Organophotocatalytic N–O Bond Cleavage of Weinreb Amides: Mechanism-Guided Evolution of a PET to ConPET Platform

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ABSTRACT: A mild, organophotocatalytic N–O bond cleavage of Weinreb amides is disclosed, thereby expanding the chemistry of this venerable motif beyond acylation. This redox neutral process begins to reconcile the ubiquity of N–O bonds in contemporary synthesis with the disproportionately harsh, stoichiometric conditions that are often required for bond cleavage. The strategy is compatible with the parent alkyl derivatives (N–OMe, N–OAlkyl) thereby complementing tailored *O*-substituent approaches that require N–OAr groups (Ar = electron deficient). A broad range of acyclic and cyclic derivatives are disclosed (>40 examples, up to 95%) and the synthetic utility of the method is demonstrated in a range of applications. In the case of cyclic Weinreb amide derivatives, this platform enables ambiphilic amide-aldehydes, of varying chain length, to be generated in a single transformation. Inspired by Emil Fischer´s seminal 1908 synthesis of aminoacetaldehyde using sodium amalgam, this method provides a milder route to access this important class of materials. Mechanistically-guided reaction development demonstrates the involvement of a photoinduced SET mechanism (PET), and this has been further advanced to a consecutive photoinduced electron transfer (ConPET) manifold: this has significantly expanded the scope of compatible substrates

Introduction

Oxidized amines are ubiquitous in organic chemistry and frequently manifest themselves in complex synthesis campaigns: the Weinreb amide is an exemplar (Figure 1).[1] As key components in an impressive portfolio of enabling technologies, routes to generate and strategically leverage N–O bonds for structural pre-organization have been intensively pursued.[2] This traceless tether features in a range of applications including target synthesis,[3] drug delivery mechanisms,[4] protein ubiquitylation[5] and asymmetric catalysis.[6] Prominent examples include the acyl nitroso Diels-Alder reaction (Figure 1A),[7] and the nitrile oxide[8] and oxime 1,3-dipolar cycloaddition[9] manifolds (Figure 1B). In contrast, methods to facilitate cleavage of the relatively labile N–O(Alkyl) bonds in Weinreb amides (∼55-65 kcal/mol) are conspicuously underdeveloped and typically rely on disproportionately harsh conditions. This is noteworthy given the difficulties associated with selective monoalkylation and the attractiveness of reductive deprotection. The current suite of methods includes base-mediated elimination approaches[10] and metal reducing agents that enable single electron transfer processes (SET): Examples of the latter include samarium diiodide (N–OBn),[11] lithium (DTBB / NH_3),[12] sodium,[13] ruthenium (Zn-Cu)[14] and titanium reagents (Figure 1C).[15] A metal-free alternative has also been demonstrated using a super electron donor.[16] Although metal-based SET methods constitute the vanguard of N–O bond cleavage platforms, this dominance must be reconciled with limited functional group compatibility and operational challenges. Elemental sulfur provides a milder alternative to the aforementioned reductants, but its use is confined to secondary amide derivatives and thus general solutions are required.[17]

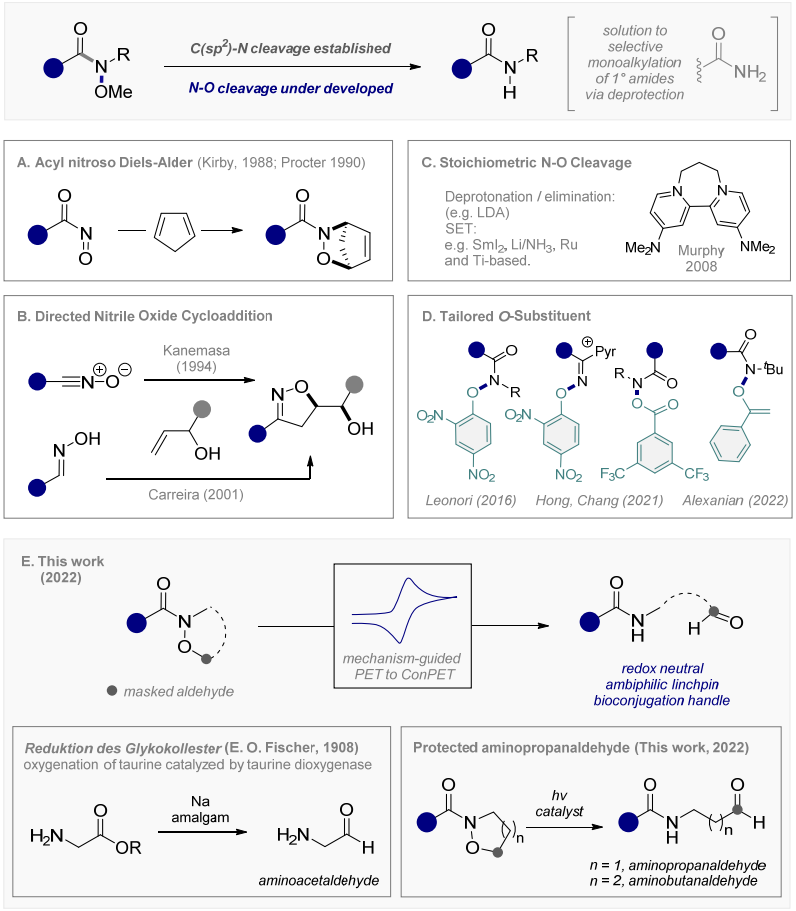


Figure 1. The importance of the N–O bond in synthesis and selected cleavage methods for modified Weinreb amides.

Photochemistry provides a versatile platform to initiate SET, enabling innovative, mild alternatives to be developed.[18] A pertinent example is the N–O bond cleavage of *N*-alkoxyamides using a high energy mercury lamp and tributyltin hydride (N–OBn).[19] Further advances in this field derive from photoredox catalysis-based methods, which mitigate the need for toxic reagents, thereby enabling the mild generation of open shell reactive species.[20] A valuable contribution has been the introduction of very effective *O*-substituents (N–OAr, OAr = 2,4-dinitrophenol, N–OC(O)Ar, Ar = 3,5-bis trifluoromethyl phenyl) (Figure 1D): This enables N–O bond cleavage to be achieved upon irradiation with eosin Y in the presence of 1,4-cyclohexadiene, for HAT, using green LEDs[21] or using an iridium photoredox catalyst.[22] The resulting amidyl radicals[23] may then be intercepted through sequential cyclization or arylation events. Importantly, the redox handle (e.g. 2,4-dinitrophenol) is critical to the success of these processes, where it serves to lower the reduction potential of the substrate.[24,25]

Motivated by the synthetic utility of Weinreb amides, and conscious of the persistent challenge presented by the parent alkyl derivatives, a redox-neutral, photocatalysis-based platform to enable efficient N–OAlkyl cleavage was devised (Figure 1E). Addressing this disparity would expand the chemistry of the Weinreb amide moiety beyond acylation and, by unmasking the aldehyde, permit a mild reinterpretation of E. O. Fischer´s celebrated 1908 synthesis of aminoacetaldehyde and related derivatives (Figure 1E, lower left).[26] To that end, a mechanism-guided investigation using the parent Weinreb amide motif was conducted to address reactivity challenges grounded in reduction potential. The reaction design was predicated on a redox neutral N–O cleavage process to simultaneously liberate the (reduced) secondary amide and (oxidized) aldehyde in a single operation (Figure 1E). This generation of an ambiphilic

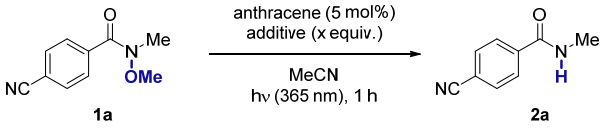
product[27] lends itself to downstream manipulations in chemical biology[28] with exogenous Lewis bases. It was envisaged that anthracene could be leveraged as a highly reducing photocatalyst ($E^0_{1/2}$ = -1.95 V vs SCE)[29] upon excitation at 365 nm. Anthracene has been validated as a competent reducing agent in sensitization-initiated electron transfer for photoredox catalysis,[30] however its use in the title transformation remains unexplored.[31] Through a mechanism-guided approach, the development of a photon induced electron transfer (PET) platform has been validated. Electrochemical limitations have been circumvented by further advancing this platform to leverage consecutive photoinduced electron transfer (ConPET) using 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) as photocatalyst.[32]

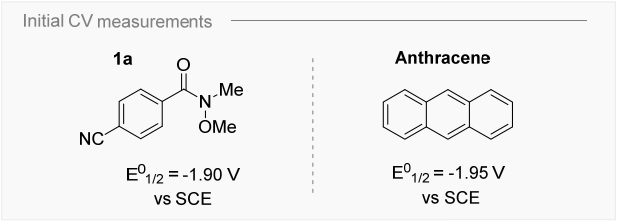
Results and Discussion

To establish the competency of anthracene as a photoredox catalyst, selected CV experiments were conducted (see Table 1 and the ESI for further details): Weinreb amide **1a** ($E^0_{1/2}$ = -1.90 V vs SCE) was selected as a model substrate for the reduction to secondary amide **2a**. Preliminary validation was established by performing the reaction with 5 mol% anthracene in acetonitrile under irradiation at 365 nm for 1 h, which furnished product **2a** in 53% yield on a 0.1 mmol scale (Table 1, entry 1). The introduction of additives enabled the yield to be further enhanced (entries 2-5). Whereas the addition of cyclohexadiene (CHD) and K_2CO_3 led to a modest improvement (entry 2, 69%), 2,2,6,6-tetramethylpiperidine (TMP) proved to be detrimental (entry 3, 48%). Triethylamine had a very positive impact on reaction efficiency (entry 4, 89%) and diisopropylethylamine (DIPEA) enabled the quantitative conversion of **1a** to **2a**. Control reactions in the absence of anthracene (entry 6) or irradiation (entry 7) completely suppressed N–O bond cleavage. Further optimization established that quantitative formation of product **2a** can be obtained using substoichiometric quantities of base (entries 8-10).

To explore the scope of the transformation, the optimized conditions were applied to a series of functionalized starting materials. The reaction was performed using either 0.5 or 1 equivalent of DIPEA (indicated as conditions **A** and **B**, respectively, in Figure 2) depending on the conversion of starting materials. In addition to electron-deficient benzamide derivatives which gave good yields with both sets of conditions (**2a-c**, up to 97% yield), it was gratifying to observe that the protocol was compatible with a range of medicinally relevant heterocycles, including quinolines, pyrazines and pyridines (**2d-f**, up to 89%). Cinnamamides were then explored to evaluate the compatibility of the method with α,β-unsaturated carbonyl derivatives (**2g-j,** up to 82% yield). It is pertinent to note that regioisomers **2h** and **2i** showed slight differences in reactivity which is likely a manifestation of two 1,3-allylic strain[33] scenarios subtly attenuating the redox potential of the substrate. Another example of the influence of 1,3-allylic strain on the redox potential is the cinnamamide **1h** and its stereoisomer **1j**, which was generated by photocatalytic isomerization.[34] They showed different behavior under the reaction conditions, however the alkene geometry is preserved fully in both cases (products **2i** and **2j**). Cognizant of the importance of diene fragments in complex natural product synthesis,[35] and the sensitivity of these structural modules to established N–O bond cleavage protocols (see Figure 1C), secondary amides **2k**, **2l** and **2m** were prepared in up to 62% yield. The presence of a C(sp^2)-B until provides a convenient handle for subsequent drown-stream manipulation.[36] Replacing the *N*–Me by *N*–pentenyl afforded the product **2n** in 59% yield: the pyrroldine-based product that would arise from amidyl radical formation and subsequent 5-*exo*-trig cyclization was not observed thereby indicating mechanistic distinction of this process compared redox auxiliary approaches (*vide infra*).[24] In a final twist of fate, a model hydroxylamide (*N*–OH), when exposed to these conditions, was smoothly converted to product **2a** and it was possible to generate the primary amide **2o**. In general, the method is limited to electron-poor substrates, with electron neutral or -rich Weinreb amides giving only traces of the desired product and the starting material was recovered.

Table 1. Reaction optimization.





Entry	Additive (equiv.)	Yield 2a (%)[a]
1	-	53
2	1,3-CHD, K_2CO_3 (2.0)	69
3	TMP (2.0)	48
4	Et_3N (2.0)	89
5	*i*-Pr_2NEt (2.0)	Quant.
6	No catalyst	0
7	No light	0
8	*i*-Pr_2NEt (1.0)	Quant.
9	***i*-Pr_2NEt (0.5)**	**Quant. (89[b])**
10	*i*-Pr_2NEt (0.2)	Quant.

[a] Reactions were carried out on 0.1 mmol scale (0.03 M in MeCN). Yield was determined by ^1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are quoted in parentheses for reactions conducted on 0.3 mmol scale. [b] 0.1 M in MeCN. CHD = cyclohexadiene. TMP = tetramethylpiperidine. CV experiments were measured using ferrocene as the internal standard.

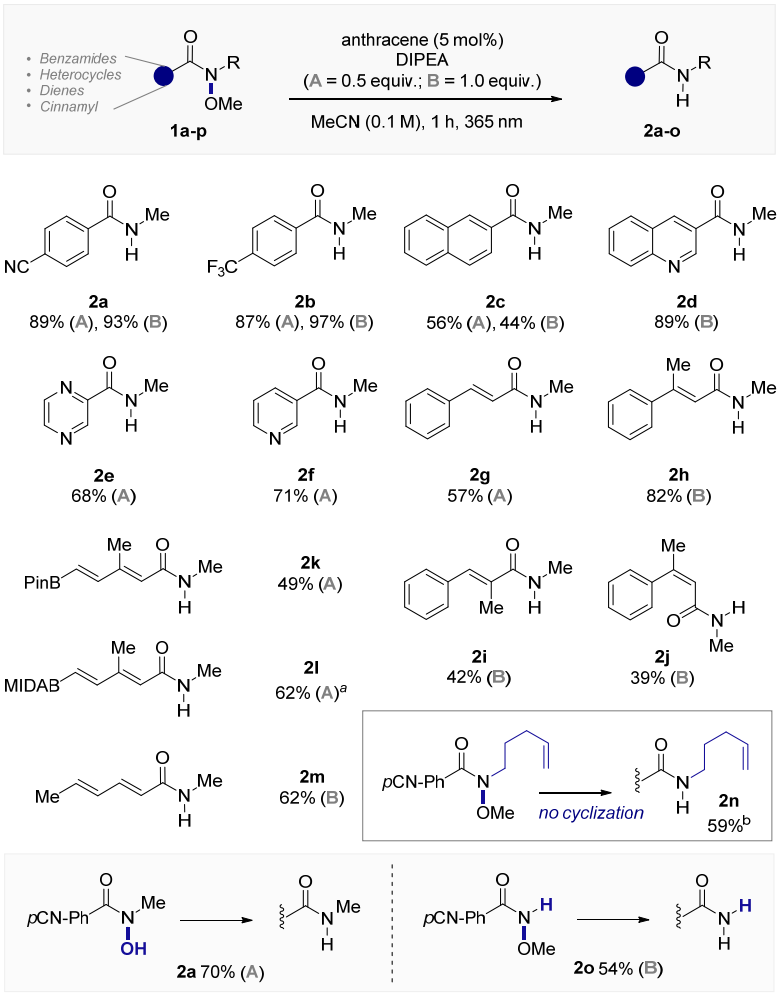


Figure 2. Exploring the scope of the organophotocatalytic N–O bond cleavage of Weinreb amides using anthracene. Reactions performed in 0.3 mmol scale. [a] Reaction performed in 0.1 mmol scale. [b] Reaction performed without DIPEA.

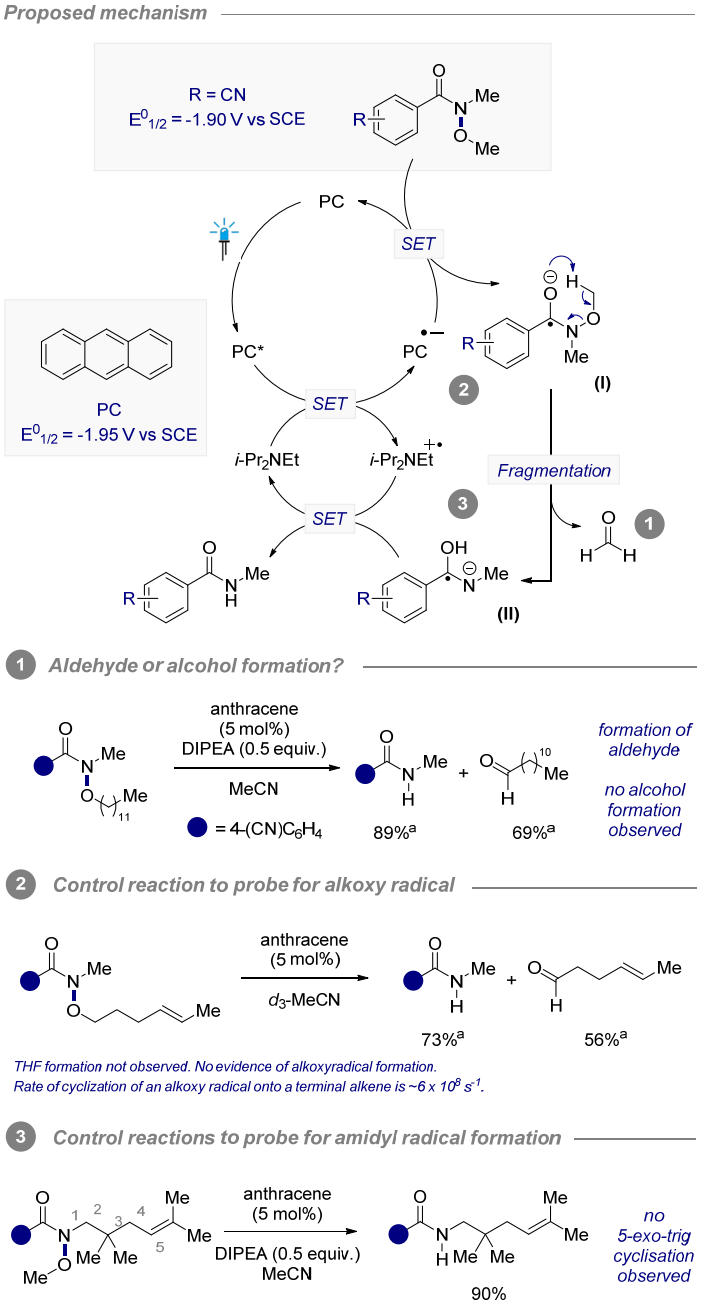


Figure 3. Postulated catalytic cycle and supporting mechanistic control experiments. [a] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

To construct and advance a postulated catalytic cycle, the reaction of **2a** (*p*-CN) and anthracene was further investigated (Figure 3). It was envisaged upon irradiation, the excited state of the anthracene photocatalyst would undergo photoinduced SET from a sacrificial reductant (DIPEA) via a reductive quenching cycle. The anthracene radical anion that is generated is a potent reducing agent ($E°_{1/2}$ = -1.95 V vs SCE) that can reduce Weinreb amide **1a** ($E°_{1/2}$ = -1.90 V vs SCE) to generate the ketyl radical (**I**). Upon a McLafferty-type β-fragmentation,[37] formaldehyde is released and radical anion **II** is formed. Following a final SET process, a secondary amide is generated with concomitant regeneration of DIPEA: this is consistent with the observation that DIPEA can be used in substoichiometric amounts (Table 1, entry 10). The possibility of intermediate **II** directly reducing excited-state anthracene cannot

be discounted. To establish that the process is redox neutral and that an aldehyde is generated, a Weinreb amide derivative with a modified (non-volatile) alkoxy group was exposed to the reaction conditions. The generation of the aldehyde in 69% is in line with the working hypothesis (Figure 3, part 1). To exclude the possibility of aldehyde formation via *in-situ* oxidation of the corresponding alcohol, various alcohols were exposed to the reaction conditions but no oxidation was observed (see ESI). To further support the involvement of a fragmentation mechanism, thereby distinguishing this from homolytic N-O bond cleavage,[21-24] a series of control experiments were performed. To exclude the possibility of alkoxy radical formation, a modified Weinreb amide with a pendant alkene was exposed to the standard conditions: both the product amide and aldehyde were formed in 73% and 56%, respectively with no cyclization product observed (Figure 3, part 2). The rates of such 5-*exo-trig* processes are known to be of the order of 6×10^8 s^{-1}.[38] Furthermore, a control substrate that would enable an amidyl radical[23] to be intercepted was exposed to the general conditions (Figure 3, part 3) but heterocycle formation was not observed. Collectively, these experiments, together with example **2n** (Figure 2), support the postulated catalytic cycle. To exclude the involvement of a 1,5-HAT process, a cyclopropyl radical clock experiment was conducted but after subjecting this material to the standard conditions, no stereomutation was observed and the corresponding aldehyde was obtained (please see the ESI for full details). In addition, UV-measurements indicate that neither EDA complex formation nor the *in situ* formation of an organic dye[39] is a causative factor in the catalysis (see ESI). Since the reaction also proceeds without the use of DIPEA (table 1, entry 1), an alternative oxidative quenching cycle cannot be excluded (see ESI). Stern-Volmer fluorescence quenching studies indicate that the photocatalyst can be quenched by both DIPEA and the substrate Weinreb amide with similar levels of efficiency (see ESI), and thus this possibility cannot be discounted. To further expand the scope of photoinduced single electron-transfer process (PET) to include electron rich substrates, it was necessary to confront the current redox limitations of anthracene. To complement the existing bandwidth, a CV investigation of electronically distinct Weinreb amides was conducted (Figure 4).

It was envisaged that Lewis acid activation could be leveraged to lower the reduction potential of previously unreactive substrates and facilitate the desired photocleavage of the N–O bond. $LiBF_4$ (LA) was chosen as an exogenous Lewis acid[40] and its competence was initially tested in CV experiments. As anticipated, the reduction potential of the phenyl, *p*-bromo and *p*-methyl substrate shifted to higher reduction potentials (Figure 4, part 3 for *p*-methyl, *p*-Br and phenyl (**B-C**) see ESI). Unfortunately, although the shifted reduction potentials are lower than that of anthracene, the desired product was only observed in trace amounts. Consequently, alternative reducing photocatalysts were considered. 4CzIPN has been demonstrated to be an attractive alternative to common transition metal-based photocatalysts due to its well-defined photophysical properties and a broad redox window.[41] Moreover, a seminal report by Wu and co-workers demonstrated that the redox window of 4CzIPN can be further expanded by a ConPET mechanism.[32] The radical anion formed upon excitation and subsequent reduction with an electron donor is long-lived and can undergo re-excitation to form a highly reducing species. We envisaged that this process utilizing a highly reductive excited catalyst radical anion could provide a solution to the obstinate challenge presented by this N–O bond cleavage event (Figure 4, part 5).

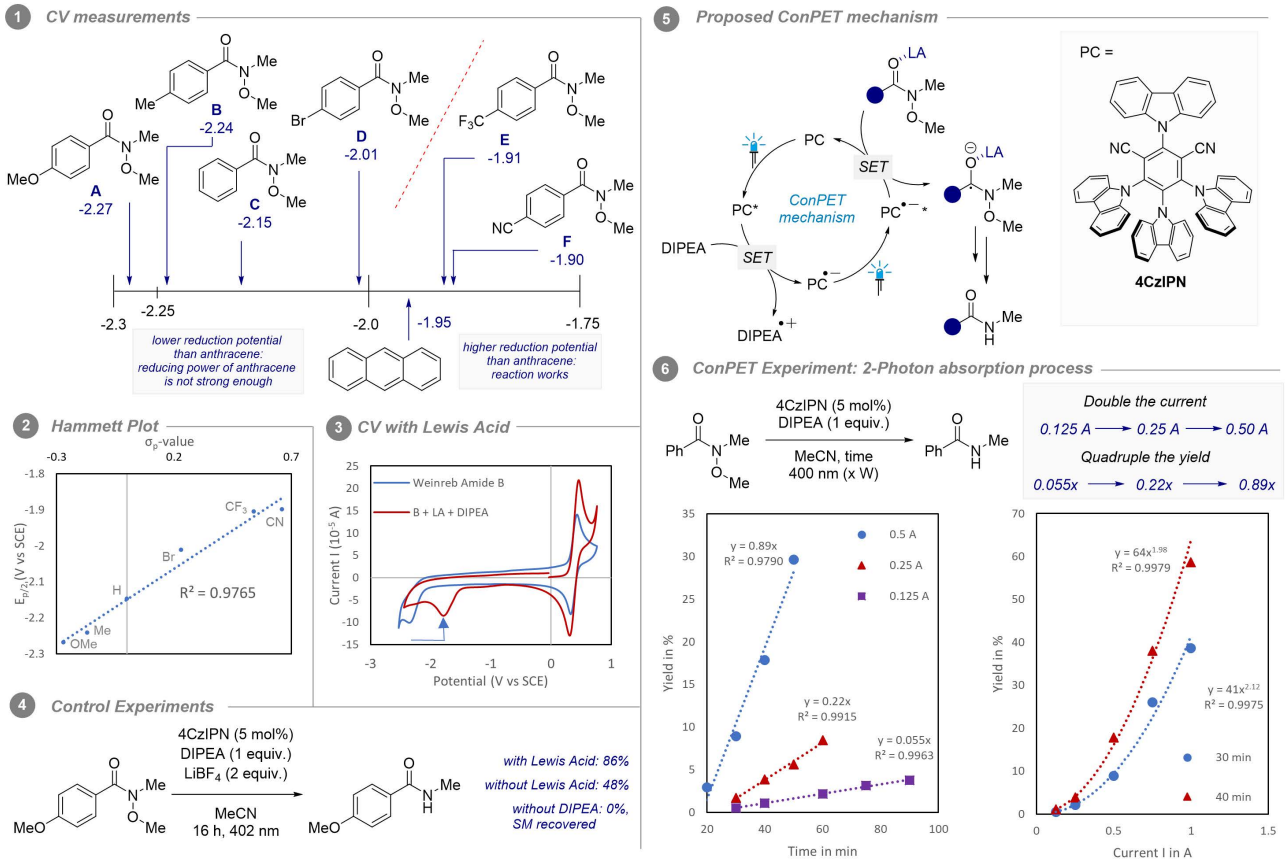


Figure 4. (1) CV measurements of selected Weinreb amides (measured using ferrocene as the internal standard). (2) The corresponding Hammett correlation of the measured reduction potentials against the Hammett values. (3) CV of Weinreb amides with Lewis acid and DIPEA shows a shift to lower reduction potentials which are still too high to be reduced by 4CzIPN. (4) Control experiment for 4CzIPN mechanism: reactions with and without Lewis Acid lead both to product formation, without DIPEA no product was formed. (5) Proposed ConPET mechanism. (6) A near quadratic dependency of the yield and the irradiation density supports the proposed ConPET hypothesis and the two-photon absorption process. R^2 is the coefficient of determination (goodness of fit).

These CV experiments support the experimental data observed above (Figure 4, part 1): electron rich substrates (**A-D**), which proved to be unreactive under the reaction conditions, have a higher reduction potential than the anthracene radical anion. Plotting the measured redox potentials against the Hammett σ_p parameters lends further support to this hypothesis ($R^2 = 0.98$) (Figure 4, part 2).

Following a short optimization process (see ESI), N-O cleavage conditions were identified that required 4CzIPN (5 mol%), $LiBF_4$ (2 equiv.) and DIPEA (1 equiv.) using 402 nm irradiation for 16 h. Control experiments in the absence of DIPEA (no product formation observed) or without the Lewis Acid (lower conversion noted) support the hypothesis (Figure 4, part 4). Further experimental proof of ConPET stems from a near quadratic dependency of the product formation and irradiation intensity (Figure 4, part 6).[42,43] By doubling the irradiation intensity, the product formation was quadrupled. This supports the two-photon excitation which is necessary for a ConPET mechanism to occur.

This advance allowed the initial substrate scope summarized in Figure 2 to be significantly expanded. As shown in Figure 5, a diverse range of functionalized electron-rich Weinreb amides were compatible with the modified procedure (up to 95% yield). Gratifyingly, these conditions also allowed the parent Weinreb amide (Ar = Ph) to be processed efficiently and smoothly to **2aa** (89%). Methylation and halogenation of the aryl group was generally well-tolerated (**2ab**-**2ai**, up to 89%), and the introduction of a proximal phenyl group to the *N*-center did not induce cyclization, enabling the biphenyl product **2aj** to be accessed (73%). Highly electron-rich substrates were compatible with the photocleavage conditions, enabling facile access to amides **2ak**, **2al**, and **2am** (86%, 84%, 36% respectively). More challenging examples include the diphenyl acetylene derivative **2an**, the furan **2ao** and the indole **2ap**. Gratifyingly, it was possible to induce direct N–O bond cleavage of the N-OH derivative (**2aa**, 35%) and to access the primary amide directly (**2aq**, 95%).

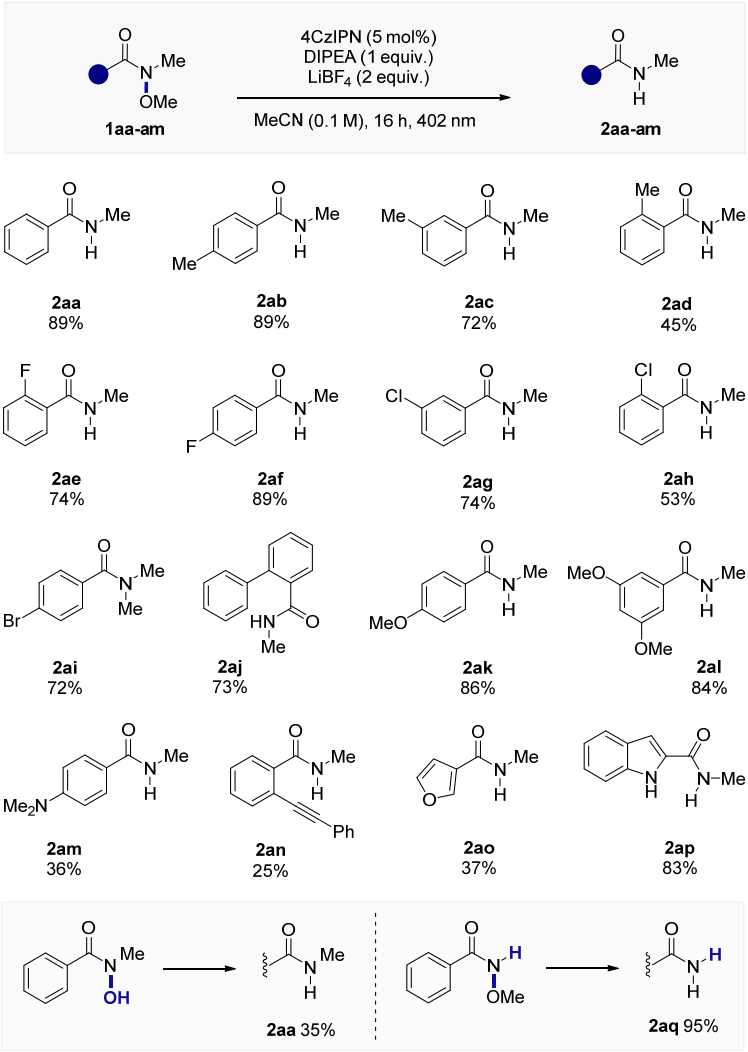


Figure 5. Photocatalytic N–O bond cleavage of electron rich Weinreb amides under the auspices of 4CzIPN.

To exploit the redox-neutral nature of the process, a series of cyclic substrates were exposed to the standard reaction conditions using anthracene. Successful cleavage to the protected aminoaldehyde not only supports the working hypothesis, but also provides a convenient platform to generate ambiphilic building blocks of varying chain length. This would complement Fischer´s remarkable

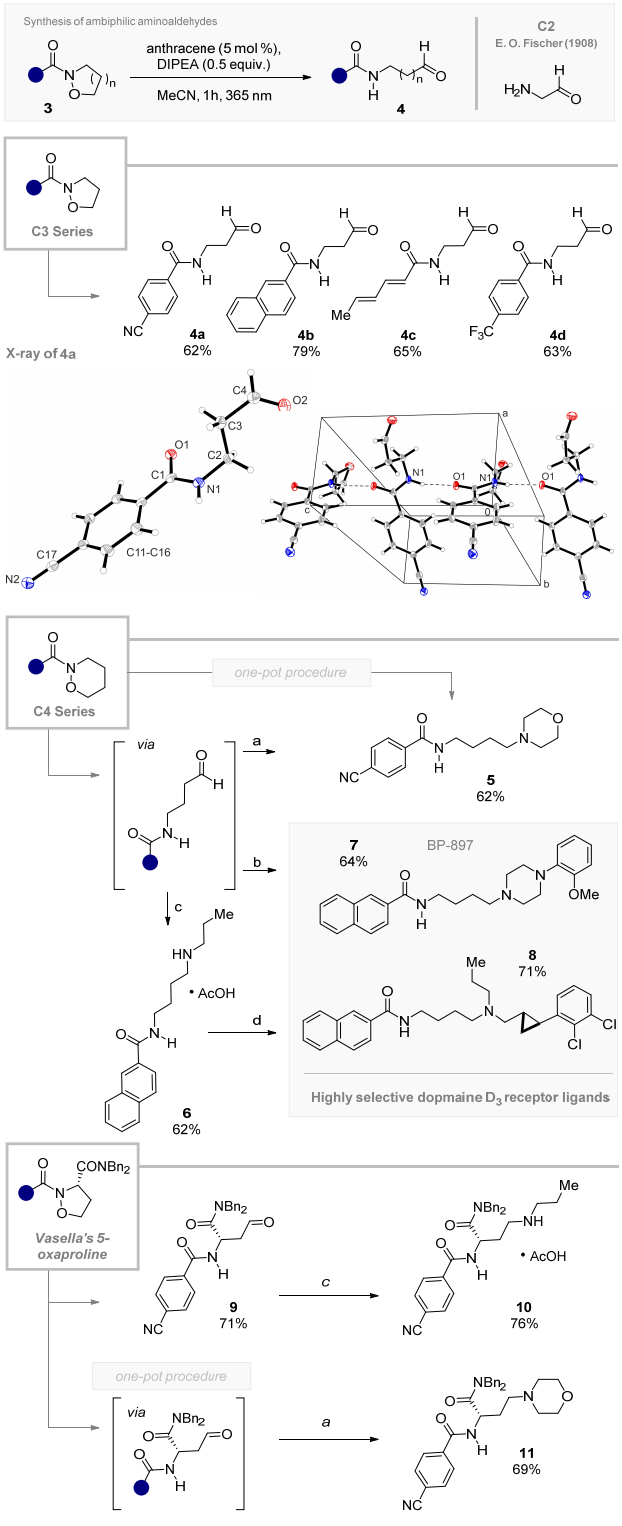
synthesis of aminoacetaldehye, a reaction lauded by Prof. Sir John Cornforth,[44,45] and enable access to the protected C_3 and C_4 congeners (Figure 6).

It was envisaged that exposure of synthetically versatile acyl 1,2-isoxazolidines[46] to the general reaction conditions would afford diverse amino aldehydes (**4a-d**), with the formyl handle enabling subsequent (bio)conjugation.[47] Product **4a** was generated in 62% yield and it was possible to unequivocally establish the molecular connectivity by single crystal X-ray analysis (Figure 6, CCDC 2173021).[48] By analogy, the naphthyl derivative **4b**, the diene **4c** and the *p*-CF_3 derivative **4d** were generated by direct N–O cleavage of the starting acyl isoxazolidines (up to 79% yield). To access the C4 series, which may be considered as masked GABA precursors,[49] acyl 1,2-oxazinanes were leveraged as convenient starting materials. However, isolation of the product aldehydes proved challenging and therefore they were generated *in situ* and used directly in a subsequent transformation.

A one-pot photocleavage ring-opening/reductive amination procedure was developed to access products **5-8** (up to 64% yield over two steps) in a single operation. Leveraging this strategy, it was possible to prepare the highly selective dopamine D_3 receptor ligands **7** (BP-897)[50] and **8**[51] in 64% and 71% yield, respectively (Figure 6, middle). Finally, an optically active 5-oxaproline analog[52] was exposed to the reaction conditions (Figure 6, low). It is pertinent to note that N–O bond cleavage of this motif was a key step in Vasella's total synthesis of Nojirimycin.[53] This strategy enabled the unnatural amino-acid aldehyde **9** to be formed smoothly in 71% yield. Reductive amination with *n*-propylamine generated the chiral 1,3-diamine **10** in good yield (76%). It was also possible to access morpholine **11** in good yield (69% after 2 steps) this one-pot protocol.

Conclusions

The selective cleavage of N-O(alkyl) bonds in acyclic and cyclic Weinreb amides is central to a plenum of enabling technologies in contemporary synthesis. Despite the lability of the bond, metal-based SET protocols continue to dominate the arsenal of methods typically employed. This often presents compatibility issues that limit functional group tolerance. To provide a mild, light-enabled alternative, a mechanism-guided approach based upon PET and ConPET platforms has been developed that harnesses anthracene and 4CzIPN as efficient organophotocatalysts. We demonstrate that the process is redox neutral through the formation of acylated amino aldehydes from cyclic substrates, and establish that amidyl radical formation is not operational. Inspired by Emil Fischer´s synthesis of aminoacetaldehyde, a series of homologated aminoaldehydes have been prepared from simple heterocyclic precursors. Finally, the method has been leveraged to generate highly selective dopamine D_3 receptor ligands and chiral 1,3-diamines. Given the popularity of linear ambiphilic derivatives in bioactive molecule design, notably in PROTAC molecules, it is envisaged that this mild N–O bond cleavage protocol will be enabling.



Conditions: (a) Morpholine (1.0 equiv.), $NaBH(OAc)_3$ (2.0 equiv.), AcOH (1.0 equiv.), THF (0.15 M). (b) 1-(2-Methoxyphenyl)piperazine (1.0 equiv.), $NaBH(OAc)_3$ (2.0 equiv.), AcOH (1.0 equiv.), THF (0.15 M). (c) Propylamine (5.0 equiv), $NaBH(OAc)_3$ (2.5 equiv.), AcOH (1.5 equiv.), THF (0.25 M). (d) 2-(2,3-dichlorophenyl)cyclopropane-1-carbaldehyde (1.0 equiv.), $NaBH(OAc)_3$ (2.0 equiv.), AcOH (1.0 equiv.), THF (0.075 M).

Figure 6. Mild generation of protected aminoaldehydes inspired by E. O. Fischer's 1908 synthesis of aminoacetaldehyde with Na amalgam. X-ray structure of **4a** (CCDC 2173021).

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