonding orbitals, populated by the total of two electrons. It is observed with highly coordinatively unsaturated species, such as as nitrenes and nitrenium ions where nitrogen can insert directly into a C-H bond. This process is analogous to carbene insertion into C-H bonds and can proceed in either a stepwise or concerted manner.[5]

In C-H activation with delayed C-N bond formation (Scheme 1b), nitrogen assists in C-H activation by breaking the C-H bond but the C-N bond forming step needs an *additional* participant (e.g., an external oxidant). This process also requires an electron-deficient nitrogen-centered intermediate, i.e., a radical[6] or a radical-cation.[7] If placed in the proximity to a C-H bond, a nitrogen centered radical can (usually intramolecularly) abstract a hydrogen atom, forming a carbon centered radical. A C-N bond is formed by trapping this radical, but usually only after a subsequent step that "prepares" the participating atoms for this event (i.e., oxidation of carbon and/or deprotonation of nitrogen).

Alternatively, activation of a C-H bond can be achieved by deprotonation of a nitrogen radical-cation, prepared by oxidation of an amine. Such deprotonation usually proceeds at the α-position where it can provide a stabilized C-centered α-radical.[8] Such radicals can be trapped in a variety of ways, many of which do not lead to the C-N bond formation. However, in conjugated radical-cations, activation of a remote C-H bond becomes possible. For example, we have shown

that it can be utilized to form C-N bonds between the activat*ing* NH_2 moiety and the activat*ed* CH_2 group five bonds away.[9,10]

In the N-*assisted* C-H activation reactions (Scheme 1c), nitrogen does not *directly* participate in the C-H activation step but can trap the C-centered reactive species once they are formed. An external reagent, such as an appropriately chosen transition metal, may be used for C-H activation. An appealing strategy is to use nitrogen as a directing group, binding to the transition metal and guiding it to the targeted C-H bond.[11] The close interactions of the transition metal center with nitrogen allow for a C-N bond forming step to proceed *after* the C-H activation event.[12] In particular, a new C-N bond can be formed via reductive elimination at the transition metal.[13]

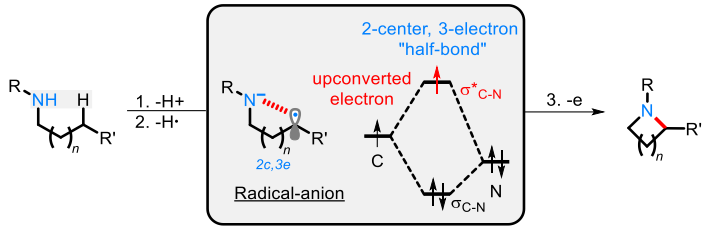
The fourth, conceptually different approach is to activate *both* the N-H and the C-H bonds by independently converting them into reactive intermediates (Scheme 1d). By decoupling the two steps, this approach potentially becomes the most flexible but the conditions for selective and independent N-H/C-H activation are not always easy to achieve. The possible situations here involve i) formation of N- and C- centered radicals, ii) formation of a radical and an anion (usually, C-radical and N-anion), and iii) formation of an N-anion and a C-anion. The latter two paths have to be terminated by 1e and 2e oxidations, respectively, to yield the "normal" two-centered/two-electron (*2c,2e*) C-N bond.

Productive combination of two reactive intermediates is efficient only when one of these intermediates is relatively persistent.[14] From that perspective, formation of stable N-anions (approaches ii and iii) is attractive (Scheme 1d).

Sarpong and coworkers illustrated that a C,N dianion, formed in the presence of strong bases can form a C-N bond upon a two-electron oxidation with I_2 (iii).[15] This approach, which can be conceptually considered "reductive elimination without a metal" allows C-N bond formation without the need for preoxidized coupling partners via the formal loss of H_2. Formation of five-, six-, and seven-membered rings was found to proceed even in conformationally unbiased substrates.

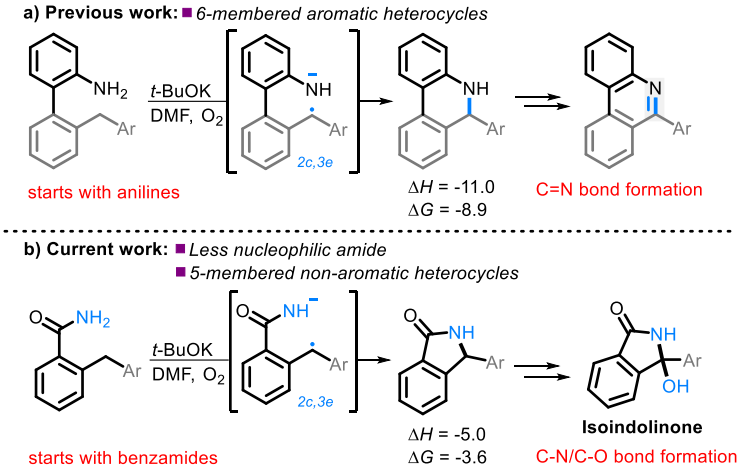
In our work, we are exploring the advantage of a three-electron approach (ii).[10] Because the three electron radical/anion interactions are potentially stabilizing, they can lead to favorable C/N precoordination that can lead to instantaneous C-N bond formation upon oxidation. In contrast, the 4e anion/anion interactions are always repulsive and, hence, the C,N-dianion may adopt a conformation that is not conducive to the bond formation.

We have recently illustrated the value of the radical-anionic approach in an intramolecular C(sp^3)-H aminations with unprotected anilines using *t*-BuOK, molecular oxygen, and N,N-dimethylformamide (DMF).[10] This method relies on a sequence of N-H deprotonations and selective H-atom transfers (HAT) from weakened C(sp3)-H bonds for generating a radical-anion intermediate (Scheme 3a). This intermediate forms a thermodynamically favored two-center/three-electron (*2c, 3e*) "half bond", where one of the electrons is forced to occupy a high energy antibonding orbital ("electron upconversion", Scheme 2).[16] The newly formed radical-anion can then be readily oxidized into a "normal" *2c,2e* bond by a mild oxidant, such as molecular oxygen. By generating a radical anion *in situ* we effectively take a weak reductant and evolve it into a more potent reductant. Such "electron upconversion"[16] allows for an effective use of such a mild oxidant as molecular oxygen. By avoiding stronger oxidants, we prevented undesired product oxidation in our cascade reactions that yield expanded N-doped polyaromatic systems.



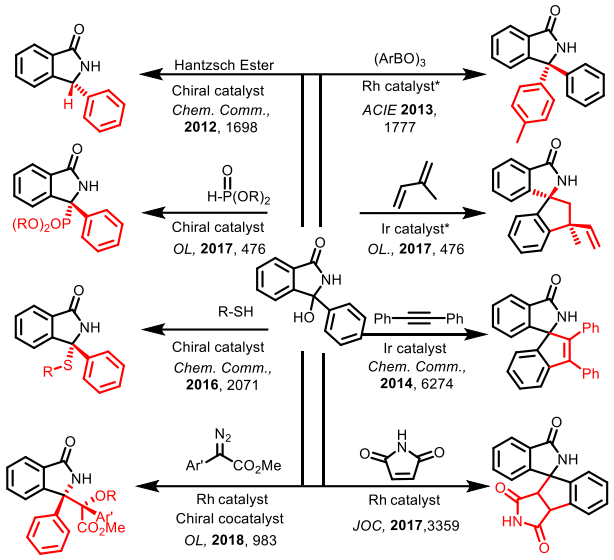
Scheme 2. Three steps in the proposed C-H/N-H activation and the mechanism of electron upconversion.

In this manuscript, we expand this approach for the construction of cyclic products using amides, a less nucleophilic nitrogen source (Scheme 3b). We will show how this structural modification of the reactants diverts the cascade towards incorporation of a C-O bond forming step,[17] so it can open a new synthetic route to 3-hydroxyisoindolinones.



Scheme 3. Expanding previous work to utilize less nucleophilic amides, as well as the formation of non-aromatic five membered heterocycles, and C-N/C-O bond formation. All energies are in kcal/mol.

This isoindolinone scaffold has been shown to produce antitumor effects by inhibiting MDM2-p53 interactions,[18] as well as serving as the antihypertensive agent Chlortalidone.[19] This heterocyclic core can be found in several natural compounds.[20] Furthermore, a variety of post-synthetic modifications of the core hydroxyisoindoline structure are possible (Scheme 4) including enantioselective transformations mediated by chiral phosphoric acids.[21-22] Transition metal catalysis was also utilized for making chiral isoindolinones and spiroisoindolinones.[23]



Scheme 4. Post-synthetic modifications for 3-hydroxyisoindolinone.

The successful use of amides as nucleophilic partners in a base-promoted oxidative C(sp^3)-H amidation yields isoindolinones under transition-metal free conditions. Because the presence of transition-metal impurities should be minimized in manufacturing medicinal compounds,[24] our transition-metal-free alternative can be an attractive choice for the synthesis of isoindolinone-based medicinal products.

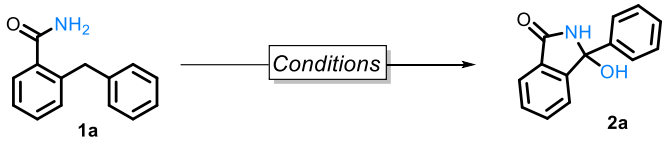
Results and discussion

We began by subjecting amide **1a** (0.01 mmol) to the previously optimized conditions, (i.e., DMF, 4 Å-molecular sieves (MS), O_2 atmosphere and 3 equivalents of t-BuOK at room temperature) for 4 hours.[9] To our delight, **2a** was formed in an excellent yield, 87% (Table 1, entry 1). When DMSO and THF were used in place of DMF, the yields of **2a** were lower (36% and 47%, entries 2 and 5). Furthermore, when DMF was replaced with acetonitrile, toluene, or DCM, **2a** was not observed (entry 3-4, 6). These results prompted us to perform the rest of our studies in DMF.

We then tested five additional bases (entry 7-11). The *tert*-butoxide salts produced **2a** in the highest yields. Interestingly, the size of the counterion impacts the conversion of **1a** into **2a**. While the difference was small for the sodium and potassium *tert*-butoxide salts (87% vs 79% respectively), a noticeable difference in yield was observed between the K, Na, and Li hydroxides (55%, 31%, <1% respectively). Fewer than 3 equivalents of base (entry 12-13) were insufficient for the full consumption of the starting material. More than 3 equivalents of base (entry 14-15) were found to be unnecessary as there was no improvement in yield.

We then varied the reaction time (entry 16-18) and observed full consumption of starting material within one hour. Finally, when the reaction vial was charged with air instead of oxygen, **2a** was produced in 75% yield (entry 19). However, the rate of the reaction was slower and not all of **1a** was consumed.

Table 1. Optimization Table



Entry	Solvent	Base	Eq	Atm	Time	Yield %
1	DMF	*t*-BuOK	3	O_2	4 h	87 %
2	DMSO	*t*-BuOK	3	O_2	4 h	36 %
3	MeCN	*t*-BuOK	3	O_2	4 h	< 1%
4	Toluene	*t*-BuOK	3	O_2	4 h	< 1%
5	THF	*t*-BuOK	3	O_2	4 h	47 %
6	DCM	*t*-BuOK	3	O_2	4 h	< 1%
7	DMF	*t*-BuONa	3	O_2	4 h	79 %
8	DMF	KOH	3	O_2	4 h	55 %
9	DMF	NaOH	3	O_2	4 h	31 %
10	DMF	LiOH	3	O_2	4 h	< 1%
11	DMF	K_2CO_3	3	O_2	4 h	< 1%
12	DMF	*t*-BuOK	1	O_2	4 h	55 %
13	DMF	*t*-BuOK	2	O_2	4 h	68 %
14	DMF	*t*-BuOK	4	O_2	4 h	85 %
15	DMF	*t*-BuOK	5	O_2	4 h	88 %
16	DMF	*t*-BuOK	3	O_2	3 h	85 %
17	DMF	*t*-BuOK	3	O_2	2 h	82 %
18	DMF	*t*-BuOK	3	O_2	1 h	84 %
19	DMF	*t*-BuOK	3	Air	1 h	75 %

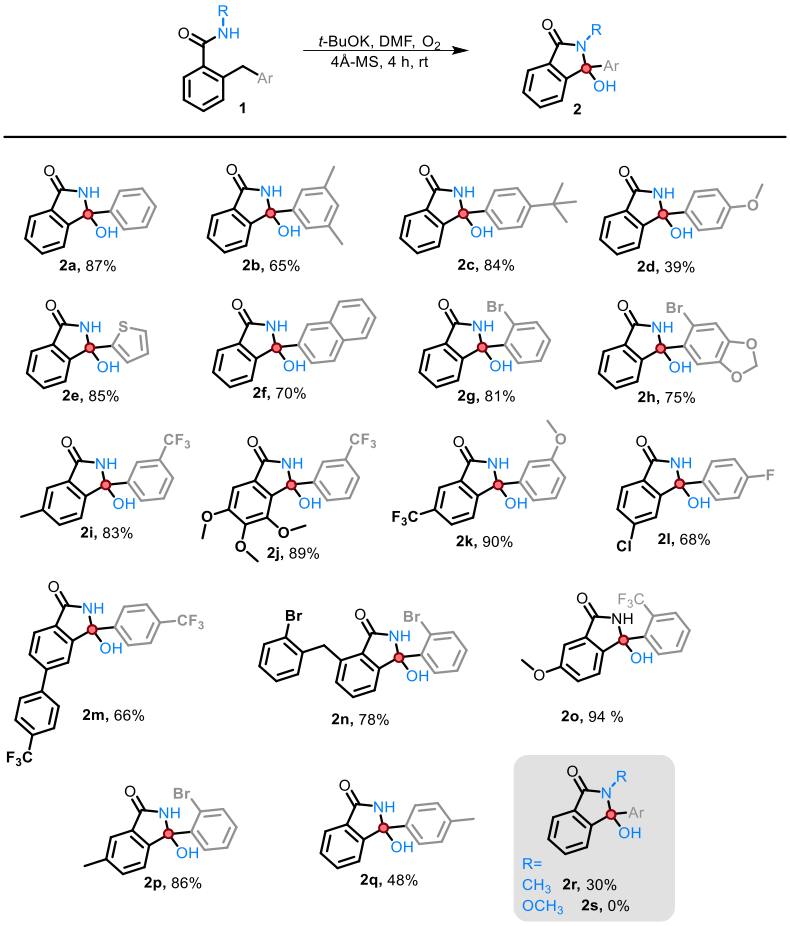
Reaction conditions: All reactions performed in a 20 mL scintillation via, **1a** (0.025M), 2.5 mL of solvent, 4 Å-molecular sieves (MS), and room temperature (22 ˚C). All yields determined by ^{1}H NMR using internal standard.

We then explored the scope of substituents that are compatible with the reaction conditions. Variation in the pendant aryl ring revealed that heterocyclic substrates, as well as the substrates with ortho, meta, and para electron withdrawing groups produced the target products in good to excellent yields. On the other hand, electron donating groups were only tolerated in the meta position. Lower conversions to the corresponding isoindolinone were observed (39% and 48% respectively) for the reactions of 4-methoxy and 4-methyl substrates. However, substrate **2c** with a para *tert*-butyl group underwent the desired transformation in high yield (84%).

Substitution in the amide ring had a smaller effect – reaction tolerated both electron donating and withdrawing groups, ortho, meta, and para to the amide. The overall transformation remained unaffected with halogens (i.e., Br, Cl, and F) on either the amide ring or pendant aryl ring, allowing for the introduction of a useful synthetic handle for future modifications.

We also investigated the possibility of introducing additional substituents at the amide nitrogen. The N-methyl amide **2r** underwent the desired transformation sluggishly (30% yield, 74% based on reclaimed starting material) under the standard conditions. On the other hand, a N-methoxy amide remained unreactive under our standard conditions (*vide infra*).

Table 2. Amide scope for C(sp^3)-H amidation and hydroxylation.



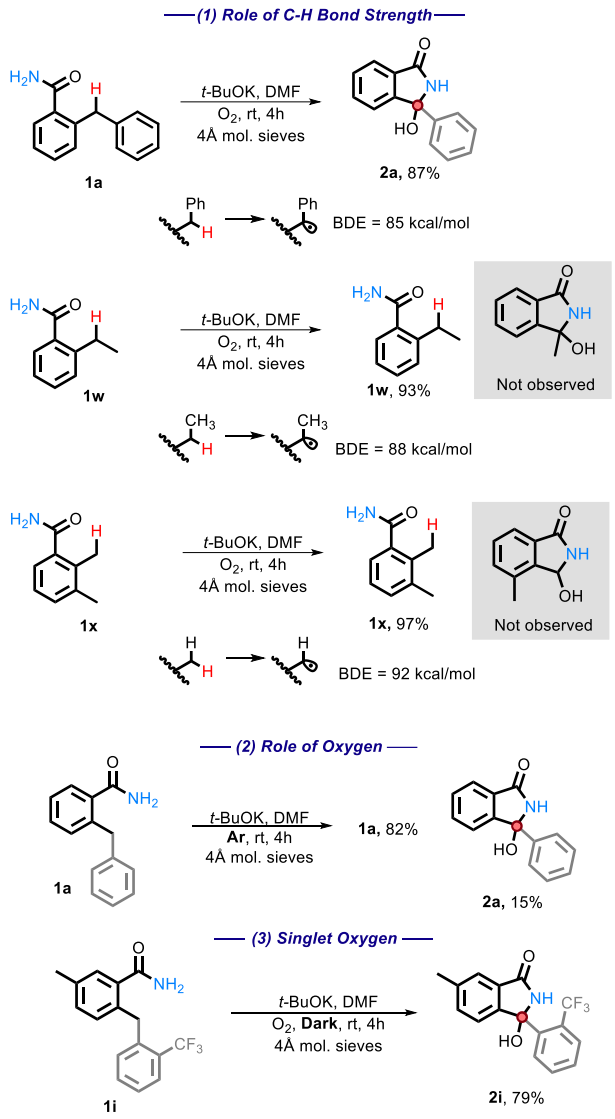
Reaction conditions: benzamide (0.025M), *t*-BuOK (3 eq.), 4Å MS, DMF, O_2 balloon and the reactions were allowed to stir for 4 hours at rt. Unless stated otherwise, the yield is of the isolated product.

Mechanistic studies

A series of studies designed to gain insight into the reactions mechanism were performed and are listed below (Scheme 5). First, the C-H bond strength is critical for the reaction success. A BDE $\leq$ 85 kcal/mol was needed and simple benzylic or alkylbenzylic C-H bonds remained unreactive under our conditions (Eq. 1).

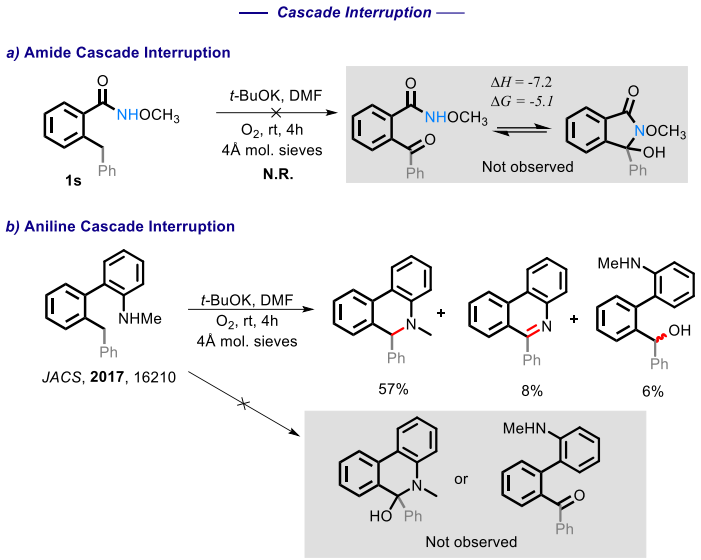
When the reaction is performed under an inert atmosphere (Ar), the consumption of **1a** is greatly diminished (Eq. 2), confirming the importance of O_2 as the oxidant.

We have also considered the possible involvement of singlet oxygen. Singlet oxygen has been shown to be synthetically useful in the oxidation of heteroatoms, cyclization reactions, and the synthesis of hydroperoxides.[25] However, **1i** was fully consumed even in the absence of light, producing **2i** in 79% yield (Eq. 3). Reactivity in the dark indicates that singlet oxygen is not involved in the main path of this reaction.



Scheme 5: Mechanistic studies for C-H bond strength and the participation of oxygen. All energies are reported in kcal/mol.

Under these oxidative conditions, one could suggest that the reaction occurs via an oxidation of the CH_2 moiety to a carbonyl intermediate.[26] This intermediate could then close the cycle via nucleophilic attack of the amide onto the carbonyl under basic conditions. We have eliminated benzylic C-H oxidation in our early work by using N-Me substituted anilines, which yield products that clearly could not originate from the ketone.[10] Obtaining such direct evidence in the present case is problematic because, unlike the aniline cascade, the present amide cascade is terminated by C-O bond formation that renders the C/N radical-anion coupling and the carbonyl pathway products identical.



Scheme 6. Interruption of the amide and aniline cascades

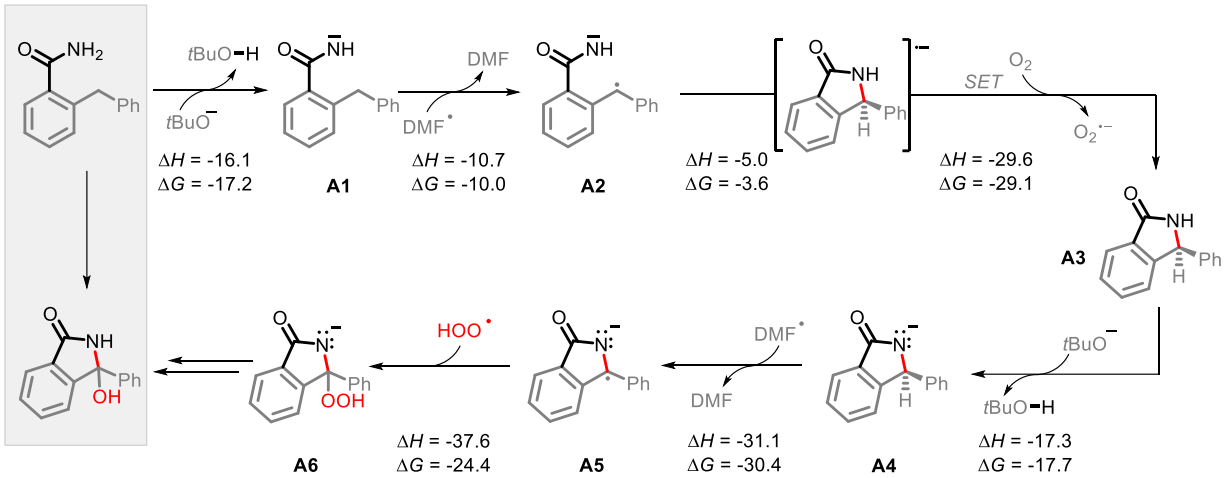
To test for the possibility of a carbonyl intermediate we wanted to use an amide that would lack reactivity and interrupt the cascade cyclization, while still allowing for the benzylic carbon to remain reactive enough to be oxidized into a ketone. However, addition of **1s** to our standard conditions resulted in no reaction occurring. Calculations show that if a ketone intermediate were formed, its cyclization would be thermodynamically favorable (ΔG = -5.1 kcal/mol). Assuming that this substitution at nitrogen does not directly change reactivity at the remote benzylic position, the lack of cyclization or benzylic oxidation suggests that the carbonyl intermediate is not formed under our conditions[10] (Scheme 6).

Computational Data

Calculations were carried using the meta-hybrid (U)M06-2X functional[27] and the 6-31+G(d,p) basis set for all atoms, with an ultrafine integration grid (99,590 points). A broken-spin approach was applied when necessary. The implicit SMD[28] solvation model was used to simulate the effects of N,N-dimethyl-formamide (DMF) throughout the calculated structures. Grimme′s D3 version (zero damping) for empirical dispersion[29] was also included. Unless otherwise noted, all results presented are at the (SMD=DMF)/(U)M06-2X(D3)/6-31+G(d,p)/int=ufine level of theory. Frequency calculations were carried for all structures to confirm them as either a minimum or a TS. All calculations were performed with the *Gaussian 09* software package.[30] Structural drawings and orbital plots were produced with CYLView 1.0.1[31] and Chemcraft 1.8.[32]

Radical Cascade Mechanism

Guided by these experimental results, we turned to computations for identifying the key intermediates of this transformation. Full thermodynamic landscape for the proposed reaction cascade is shown in Scheme 7. Each step in this cascade is thermodynamically favorable. In subsequent individual sections, we will discuss the individual steps along with the respective experimental evidence.



Scheme 7. Proposed mechanism and calculated reaction thermodynamics for the individual steps in the N-H/C-H amidation. All energies are in kcal/mol.

Deprotonation/ H-Atom Transfer

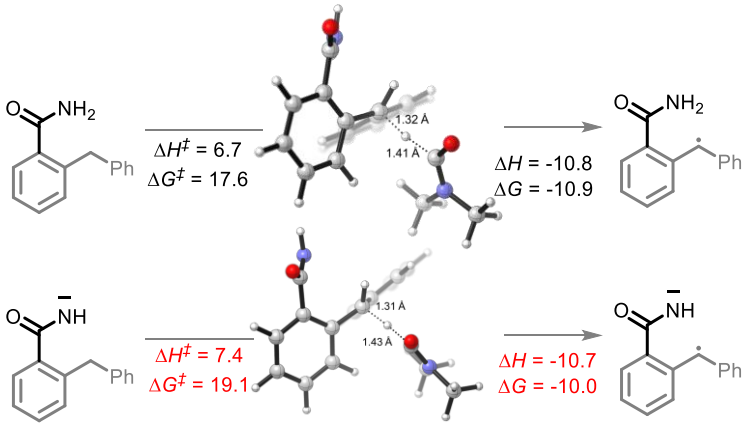
The unusual nature of our intramolecular C-H amination stems from the generation of a radical and an anion *in situ*. To achieve this, two criteria must be met. First, an acidic proton is needed for a deprotonation that produces a persistent N-anion. Second, the substrates should have a sufficiently weak C-H bond that undergoes HAT with the formation of a C-radical.

The cascade mechanism begins with the deprotonation of the mildly acidic benzamide by *tert*-butoxide, ΔG = -17.2 (Scheme 7, **A1**). Following the generation of a persistent nitrogen anion, the bis-benzylic C-H bond (BDE = 85 kcal/mol) is sufficiently weak to engage in a HAT with DMF radical (see the SI for discussion of DMF radical formation), ΔG = -10.0 kcal/mol (Scheme 7, **A2**). This step yields a relatively stable C-centered radical and our initial radical-anion intermediate. While the HAT $\Delta G^{\ddagger}$ and ΔG are slightly lower for the neutral amide than the deprotonated amide ($\Delta G^{\ddagger}$ = 17.6 vs 19.1, ΔG = -10.9 vs -10.0 kcal/mol), the higher concentration of base and the overall thermodynamically favored deprotonation step will result in HAT occurring after deprotonation (Scheme 8).

Upon further inspection, our calculations show an interesting transition state for the initial HAT. At stage where the benzylic C-H bond begins to break to form the C-centered radical, the benzylic C-H is *misaligned* with the aromatic π-system. Hence, the forming radical finds itself in alignment only with the pendant aromatic ring. One might expect that as this radical would prefer to be in a close alignment with both aromatic rings to take advantage of stereoelectronic stabilization. This finding explains why the pendant aryl group is necessary – although the CH_2 groups in substrates **1w** and **1x** are formally "benzylic" (Scheme 5), the core aryl group does not directly contribute to their C-H activation. Under these intramolecular stereoelectronic constraints, their relatively low BDE values are somewhat misleading.

Furthermore, the amide is rotated out of conjugation the aromatic π-system in a nearly orthogonal geometry.[33] Steric hindrance between the two relatively large ortho-substituents contributes to this geometric preferences. In addition, the electron cloud of the amide may have substantial through-space interactions with the back lobe of the anti-bonding orbital of the breaking

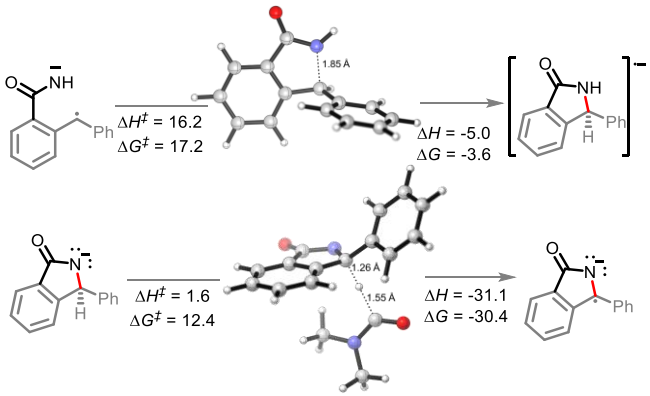
C-H bond. In other words, the amide may be assisting in the C-H activation process by helping to stabilize the newly forming radical via a through-space interaction.



Scheme 8. Reaction energy profiles and twisted transition states for C-H activation in neutral and deprotonated substrates. All energies are in kcal/mol.

Radical-Anionic Cyclization and C-N Bond Formation

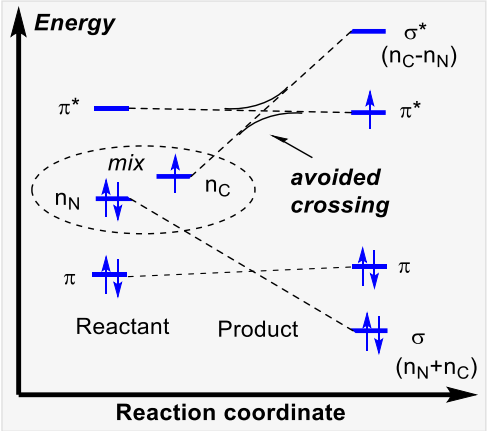
The N-anion and the C-centered radical in **A2** react to form a *2c,3e* "half" bond, also making a cyclic radical-anion in the process. Interestingly, this process occurs without the apparent loss of amide resonance since it is the 2nd "in-plane" lone pair of nitrogen that is involved in the N-C coupling. On the other hand, the radical center rotates out of conjugation with the central aryl ring as well. The latter stereoelectronic penalty is likely to account for a relatively high, 17.2 kcal/mol, Gibbs barrier and the low thermodynamic driving force, ΔG = -3.6 kcal/mol, for this seemingly trivial step (Scheme 9).



Scheme 9. Transition states for the C-N bond formation and second HAT.

Additionally, the three non-bonding electrons of the radical and anion reacting partners have to find "a new home" in this step. Two of these electrons are accommodated in the newly formed σ orbital of the C-N bond. The third electron avoids its apparent destiny of ending up at the high energy $\sigma^*_{C\text{-}N}$ orbital by "hopping" to a lower energy π* orbital of the aromatic ring

(Scheme 10). This state crossing, not unusual for radical-anionic reactions,[34] stabilizes the product by creating a delocalized π-type radical-anion.



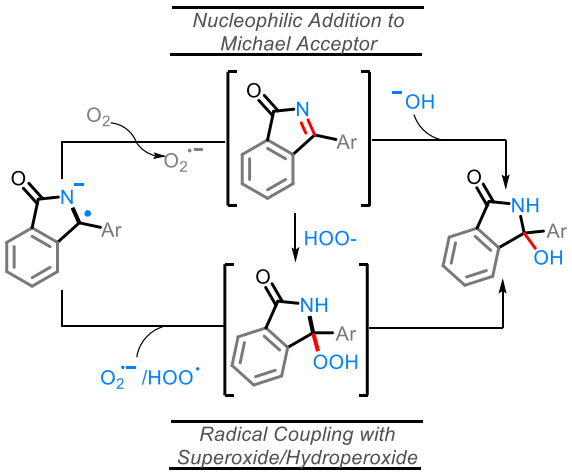
Scheme 10. State crossing avoids populating the high energy $\sigma^*_{C\text{-}N}$ orbital.

Nevertheless, the *2c,3e*-bond reactant is evolved from a mild reductant (electron in a non-bonding orbital) into a more potent reductant (electron is an antibonding orbital). The high reducing power of the cyclic product allows its reaction with a mild oxidant, such as molecular oxygen. This reaction (i.e., single electron transfer) removes the antibonding electron, converting a *2c,3e*-bond into a normal *2c,2e* C-N bond. This step simultaneously forms superoxide in a thermodynamically favorable way with ΔG = -29.1 kcal/mol (Scheme 7, **A3**).

After the benzamide is cyclized into an isoindolinone, the cyclic intermediate is deprotonated to give anion **A4** (Scheme 7, ΔG = -17.7 kcal/mol). The α-C-H bond in this anion is sufficiently weakened to form a stabilized radical-anion **A5** (ΔG = -30.4 kcal/mol after a HAT to DMF radical).

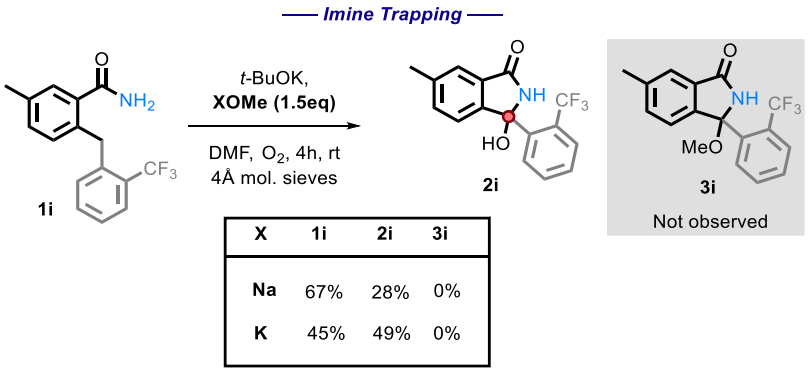
Diverting from C=N to C-O bond formation

From the stabilized radical intermediate **A5**, one can envision two possible mechanistic routes for the formation of the C-O bond (Scheme 11). The first possibility is similar to what we reported in our previous work[10], in which the intermediate is oxidized a second time by molecular oxygen to form the C=N moiety of an imine intermediate. This intermediate may then be intercepted by a suitable nucleophile generated *in situ*, such as superoxide or hydroxide. In particular, superoxide is known to undergo disproportionation to give O_2 and hydroxide under aqueous conditions.[35] It is possible that a similar process to generate hydroxide could occur under the conditions of our C-H amination reaction, whereas *t*-BuOH would be our proton source instead of H_2O. The second possibility, is that a radical coupling partner such as superoxide or hydroperoxyl radical may couple to the C-centered radical making a hydroperoxide intermediate.



Scheme 11. Possible routes to product from stabilized radical-anion intermediate.

We initially tested to see if the addition of an external nucleophile could be used to trap the plausible imine intermediate. The addition of either sodium or potassium methoxide hinders the reaction, with no methoxy product observed in these experiments (Scheme 12).

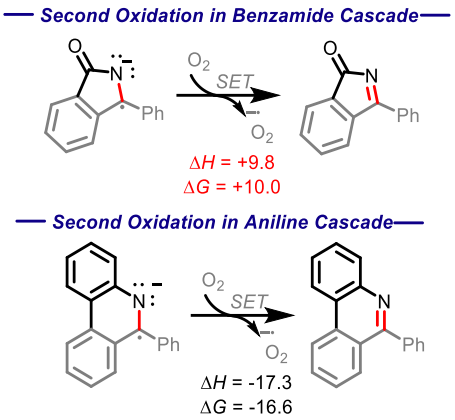


X	1i	2i	3i
Na	67%	28%	0%
K	45%	49%	0%

Scheme 12. Attempting to trap the hypothetical imine intermediate.

Our calculations show the oxidation of **A5** by O_2 is thermodynamically uphill (ΔG = +10.0 kcal/mol, Scheme 13). While this is not a prohibitive price to pay, it is worth noting that this oxidation step is 39.1 kcal/mol more endergonic than the initial oxidation step. This substantial increase stems from several factors, including lack of aromatic stabilization in the N-heterocyclic part as well as the additional radical and charge stabilization, not only through the bis-phenyl groups, but additionally through the nitrogen and carbonyl.

This finding contrasts our previous work with anilines where the second oxidation step was favorable (ΔG = -16.6 kcal/mol) due to the formation of an aromatic system.[10] In the present case, the situation is different and this differences manifests itself in a divergent reaction pathway (formation of a C-O bond instead of C=N moiety). In order to understand this step better, we explored the possibility of radical coupling being responsible for the final C-O formation.



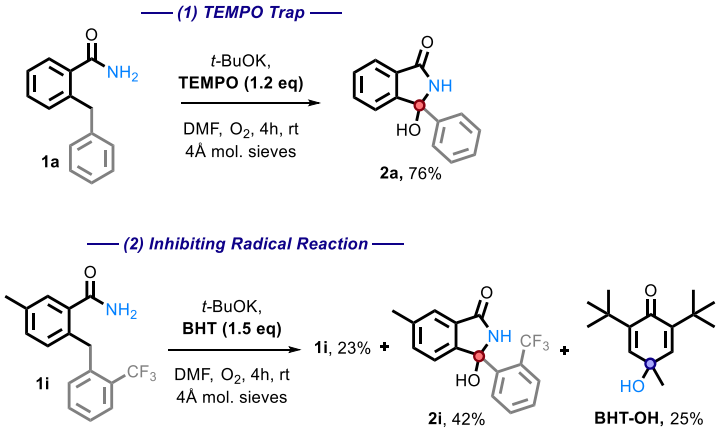
Scheme 13. Contrasting thermodynamics (kcal/mol) for the C=N forming oxidations in the amide and aniline cascades

A series of studies designed to gain insight into the possible radical coupling of **A5** were performed and are listed below (Scheme 14).

We then employed the use of two common radical trapping agents, attempting to either trap a radical intermediate or to inhibit the reaction. In the case of TEMPO, there was a slight decrease in isolated yield (87% vs 76%) but, no TEMPO trapped product or recovered starting material was observed (Eq. 1). This finding is consistent with the radical mechanism if intramolecular radical trapping (i.e., the cyclization) is faster than the intermolecular trapping, or if TEMPO can play an alternative role by promoting the C-H activation step. More detailed discussion on the possible role of TEMPO will be given in a subsequent section.

We also tested the effect of a common radical and peroxide trapping agent, 3,5-di-tert-4-butylhydroxytoluene (BHT), at the standard reaction conditions (Eq. 2). The phenol moiety of BHT is often used to halt the autoxidation of organic molecules with oxygen, analogous to that of vitamin E. BHT can deactivate two (usually peroxy) radicals – the first one by a hydrogen atom transfer and the second one by reaction at the cycle.[36]

We found that the reaction is partially inhibited (**2i** was isolated in a 47% yield, starting material recovered in 27% isolated yield. Furthermore, BHT-OH was additionally isolated, 25% yield (low yields are a result of isolation difficulties). Formation of this product further suggests that a radical pathway is involved.

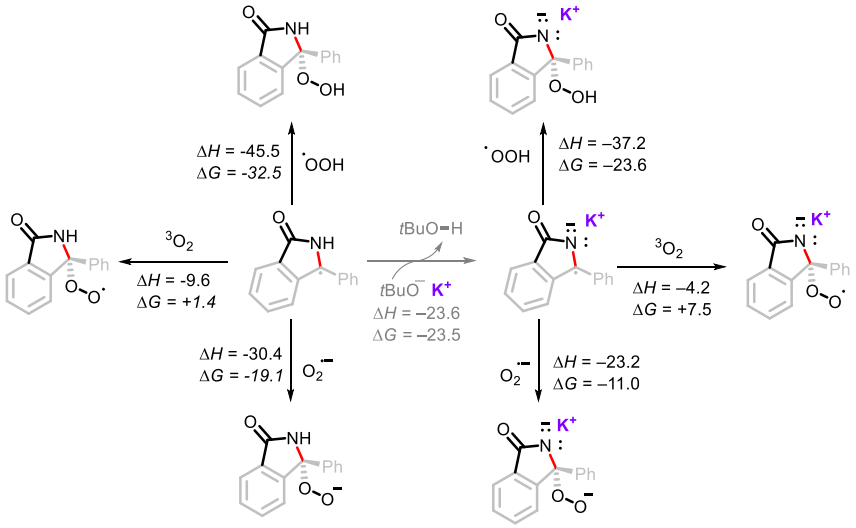


Scheme 14. Radical coupling mechanistic studies. [a] Yield determined by NMR.

Addition of Superoxide/Hydroperoxyl Radical to the Radical-Anion A5

It is unlikely that the OH group in the final product is a result of radical coupling with hydroxide radical, as it is highly reactive and will likely abstract a hydrogen atom from the solvent or *t*-BuOH before reaching the reactant.[37] This consideration led us to explore the possibility of radical coupling with superoxide, or with its conjugate acid, i.e., the hydroperoxyl radical (HOO•).[38]

Our calculations show this to be a favorable path for forming the C-O bond (Scheme 15). In particular, radical addition to intermediate **A5** via HOO• was found to be highly exergonic, ΔG = -23.6 kcal/mol. Addition of superoxide (the precursor of HOO•) to **A5** was favorable, ΔG = -11.0 kcal/mol. On the other hand, the addition of molecular oxygen was found to be endergonic, ΔG = +7.5 kcal/mol. It is worth noting that all three of these proposed pathways are thermodynamically more favorable than an oxidation of **A5** by O_2 (ΔG = +10.0 kcal/mol).



Scheme 15. Computational thermodynamic data for the addition of molecular oxygen, superoxide, and hydroperoxyl radical to the stabilized radical intermediate. Energies in kcal/mol.

Superoxide has been shown to act as a Brønsted base in aprotic media and deprotonate weak acids such as 1-butanol in DMF (pKa = 33.3 in DMF)[39]. It is therefore possible, that superoxide may deprotonate t-BuOH (estimated pKa ≈ 34-35 in DMF) generated *in situ*, forming HOO•. Hence, both HOO• and superoxide may couple with **A5**.

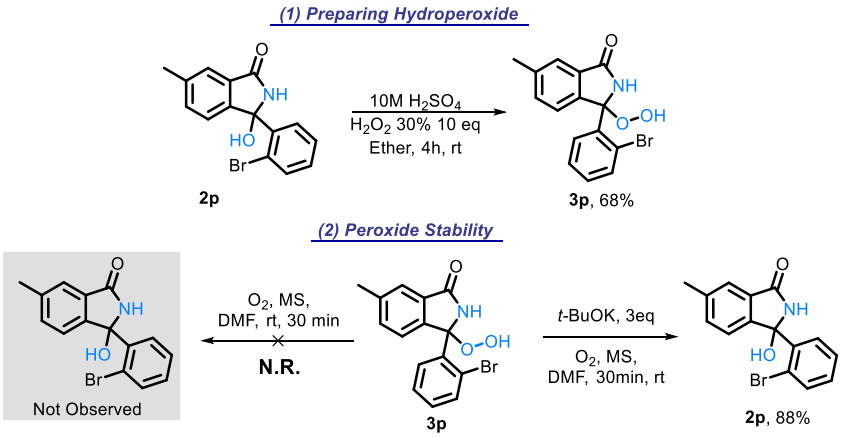
The evidence that we have presented up to this point suggests that formation of a hydroperoxide intermediate[40] should be considered (Scheme 7, **A6**). In order to explore this possibility, we have prepared this intermediate and tested its properties as described in the following section.

Hydroperoxide Intermediate

The hydroxy group of **2p** was converted into hydroperoxy group of **3p** (Scheme 16, Eq 1) by acid-catalyzed reaction with H_2O_2. The reference spectra contained the characteristic broad downshifted peak of a hydroperoxide that readily underwent deuterium exchange.[41] After subjecting **3p** to our standard conditions the formation of **2p** could be seen via TLC within five

minutes, the reaction was left to proceed for half an hour and **2p** was obtained in 88% yield (Scheme 16, Eq 2). The lack of **3p** reactivity in the absence of *t*-BuOK (Scheme 16, Eq 2) indicates the important role of *t*-BuOK in the reduction of the hydroperoxide intermediate into the final product.

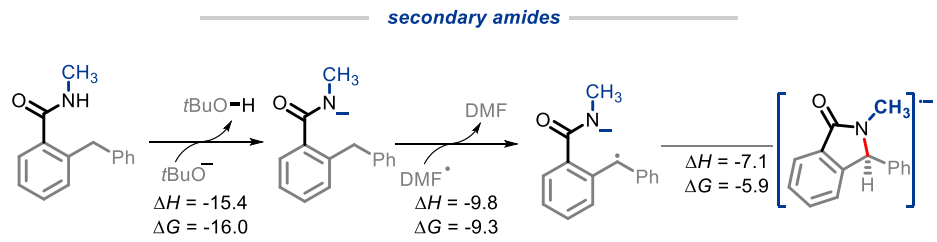
Because of the rapid consumption of hydroperoxide in the presence of base, we anticipate its existence *in situ* to be fleeting. The existence of transient hydroperoxide intermediates, that convert to an OH-bearing final products, has previously been reported in O_2-mediated oxidations of C(sp^3)-H bonds.[42] Indeed, in several experiments, ^{1}H NMR of the reaction mixtures showed a broad downshifted singlet, potentially indicative of the hydroperoxide (See Supporting Information for additional details). Although this intermediate was too unstable to persist and to be reliably detected under the reaction conditions, these findings suggest that a hydroperoxide intermediate (Scheme 7, **A6**) is formed transiently and reduced by *t*-BuOK/*t*-BuOH into the final isoindolinone product.



Scheme 16. Preparation and instability of the suggested hydroperoxide intermediate.

Secondary Amides

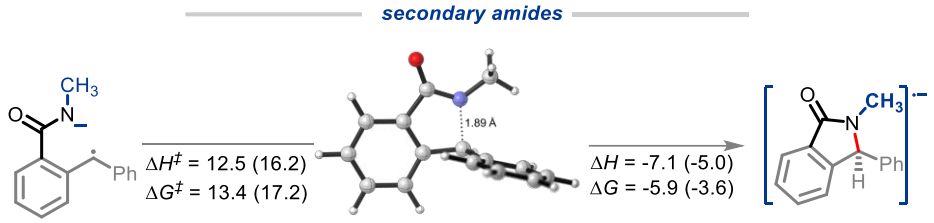
We were intrigued by the sluggish reactivity of the secondary amides. Since we get back the unreacted starting material, the reaction is stalling out in the initial stages of the reaction. Yet our thermodynamic calculations find that each of the three initiation steps, i.e., the deprotonation (ΔG = -16.0), HAT (ΔG = -9.3), and the radical-anion cyclization (ΔG = -5.9), for **1r** are thermodynamically favorable (Scheme 17).



Scheme 17. Thermodynamic calculations for the deprotonation, HAT, and radical-anion cyclization of **1r**. All energies are reported in kcal/mol.

We used computed activation barriers to understand why the secondary amides are unreactive (See Supporting Information). Our analysis suggests that the barrier for the H-abstraction is about 1.2 kcal/mol higher for the secondary amides than it is for the primary amides. Such difference in the barrier should correspond to a ca. 10-fold rate decrease for this step, providing a possible explanation for the low reactivity of the secondary amide substrates under the reaction conditions.

Conversely, the calculated barrier for the C-N bond formation is *lower* for the secondary amides, indicating that this step is unlikely to be the cascade bottleneck (Scheme 18). Aimed by these observation, we have concentrated our attention on the H-transfer step.

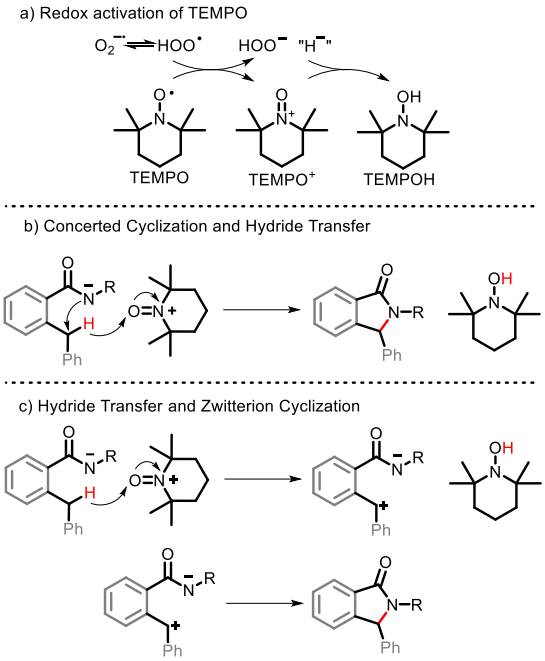


Scheme 18. Computed activation and reaction enthalpies and Gibbs energies for the cyclization of secondary amide **1r**. Numbers in parenthesis are for primary amide **1a**. All numbers reported in kcal/mol.

Indeed, focus on C-H activation allowed us to solve the problem of secondary amides as described below. Recalling that TEMPO had no detrimental effect on our radical reaction, we decided to consider the possibility of TEMPO assisting in C-H activation.

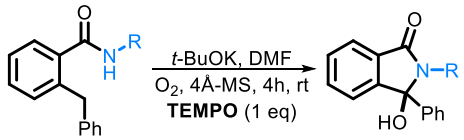
Indeed, literature suggests that TEMPO can be a useful additive to the oxidation of benzylic C(sp^3)-H's. For example, TEMPO can be oxidized into an oxoammonium salt (TEMPO+) in the presence of hydroperoxyl radical, peroxyl radicals, or a secondary oxidant (e.g. NaOCl) as shown in Scheme 19a.[43] The latter has been shown to act as an oxidant that may facilitate the forward progression of redox reactions.[44] In particular, TEMPO+, generated *in situ*, from TEMPO was used as a cocatalyst in the aerobic oxidation of benzylic C(sp^3)-H into carbonyls.[45] Even if the carbonyl intermediate is formed in this case, it would, as we previously discussed in Scheme 6, readily cyclize under basic conditions into our isoindolinone product.

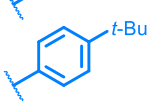
Additionally, TEMPO+ has been suggested to facilitate benzylic hydride transfers.[46] It is plausible that in our case, a concerted C-N bond formation and benzylic hydride transfer to TEMPO+ occurs generating TEMPOH and our cyclized product (Scheme 19b). Alternatively, one can consider a hydride transfer to TEMPO+ forming a benzylic carbocation that is immediately trapped intramolecularly via cyclization (Scheme 19c).



Scheme 19. Potential pathways for TEMPO assistance in C-H activation.

Although the exact mechanistic path for C-H activation in our system is so far unknown, the combination of possible attractive scenarios motivated us to test the effect of TEMPO on the reaction. To our delight, we observed the nearly full consumption when secondary amide **1r** was subjected to the optimized conditions along with TEMPO (1 eq.). Interestingly, no TEMPO-trapping product was present in the reaction mixture. Instead, **2r** was obtained in 74% isolated yield - a dramatic improvement over the standard conditions (30% without TEMPO vs. 74% with TEMPO, Scheme 20). Motivated by this finding, we tested reactivity of **1s** in the presence of TEMPO. Gratifyingly, the reaction affords **2s**, albeit in a moderate yield of 31% (the majority of reaction mixture is unreacted **1s**). Furthermore, substrates **1t**, **1u**, and **1v** also showed a substantial increase in reactivity with the addition of TEMPO and the products **2t**, **2u**, and **2v** were isolated in 87%, 54%, and 55% respectively.



Substrate		Product	Yield, %
1r		**2r**	30[a], 74[b], 86[c]
1s		**2s**	0[a], 31[b], 94[c]
1t		**2t**	49[a], 87[b], 87
1u		**2u**	33[a], 54[b], 71[c]
1v		**2v**	25[a], 55[b], 87[c]

Scheme 20. Improved C-H activation with TEMPO as an additive. Reaction conditions: Secondary benzamide (0.025 M), *t*-BuOK (3 eq), DMF (2 mL), 4Å MS, O_2 balloon, reactions

stirred at r.t. overnight. (a) Isolated yields for reaction performed under standard conditions. (b) Isolated yields for reactions with the addition of TEMPO (1 eq). (c) Yields based of reclaimed starting materials with the addition TEMPO (1 eq).

Conclusion

We have developed a direct method for converting C(sp^3)-H bonds into C-N and C-O bonds under mild conditions with the aid of base, molecular oxygen and DMF. Each component of the overall reaction has a pivotal role in a coordinated sequence of deprotonation, H-atom transfer, and electron transfer that forges the C-N bond. The base has three main functions: 1) to deprotonate the N-H bond, 2) to provide an adequate concentration of DMF carbamoyl anion to be converted to DMF radical, and 3) to convert the hydroperoxide intermediate into the final hydroxyl product. The role of DMF radical is to perform selective HAT at the di-benzylic C(sp^3)-H that forms a C-centered radical. The C-N bond is formed initially through a *2c,3e* interaction between the N-anion and C-radical. Oxidation of the radical-anion intermediate by oxygen completes the C-N bond forming sequence. Computation data suggest that the stabilized radical anion formed after the second HAT could not be oxidized by molecular oxygen. Instead superoxide/hydroperoxide couples with the radical to generate a hydroperoxide intermediate that ultimately decomposes to form the hydroxide product. Addition of TEMPO opens the door for the use of secondary amides and improves the performance of insufficiently reactive primary amides. This process allows for the formation of functionalized N-heterocycles in an operationally simple and robust fashion.

ASSOCIATED CONTENT

Supporting Information

Full experimental details, ^{1}H NMR, ^{13}C NMR, HR-MS and NMR spectra for all newly reported compounds and computational details for all calculated structures. The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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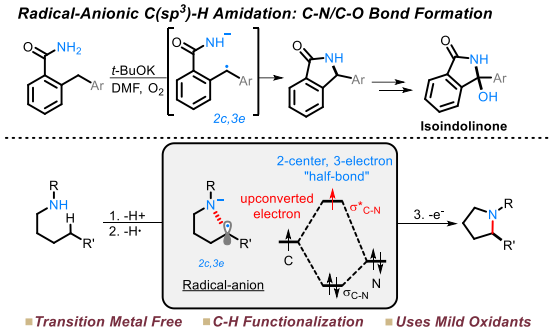
TOC Graphic:



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