Perspective

Catalytic C-N Bond Forming Reactions Enabled by Proton-Coupled Electron Transfer Activation of Amide N-H Bonds

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Catalytic C-N Bond Forming Reactions Enabled by Proton-Coupled Electron Transfer Activation of Amide N-H Bonds

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ABSTRACT: Over the past three years, our group has become interested in the ability of proton-coupled electron transfer (PCET) to facilitate direct homolytic bond activations of common organic functional groups that are challenging substrates for conventional hydrogen atom transfer catalysts. This perspective details our efforts to develop oxidative PCET platforms for activating the strong N-H bonds of amides, providing catalytic access to synthetically useful amidyl radicals. We successfully identified compatible combinations of one-electron oxidants and Brønsted bases that, while unable to activate the amide substrates independently, act concomitantly with the requisite energetics to selectively homolyze the N-H bond via concerted PCET. The resulting amidyls were utilized in the development of new catalytic protocols for alkene carboamination and hydroamidation. We also highlight our efforts to develop a PCET-based bond-weakening protocol for the catalytic conjugate aminations using amide substrates. In this work, coordination to a Ti(III) catalyst significantly decreases the strength of a ligated amide N-H bond, enabling a facile PCET event to occur with the weak H-atom acceptor TEMPO. While this discussion focuses on amide activation, we anticipate that the design parameters presented here are general and should provide a framework for the development of PCET catalyst systems for other challenging homolytic bond activations as well.

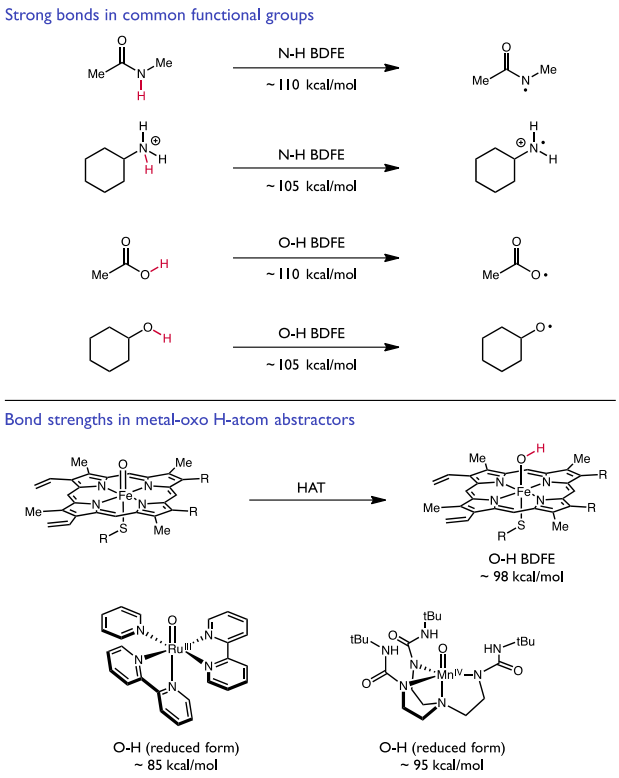
I. Introduction

Hydrogen atom transfer (HAT) reactions play a central role in organic free radical chemistry, enabling the direct generation of open-shell intermediates from unfunctionalized starting materials. While significant advances in HAT catalysis have been made in recent years,[1] there are currently no general catalytic methods for H-atom abstraction from many of the most common organic functional groups, such as the O-H bonds of aliphatic alcohols or the N-H bonds of amides.[2] This deficit is due in part to the fact that these polar E-H bonds are exceptionally strong, with bond dissociation free energies (BDFEs) often well in excess of 100 kcal/mol (Scheme 1).[3] As such, even the most powerful known molecular H-atom acceptor catalysts are not sufficiently reactive to effect efficient H-atom abstractions from these donor bonds, nor to selectively activate them in the presence of much weaker aliphatic C-H bonds that are often present in the same substrates.

Our group has recently become interested in the ability of concerted proton-coupled electron transfer (PCET) reactions to address these limitations and expand the scope of substrates amenable to homolytic bond activation in a catalytic manifold. In this perspective, we highlight several recent results relating to the development of oxidative PCET reactions of *N*-aryl amide substrates and applications of the resulting intermediates in catalytic C-N bond forming reactions.

II. Background

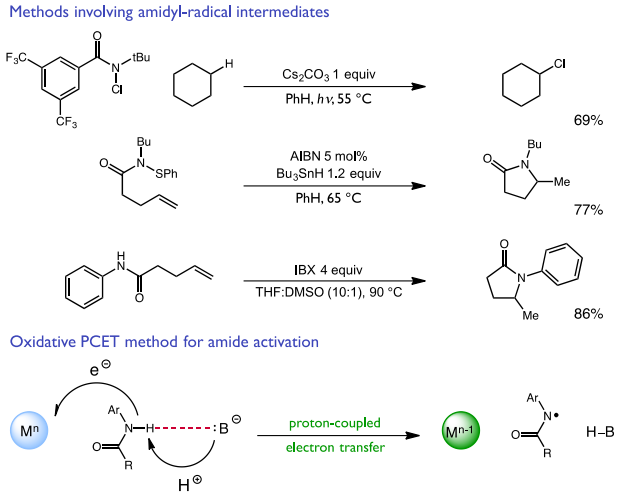
Amidyls are electrophilic, nitrogen-centered radicals that are key intermediates in a wide range of classical radical reactions, including olefin additions and remote C-H functionalization via directed H-atom abstraction.[4] Conventional methods for amidyl generation require either stoichiometric prefunctionalization of the amide to its corresponding *N*-halo-, *N*-nitroso-, or *N*-phenylthioamide derivative, or the use of strong stoichiometric oxidants (Scheme 2).[5] While powerful, these methods have requirements that may limit their applications in more complex contexts, where selective *N*-functionalization can be difficult to achieve. Moreover, as the activating group is often incorporated into the product, these approaches restrict the scope of possible transformations that can be accommodated. Accordingly, catalytic methods that enable the direct generation of amidyls from unfunctionalized amide N-H bonds are highly desirable.[6]



Scheme 1. BDFE values of common organic functional groups and examples of hydrogen atom abstractors

In considering these issues, we became aware of recent advances in the understanding and applications of proton-coupled electron transfer.[7] PCET reactions are unconventional redox processes that couple proton motion with an electron exchange event. PCET can occur in a stepwise manner, or in a concerted fashion wherein both particles are exchanged through a single transition state. In this framework, classical HAT reactions can be considered as a subset of concerted PCET reactivity in which the proton and electron travel jointly from a single bond in the donor to a single bond in the acceptor. Multisite concerted PCET reactions are also common, where the elec trons and protons travel to or from independent molecular acceptors and donors. While this type of concerted PCET activation has rarely been invoked in synthetic applications, it is now recognized to be an important mechanism for charge transfer in biological redox catalysis, playing a key role in photosynthetic water oxidation, oxygen reduction, ribonucleotide reduction, and DNA repair.[8] Similarly, PCET has been incorporated as a design feature in numerous synthetic inorganic catalysts for small molecule activations relevant to renewable energy concerns.[9]

Based on these precedents, we questioned whether oxidative PCET might serve as a viable mechanism for homolytic activation in organic synthesis as well. In particular, we hoped that several distinct mechanistic features of multisite PCET might enable the development of new catalytic methods for the selective homolysis of strong σ bonds found in many common organic functional groups,



Scheme 2. Established methods of amidyl generation and proposed oxidative PCET methods

including the N-H bonds of amides, that are not traditionally substrates for classical H-atom transfer activation. These efforts evolved out of prior work from our group on the reductive PCET activation of ketones to catalytically furnish neutral ketyl radicals that can participate in a variety of catalytic and enantioselective C-C bond forming reactions.[10] In the following section, we highlight several recent contributions from our lab toward the design and implementation of oxidative PCET-based mechanisms for amide N-H bond activation and the use of the resulting nitrogen-centered radical intermediates in the development of new catalytic C-N bond forming reactions.

III. Advantages of oxidative PCET activation

The goals above are predicated on several distinct features of multisite PCET mechanisms that are particularly well suited for strong bond activation. The first is that the thermochemistry of multisite PCET is highly modular and, in principle, covers a much broader range of energies than is possible with conventional H-atom acceptor technologies. To illustrate this point, it is useful to draw an analogy between the energetics of multisite PCET reactions and the conventions used to define the strengths of normal covalent bonds to hydrogen. Typically, BDFEs are evaluated using a thermodynamic cycle comprised of two readily accessible experimental parameters: pK_as and redox potentials. In this scheme, the BDFE is defined as the energy required to heterolytically break the bond (represented as a pK_a value) summed together with the energies required to oxidize the resulting anion to a neutral radical and reduce the remaining proton to H• (Figure 1).[11] In principle, this formalism provides actionable design parameters for engineering more reactive molecular HAT catalysts. For example, to create a more reactive molecular H-atom acceptor, one must make the abstracting species either a stronger one-electron oxidant, the resulting reduced state a stronger Brønsted base, or some combination thereof. Unfortunately, within a single molecule

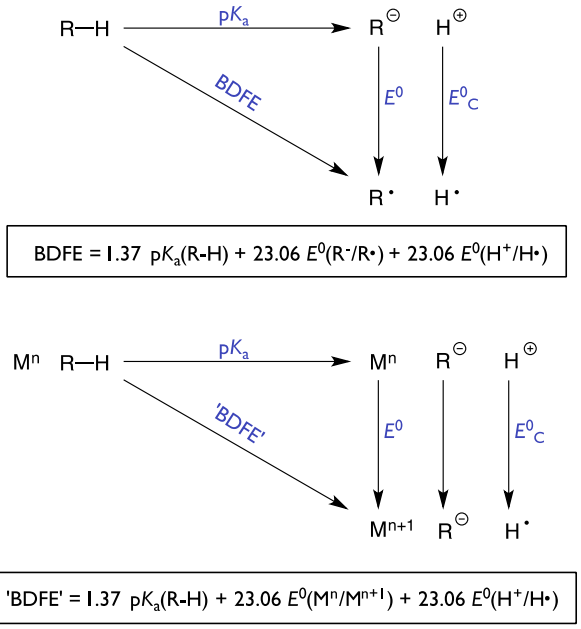


Figure 1. Thermodynamic cycle for the determination of formal BDFE values.

these two physical properties are inversely correlated and interdependent.[12] The energetic benefits of making an acceptor more oxidizing will be largely compensated for by a concomitant loss in basicity. Analogous difficulties arise in the design of new reductive HAT reagents, where in any increase in the acidity of an H-atom donor will be compensated in part by a correlated decrease in the reducing power of the conjugate base. These phenomena complicate the rational design of more powerful H-atom donors and acceptors through the variation of Brønsted acidity and redox potentials alone.

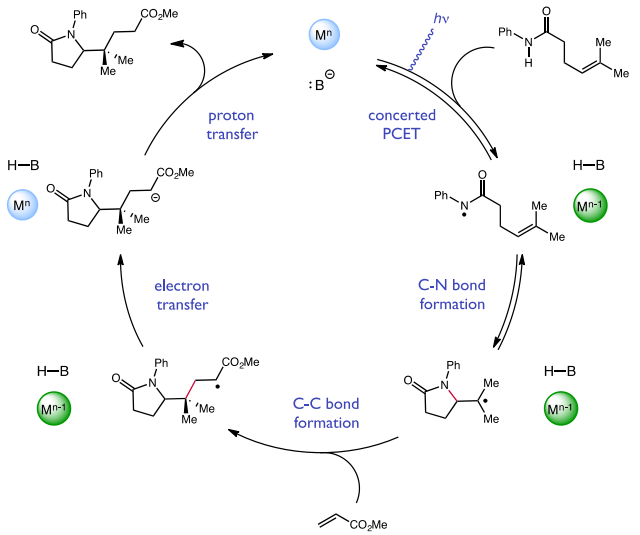
PCET provides a means for overcoming this intrinsic compensation problem. As described by Mayer and coworkers, the thermochemistry of multisite PCET reactions involving independent Brønsted bases and single electron oxidants can be described using an analogous thermochemical cycle (Figure 1) to the one described above, wherein the free energy on the diagonal is likened to an 'effective' bond strength.[13] This 'BDFE' value represents a quantitative measure of the strength of a bond that a given oxidant/base pair can break in a thermoneutral reaction. However, unlike the HAT process, the protons and electrons in a multisite PCET are site-decoupled and can be varied independently. As such, the effective BDFE can be tuned over an arbitrarily wide range of energies, including combinations that are thermodynamically competent to oxidize very strong σ bonds.

In addition to meeting the thermodynamic requirements for the homolysis of strong bonds, multisite PCET also provides a mechanism for their selective activation in the presence of much weaker aliphatic C-H bonds. Unlike classical HAT reactivity where the weakest bonds in a substrate are abstracted most rapidly, multisite PCET requires a pre-equilibrium hydrogen bond between the proton acceptor and the breaking bond prior to the electron transfer step.[14] Since most polar N-H and O-H bonds are excellent H-bond donors, we expected that it would be possible to homolyze them selectively.

Lastly, the rates of multisite PCET mechanisms can be significantly faster than the competing sequential transfer pathways.[15] As in electron transfer, PCET kinetics are functions, in part, of the net driving force for the transfer events. The concerted pathways lead directly to low energy products and avoid the higher energy intermediates formed along the stepwise reaction coordinates. When both stepwise intermediates are significantly high in energy relative to the reactants, the concerted pathways will often dominate, providing a mechanism for cooperative substrate activation by the oxidant-base pair under conditions where neither partner is competent to engage the substrate alone.[16] Taken altogether, these advantages provided the foundation for our initial studies on amide activation via PCET.

IV. Carboamination

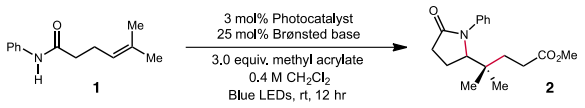
Our initial synthetic efforts focused on developing a new suite of catalytic olefin aminofunctionalization protocols. To begin, we focused on developing a novel catalytic method for olefin carboamination.[17] We envisioned a catalytic cycle wherein a Brønsted base first engages with a secondary anilide substrate via a hydrogen-bonded complex to facilitate the PCET process with the excited state of a visible light photoredox[18] catalyst (Scheme 3). The newly formed amidyl radical would then cyclize onto a pendant alkene to form a C-N bond and an adjacent carbon-centered radical. The nascent carbon-centered radical would then undergo addition to an acrylate acceptor to form a new C-C bond and an α-carbonyl radical.



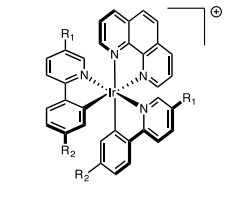
Scheme 3. Proposed catalytic cycle for PCET-based amidyl carboaminations

Subsequently, reduction of this electrophilic radical to an enolate by the reduced-state photocatalyst and favorable proton transfer from the conjugate acid would furnish the closed shell neutral product and regenerate the base and photoredox catalysts to complete the catalytic cycle.

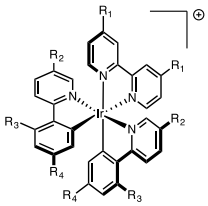
Table 1. Optimization of olefin carboamination



Entry	Photocatalyst	Base	'BDFE'	Yield (%)
1	$Ir(ppy)_2(phen)PF_6$	$NBu_4OP(O)(OBu)_2$	80	0
2	$Ir(Fmppy)_2(dtbbpy)PF_6$	lutidine	83	0
3	$Ir(Fmppy)_2(phen)PF_6$	DMAP	90	6
4	$Ir(ppy)_2(phen)PF_6$	NBu_4OBz	92	20
5	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$	lutidine	93	22
6	$Ir(Fmppy)_2(phen)PF_6$	NBu_4OBz	95	35
7	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	$NBu_4OP(O)(OBu)_2$	97	92
8	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	lutidine	98	24
9	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	DMAP	103	16
10	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	NBu_4OBz	108	50



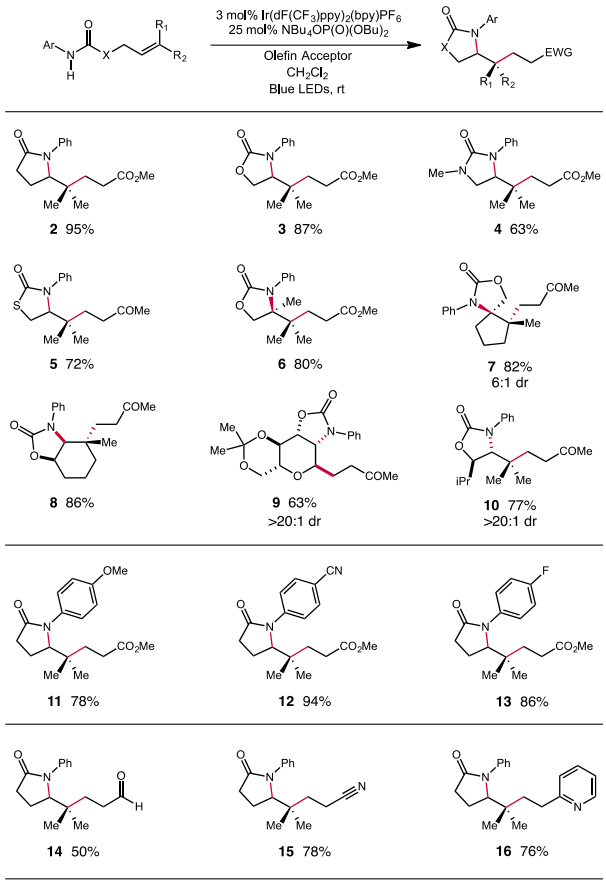
$Ir(ppy)_2(phen)$: R_1 = H, R_2 = H
$Ir(Fmppy)_2(phen)$: R_1 = Me, R_2 = F



$Ir(Fmppy)_2(dtbbpy)$: R_1 = t-Bu, R_2 = Me, R_3 = H, R_4 = F
$Ir(dF(CF_3)ppy)_2(dtbbpy)$: R_1 = t-Bu, R_2 = CF_3, R_3 = F, R_4 = F
$Ir(dF(CF_3)ppy)_2(bpy)$: R_1 = H, R_2 = CF_3, R_3 = F, R_4 = F

To assist in the identification of effective base/oxidant combinations competent to homolyze the anilide N-H bond (BDE ~ 100 kcal/mol), we made use of Mayer's effec tive bond-strength formalism.[12] Combinatorial evaluation of five Ir(III) photocatalysts and four Brønsted bases with effective BDFEs ranging from 80 kcal/mol to 110 kcal/mol resulted in product formation only in the cases where the effective BDFE is sufficiently close to or above the strength of the N-H BDFE of the anilide (Table 1). Remarkably, all of the iridium catalysts and all of Brønsted the bases were found to successful in at least one combination, even when their respective pK_as or redox potentials fall short of those required to act directly on the amide substrate. As in our early work with PCET of ketones, these results suggest that simple thermodynamic considerations can serve as a meaningful indicator of the feasibility of multisite activation with a given catalyst pair.[10]

From these results, we next explored the scope of the carboamination process using the optimal $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ / dibutyl phosphate catalyst pair with irradiation from blue light-emitting diodes (LEDs) (Scheme 4). These conditions enabled high yielding carboaminations of a variety of amide substrates, as well as structurally related *N*-aryl carbamates and ureas. In addition, this system is capable of accommodating a wide variety of olefinic partners, including hindered trisubstituted and tetrasubstituted alkenes that are often challenging substrates for metal-mediated carboamination protocols involving migratory insertion into a M-N bond.[19] In addition, more structurally complex systems can also be accommodated, generating spirocyclic and fused bicyclic systems, often with high diastereoselectivity. With regard to the *N*-arylamine component, we found that electron-rich, electron deficient, and heteroarene substrates were all well-accommodated. Of particular note, the potential for direct one-electron oxidation of the electron deficient *para*-CN carbamates is ~600 mV more positive that that of the Ir(III) excited state ($*E_{1/2}$ = +1.0 V vs Fc/Fc+ in MeCN),[20] highlighting the ability of coupled proton exchange to enable electron transfer reactions that are otherwise prohibitively endergonic.



Scheme 4. Substrate scope for olefin carboamination

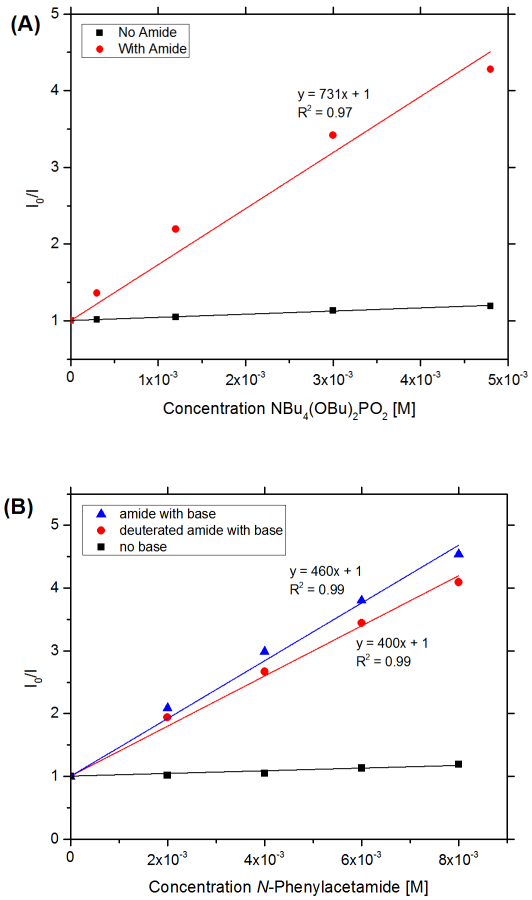
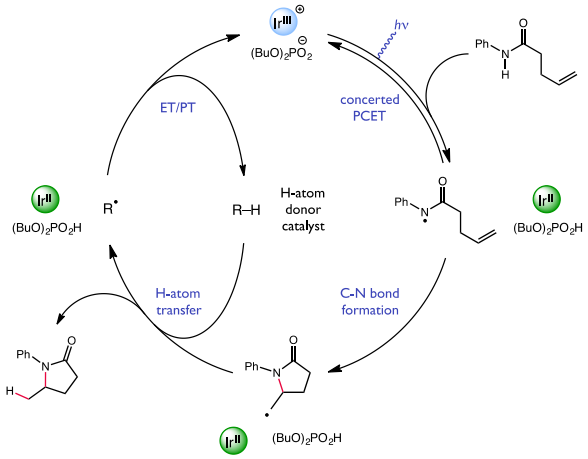


Figure 2. (A) Ir luminescence quenching (red dot) solution with constant *N*-phenylacetamide and varying concentrations of phosphate base (black square) solution with no *N*-phenylacetamide and varying concentrations of phosphate base. (B) Ir luminescence quenching (blue triangle) solution with constant phosphate base and varying concentrations of *N*-phenylacetamide (red dot) solution with constant phosphate base and varying concentrations of deuterated *N*-phenylacetamide (black square) solution with no phosphate base and varying concentrations of *N*-phenylacetamide.

Kinetic and spectroscopic results were found to be consistent with a concerted PCET mechanism for amidyl formation. Luminescence quenching experiments demonstrated that simple *N*-phenyl acetamide ($E_{1/2}$ = 1.2 V vs Fc/Fc+) does not measurably quench the excited state of the iridium photocatalyst, while the phosphate base alone is a weak quencher (k_{SV} = 41 M^{-1}). However, solutions containing both amide and phosphate lead to highly efficient quenching (k_{SV} = 731 M^{-1}) (Figure 2a). Further experiments demonstrated that excited state quenching exhibited a first-order kinetic dependence on the concentration of each component. Lastly, independent reactions of the N-H and N-D isotopologues of the amide substrate led to an isotope effect of 1.15, consistent with the notion that the labeled bond plays a specific role in the excited state quenching event (Figure 2b).[21] Both concerted PCET and stepwise, rate-limiting deprotonation of the *N*-phenyl acetamide by the phosphate base followed by oxidation of the anilide anion are consistent with these observations.



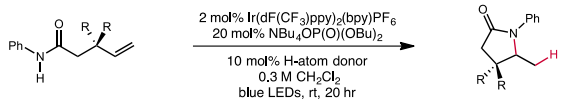
Scheme 5 Proposed catalytic cycle for PCET-based amidyl hydroamidation

However, the stepwise pathway was ruled out on thermodynamic grounds. Specifically, the large pK_a difference (pK_a ~ 20) between the substrate and base suggests that the N-H deprotonation would not be kinetically competitive with luminescent decay of the Ir(III) excited state (τ = 2.3 μs).[22] Taken together, these data are consistent with a concerted PCET mechanism of amidyl formation being operative in this carboamination protocol.

V. Hydroamidation

We sought to further extend the utility of this PCET-based platform for amidyl generation by developing a new catalytic method to an olefin hydroamidation.[23] As in the carboamination reaction, the proposed catalytic cycle for such a process begins with the same excited state Ir(III) photocatalyst and dialkyl phosphate base jointly activat-

Table 2. Optimization of olefin hydroamidation



Entry	R	H-atom donor	Yield (%)
1	H	None	24
2	Me	None	0
3	H	Phenol	18
4	H	2,4,6-tBu-phenol	19
5	H	4-Aminopyridine	21
6	H	Diphenyl acetonitrile	28
7	H	Ph_3SiH	16
8	H	Thiophenol	95
9	H	2-Naphthalenethiol	45
10	H	4-Trifluoromethyl thiophenol	86
11	H	2,4,6-iPr-thiophenol	83

ing an anilide N-H bond to generate the corresponding amidyl radical (Scheme 5). This species would then undergo addition to a pendant olefin to form a new heterocycle and an exocyclic alkyl radical. Unlike in the carboamination protocol, direct reduction of this radical to its corresponding anion via electron transfer with iridium(II) state of the catalyst is prohibitively endergonic. Instead, we reasoned that inclusion of an appropriate H-atom do-

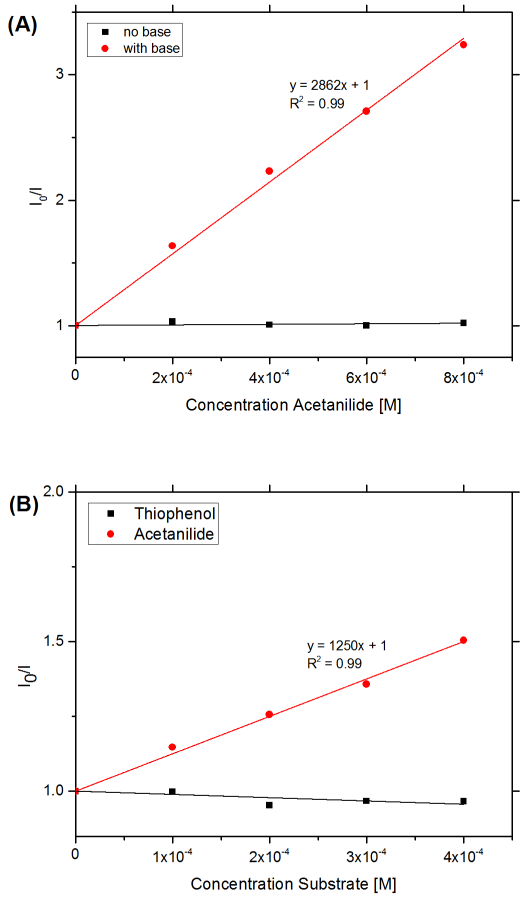
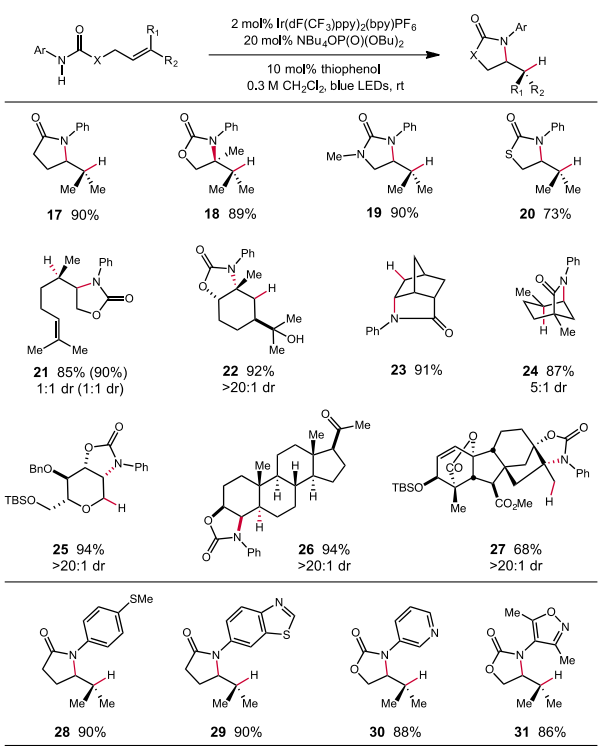


Figure 3. (A) Ir luminescence quenching (red dot) solution with constant phosphate base and varying concentrations of acetanilide (black square) solution with no phosphate base and varying concentrations of acetanilide. (B) Ir luminescence quenching (red dot) solution with constant phosphate base, constant thiophenol, and varying concentrations of acetanilide (black square) solution with constant phosphate base, constant acetanilide, and varying concentrations of thiophenol.

nor would reduce the carbon centered radical in a more favorable process, forming the desired hydroamidation product. Next, the oxidized form of the hydrogen-atom donor would accept an electron from the reduced form of the photocatalyst to form the corresponding anion. In turn, the anion would be protonated by the phosphoric acid produced during the PCET step to regenerate the active forms of all three catalytic components.

Within this scheme, we were initially concerned about the feasibility of effectively homolyzing a strong amide N-H bond in the presence of a conventional H-atom donor. Many HAT catalysts are known substrates for multisite PCET, while others might be expected to reduce the amidyl intermediate directly at the expense of productive C-N formation. Wary of these concerns, our initial trials demonstrated that upon irradiation of our model amide with blue LEDs in the presence of both phosphate base and iridium photocatalyst, the reaction mixture generated small amounts of the desired lactam together with equal amounts of unproductive substrate consumption in the absence of an added H-atom donor (Table 2, Entry 1). Further study suggests that following amidyl cyclization, the resulting carbon centered radical can abstract an H-atom from the weak, allylic C-H bonds present in the starting material. Consistent with this hypothesis, when these allylic C-H bonds were replaced with methyl groups, no product was observed (Table 2, Entry 2). Evaluation of a wide range of common H-atom donors, such as phenols, arylamines, diphenyl acetonitriles, and triphenyl silanes did not result in any meaningful enhancement over the background reaction (Table 2, Entries 3-7). However, simple thiophenol H• donors proved highly effective, with inclusion of as little as 10 mol% of thiophenol providing the desired hydroamidation product in 95% yield (Table 2, Entry 8). Initially, this result was surprising in the fact that aryl thiols are known substrates for multisite PCET activation and the S-H bond strength in thiophenol (BDFE ~ 79 kcal/mol) being more than 20 kcal/mol weaker than that of the amide substrate's N-H bond (BDFE ~99 kcal/mol).[24]

To study the selectivity for N-H versus S-H bond activation, a series of competitive luminescence quenching experiments were designed. As expected, neither the acetanilide nor the thiophenol alone were able to quench the excited state of the Ir photocatalyst (Figure 3a). However, solutions containing either the amide or thiol together with a phosphate base resulted in concentration-dependent luminescence quenching consistent with PCET activation (acetanilide k_{sv} = 2860 M^{-1} and thiophenol k_{sv} = 470 M^{-1}). However, in solutions containing varying concentrations of amide together with fixed concen-



Scheme 6. Substrate scope of olefin hydroamidation

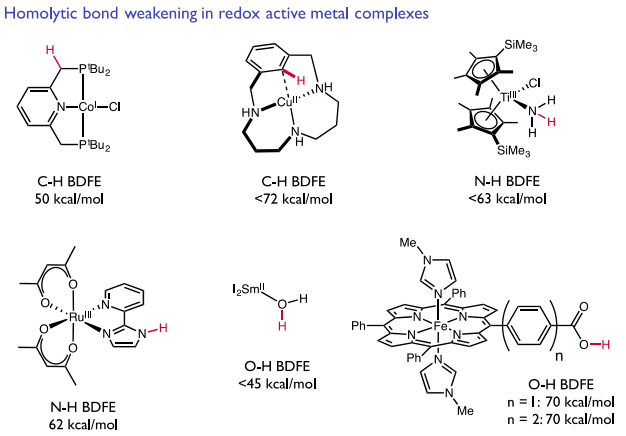
tration of thiol and phosphate, luminescence quenching retained a first-order kinetic dependence on the amide concentration, albeit with slightly reduced efficiency (k_{sv} = 1250 M^{-1}). However, analogous experiments employing varying concentrations of thiol and fixed concentrations of amide and phosphate exhibited no additional quenching above background (Figure 3b). These results provide strong support for amide activation via PCET as a kinetically dominant pathway for radical generation from the Ir(III) excited state. The origin for this selectivity likely resides within the differential hydrogen bond donor abilities between the amide and thiol moieties, a prerequisite for multisite PCET activation. Density functional calculations (ωB97XD 6-31G++(2d,2p)CPCM=CH_2Cl_2) indicate that formation of the amide-phosphate H-bond complex is more favorable than the corresponding thiophenol-phosphate H-bond complex by more than 5 kcal/mol, translating to a significantly higher concentration of the redox active amide-phosphate complex in solution.[25]

With respect to scope, we found that this catalytic hydroamidation process accommodates extensive modifications to the substrate backbone, olefin, and *N*-aryl substitution (Scheme 6). Hydroamidations of carbamates **18**, ureas **19**, and thiocarbamates **20** proceeded efficiently along with amide substrates under standard conditions. With respect to the olefin component, a wide variety of di-, tri-, and tetrasubstituted olefins with differing substitution patterns were all efficiently hydroamidated. In addition, electron-deficient, electron-rich, and heteroaryl amides substrates could also be accommodated. Lastly, even more complex natural product-derived substrates could be readily amidated in good yields, suggesting that this catalytic protocol may find use in the synthesis of more challenging targets as well.

The success of both our olefin carboamination and hydroamidation demonstrates that concerted multisite PCET can be effectively employed to both activate strong amide N-H bonds and utilize the resulting amidyl radical in efficient bond forming reactions. The homolytic activation of strong N-H bonds can be achieved with a combination of an oxidant and base that provides the necessary 'effective' bond strength. Moreover, we show that that the selectivity for the PCET event is governed in part by hydrogen bonding properties of the donor, enabling contrathermodynamic oxidations in the presence of much weaker C-H and S-H bonds.

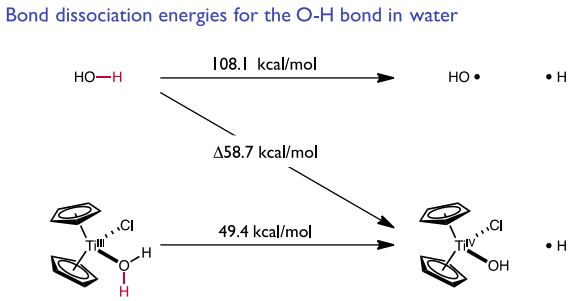
VI. Bond Weakening

While the studies above outlined our efforts to directly homolyze amide N-H bonds using multisite PCET, we have also explored an alternative method based on complexation-induced bond weakening. The ability of redox-active metals to homolytically weaken the bonds in coordinated ligands has been documented for a wide range of different metals and ligand-types.[26] Mechanistically, these processes function by kinetically coupling H-atom abstraction from a datively coordinated ligand to a one-electron oxidation of the metal center and formation of a



Scheme 7. Examples of homolytic bond weakening of ligands in redox active transition metals

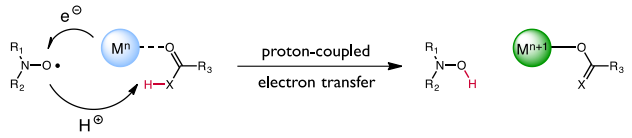
new covalent M-L bond. When favorable, these changes can provide the driving force necessary to enable the homolysis of normally strong bonds with comparatively weak H-atom acceptors. Often, the degree of destabilization can be dramatic (Scheme 7);[27] however, this general observation has not been systematically exploited in the development of new catalytic methods. In fact, the stoichiometric studies of Wood, Renaud, and Barrero on bond weakening in water-complexed alkyl boranes are among the only established synthetic examples.[28] We believed that these mechanisms might serve as the basis for a series of novel 'soft' hydrogen atom transfer reactions, wherein normally strong bonds in a metal-coordinated substrate could be formally abstracted using weak H-atom acceptors to form reactive organometallic intermediates that can be further utilized in subsequent bond forming processes.



Scheme 8. Cuerva's calculated BDE values for the O-H bond in water B3LYP/6-31G(d)

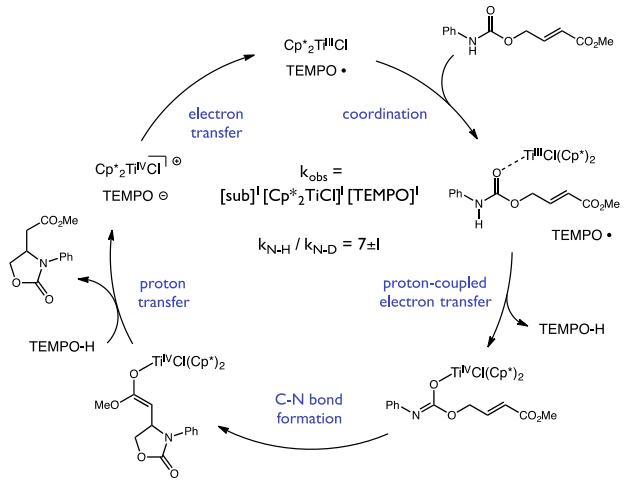
In line with the discussion above, we sought to develop catalytic C-N bonding forming reactions based on the 'soft homolysis' of amide N-H bonds.[29] In seeking catalyst platforms to examine for this chemistry, we elected to use TEMPO as the PCET oxidant given its ease of use and the strongly negative potentials required for its one-electron reduction. With respect to metal complexes, we were drawn to reports from Cuerva and coworkers demonstrating that the O-H bonds in water are weakened by nearly 60 kcal/mol when complexed to $Cp_2Ti(III)Cl$ (Scheme 8).[30] We questioned whether the N-H bonds in amide

compounds could be similarly weakened upon complexation, potentially enabling PCET activation by TEMPO radical in solution. Such a process would then generate a metallated aza-enolate nucleophile under completely neutral conditions in the absence of an identifiable Brønsted base. These intermediates could in turn serve as nucleophiles in subsequent C-N bond forming reactions.



Scheme 9. Complexation induced HAT with TEMPO via PCET

However, in considering this system, we were also cognizant of the work of Waymouth demonstrating that TEMPO reversibly forms a covalent adduct with an unusually weak Ti(IV)-O bond in its reactions with Cp_2TiCl.[31] We reasoned that this undesired reactivity might be avoided in the more sterically encumbered titanocene complexes, which would be too bulky to bind TEMPO as



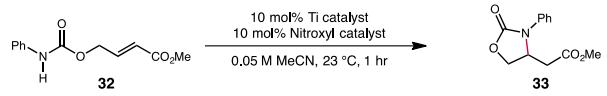
Scheme 10. Proposed catalytic cycle for bond-weakening induced conjugate amination

a ligand, but would still enable substrate binding and cooperative bond activation in combination with the nitroxyl oxidant (Scheme 9). In effect, such a process would constitute a single-electron analogue to the popular 'frustrated' Lewis pair catalyst systems, wherein the reactive catalyst components are sterically prevented from binding strongly to each other but are competent to jointly activate a ligated substrate.

We chose to test the feasibility of these ideas in the context of developing a new catalytic conjugate amination reaction. We proposed a catalytic cycle where an amide substrate first complexes with a titanocene(III) catalyst (Scheme 10). Next, TEMPO abstracts H• from the weak N-H bond of this complex via PCET. This step generates TEMPO-H and a closed-shell Ti(IV) aza-enolate intermediate that subsequently undergoes C-N bond formation with a pendant acrylate. TEMPO-H protonates the resulting titanium enolate to form the desired product and effects an electron transfer to generate Ti(III), thereby regenerating the catalysts.

We evaluated the validity of this scheme by screening a variety of differentially hindered titanocene catalysts in conjunction with TEMPO in the conjugate amination of *N*-aryl carbamate **32** (Table 3). Accordingly, $Cp_2Ti(III)Cl$

Table 3. Optimization of conjugate amination enabled by bond-weakening

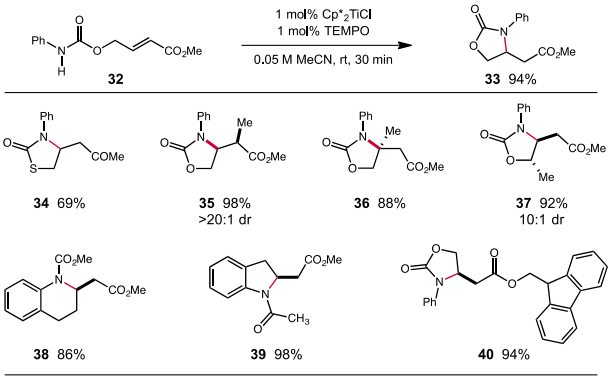


32 **33**

Entry	Ti catalyst	Nitroxyl catalyst	Yield (%)
1	Cp_2TiCl	TEMPO	0
2	$(t\text{-BuCp})_2TiCl$	TEMPO	0
3	CpCp*TiCl	TEMPO	95
4	Cp^*_2TiCl	TEMPO	98
5	Cp^*_2TiCl	AZADO	96
6	-	TEMPO	0
7	Cp^*_2TiCl	-	0
8	$Cp^*_2TiCl_2$	TEMPO	0
9	Cp^*_2TiCl (1 mol%)	TEMPO (1 mol%)	95

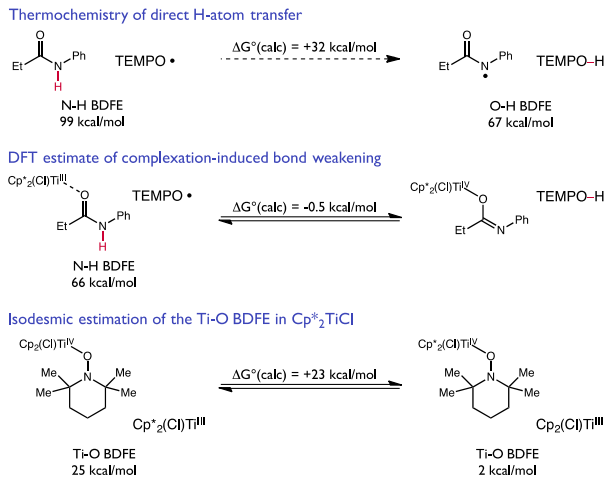
was not an effective catalyst, likely due to strong and unproductive complexation to TEMPO. However, the more reducing and hindered $Cp^*_2Ti(III)Cl$ and $Cp(Cp^*)Ti(III)Cl$ variants were highly effective, generating quantitative yields of product **33** in 1 h at room temperature (Table 3, Entries 3-4). Other nitroxyl radicals, such as AZADO, could be also be used without diminishing yields (Table 3, Entry 5).

Our optimal conditions for the Ti(III)-catalyzed conjugate amination of carbamate **32** gives the cyclized oxazol-



Scheme 11. Substrate scope for bond-weakening enabled conjugate amination

idinone product **33** in 94% yield (Scheme 11). The system is also amenable to substitution with other atoms, providing access to N-phenyl pyrrolidone, thiazolidinone, and imidazolidinones in good yields. One important note is the accommodation of a base-sensitive fluorenylmethyl ester (Fmoc) substrate **40** that successfully cyclized without a detectable loss of the protecting group. Notably, these conditions were not effective in cyclizing N-alkyl amides, suggesting that $Cp^*_2Ti(III)Cl$ does not weaken the



Scheme 12. Bond-weakening DFT calculations (UB3LYP 6-31G(d) CPCM(MeCN))

N-H bonds of those substrates (~110 kcal/mol) sufficiently for a favorable HAT with TEMPO.

Preliminary mechanistic studies and calculations are consistent with our proposed 'soft homolysis' mechanism of substrate activation. We first quantified the ability of $Cp^*_2Ti(III)Cl$ to weaken the anilide N-H bonds. The coordination of the Ti complex with *N*-phenyl propionamide

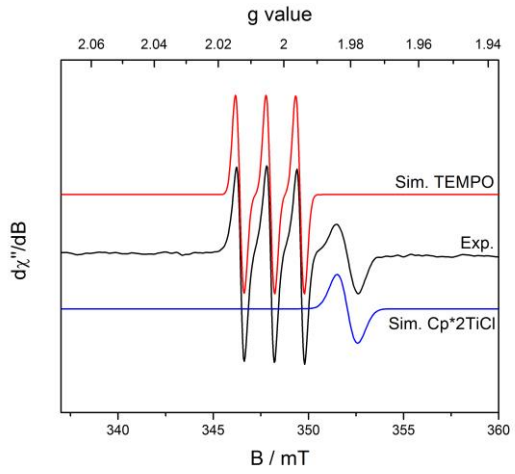


Figure 4. EPR spectra and simulations demonstrating compatibility of Cp*2TiCl and TEMPO in MeCN solution.

decreased the N-H bond strength from 99 to 66 kcal/mol, a weakening effect of 33 kcal/mol (Scheme 12). The destabilization effect is even greater in the N-H bonds of carbamate substrates, characterized by a 39 kcal/mol weakening. These BDFE values enable abstraction from the N-H bond to TEMPO to be energetically feasible (O-H BDFE TEMPO-H = 68 kcal/mol). Further DFT calculations indicated that Ti-O bond between $Cp^*_2Ti(III)Cl$ and TEMPO is extraordinarily weak, with a BDFE of only ~2 kcal/mol, some 23 kcal/mol less favorable than the Ti-O bond in the less hindered $Cp_2Ti(III)Cl$–TEMPO complexes reported by Waymouth.[31,32]

The lack of appreciable binding was further corroborated by EPR experiments (Figure 4). Specifically, favorable complexation of Ti(III) with TEMPO would result in a closed-shell Ti(IV) species that would be EPR silent.[31] However, spectra of solutions containing a 1:1 mixture of $Cp^*_2Ti(III)Cl$ and TEMPO exhibited signals identical to those of each component alone, suggesting that the free form of each catalyst is present in solution. Addition of carbamate to a solution of both catalysts also resulted in no observable EPR spectra changes, which suggests a solvent-bound resting state for the titanocene catalyst. Lastly, the rate of the catalytic reaction was found to exhibit first order kinetic dependence on the concentrations of the carbamate substrate, $Cp^*_2Ti(III)Cl$, and TEMPO. Additionally, a significant primary kinetic isotope effect of 7±1 was observed for the independent reactions of the substrate N-H and N-D isotopologues. Taken together, these results are consistent with a soft homolysis mechanism whereby $Cp^*_2Ti(III)Cl$ weakens an N-H bond followed by a rate-limiting abstraction by TEMPO.

VII. Conclusions

In this perspective, we have outlined the design and development of two mechanistically distinct catalytic platforms for the homolytic activation of strong N-H bonds using PCET. In the first approach, we relied on the ability of multsite PCET to decouple the electron and proton transfer sites to overcome the thermodynamic challenges typically associated with strong E-H bond activation, enabling the catalytic generation of amidyl radicals via rationally selected oxidant-base pairs. We demonstrated that the resulting amidyl radicals could be utilized in novel and efficient catalytic protocols for olefin carboaminations and hydroamidation. In addition, we developed an orthogonal PCET-based protocol for amide activation based on complexation-induced bond weakening. We illustrated the use of bond weakening as the mechanism of substrate activation in a catalytic conjugate amination process, whereby coordination to a simple Ti(III) catalyst decreases the bond strength of an amide N-H bond by more than 33 kcal/mol for facile HAT with TEMPO. Synthetically these processes enable the generation of metallated organometallic species under completely neutral conditions. Although this perspective only describes work relating to the activation of *N*-aryl amides, these PCET-based protocols are potentially amenable to the activation of many other common functional groups, as well, including the much stronger N-H bonds found in *N*-alkyl amides and the O-H bonds in alcohols. Efforts toward these goals are currently underway in our laboratory and will be reported in due course.

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The manuscript was written jointly by both authors.

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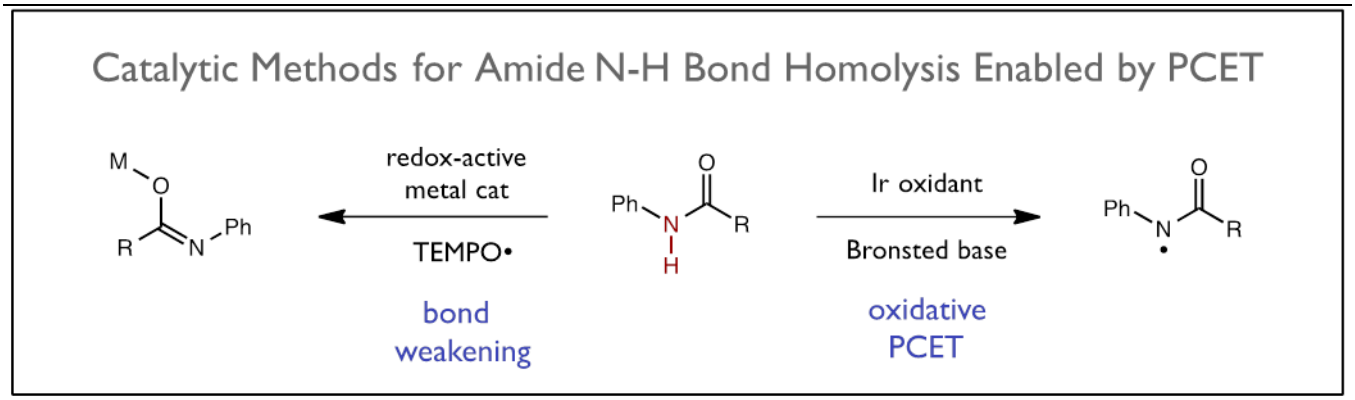

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