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Synthetic Applications of Proton-Coupled Electron Transfer

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Conspectus

Redox events in which an electron and proton are exchanged in a concerted elementary step are commonly referred to as proton-coupled electron transfers (PCETs). PCETs are known to operate in numerous important biological redox processes, as well as recent inorganic technologies for small molecule activation. These studies suggest that PCET catalysis might also function as a general mode of substrate activation in organic synthesis. Over the past three years, our group has worked to advance this hypothesis and to demonstrate the synthetic utility of PCET through the development of novel catalytic radical chemistries. The central aim of these efforts has been to demonstrate the ability of PCET to homolytically activate a wide variety of common organic functional groups that are energetically inaccessible using known molecular H-atom transfer catalysts.

To do so, we made use of a simple formalism first introduced by Mayer and coworkers that allowed us to predict the thermodynamic capacity of any oxidant/base or reductant/acid pair to formally add or remove H• from a given substrate. With this insight, we were able to rationally select catalyst combinations thermodynamically competent to homolyze the extraordinarily strong E-H σ-bonds found in many common protic functional groups (BDFEs >100 kcal/mol) or to form unusually weak bonds to hydrogen via the reductive action of common organic π-systems (BDFEs <35 kcal/mol). These ideas were reduced to practice through the development of new catalyst systems for reductive PCET activations of ketones and oxidative PCET activation of amide N-H bonds to directly furnish reactive ketyl and amidyl radicals, respectively. In both systems the reaction outcomes were found to be successfully predicted using the effective bond strength formalism, suggesting that these simple thermochemical considerations can provide useful and actionable insights into PCET reaction design.

The ability of PCET catalysis to control enantioselectivity in free radical processes has also been established. Specifically, multisite PCET requires the formation of a pre-equilibrium hydrogen-bond between the substrate and a proton donor/acceptor prior to charge transfer. We recognized that these H-bond interfaces persist following the PCET event, resulting in the formation of non-covalent complexes of the nascent radical intermediates. When chiral proton donors/acceptors are employed, this association can provide a basis for asymmetric induction in subsequent bond-forming steps. We discuss our efforts to capitalize on this understanding via the development of a catalytic protocol for enantioselective aza-pinacol cyclizations.

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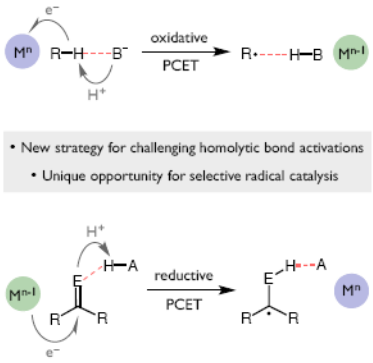
Lastly, we highlight an alternative PCET mechanism that exploits the ability of redox-active metals to homolytically weaken the bonds in coordinated ligands, enabling nominally strong bonds (BDFEs ~100 kcal) to be abstracted by weak H-atom acceptors with concomitant oxidation of the metal center. This ‘soft homolysis’ mechanism enables the generation of metallated intermediates from protic substrates under completely neutral conditions. The first example of this form of catalysis is presented in the context of a catalytic C-N bond forming reaction jointly mediated by bulky titanocene complexes and the stable nitroxyl radical TEMPO.

Graphical abstract



Introduction

Hydrogen atom transfer reactions are powerful elementary steps that directly generate free radical intermediates from simple starting materials. While this reactivity has created significant interest in the development of catalytic HAT reactions for the activation and functionalization of aliphatic C-H bonds,[1,2,3,4] analogous strategies for the homolytic activation of most common organic functional groups are largely unknown. For example, there are few or no general HAT methods for the direct homolytic activation of the O–H bonds of alcohols and carboxylic acids, the N–H bonds of amides, amines and ammonium ions, or reductive HAT to the π-bonds in ketones, imines and arenes (Figure 1). If successfully developed, such methods would enable straightforward access to a wide range of useful radical intermediates from their native functional group precursors, and simplify both the practical and strategic aspects of their use in synthesis.

However, intrinsic thermochemical constraints have limited the developments of such technologies.[5] Specifically, the addition of H• to an organic π-system, such as a ketone or imine, generates a new bond to hydrogen that is extraordinarily weak (BDFEs typically <35 kcal/mol) by virtue of being adjacent to an unpaired electron.[6] Accordingly, the generation of these intermediates requires H-atom exchange from a similarly weak donor bond. However, all known molecular H-atom donors exhibit BDFEs far above these values and characterized examples with BDFEs less than 50 kcal/mol are rare.[7,8,9] In a similar sense, many common protic functional groups, such as amides and alcohols, possess bonds to hydrogen with BDFEs well in excess of 100 kcal/mol. As such, even the most powerful molecular H-atom acceptors are typically unable to activate these strong E-H bonds, much less to selectively abstract them in the presence of weaker aliphatic C-H bonds.[10]

Over the past three years, our group has aimed to advance the use of concerted proton-coupled electron transfer (PCET) as an alternative mechanism for homolytic bond activation that overcomes these energetic limitations. PCETs are non-classical redox processes in which a proton and electron are exchanged in a concerted elementary step. Though uncommon in synthetic contexts, concerted PCET reactions are well documented, and play a key role in both biological redox catalysis[11] and inorganic technologies for small molecule activation.[12,13] Unlike classical HAT, wherein the proton and electron travel concurrently from a single donor to a single acceptor, the proton and electron in a multisite PCET mechanism can originate from two separate donors, or travel to two distinct acceptors. Both reaction classes produce identical free radical intermediates, but the scope of PCET reactions is potentially much broader due to its more expansive thermodynamic range.

To illustrate this point, it is useful to consider the energetic relationships commonly used to assess the strengths of bonds to hydrogen. These values are often described using a simple thermodynamic cycle (Figure 2a) in which the observed BDFE is equal to the sum of the energies needed to heterolytically break a given bond to hydrogen (represented as a pK_a value) and the energies required for the one-electron oxidation of the conjugate base to a neutral free radical R• and the reduction of H+ to H• (represented as redox potentials).[14,15] This correlation suggests that to engineer a more reactive H-atom donor one must increase the acidity of the donor bond, make its conjugate base more reducing, or some combination thereof. However, within any molecule, these two properties are intrinsically linked and diametrically opposed.[16] For example, to make a molecule more acidic one must typically introduce electron-withdrawing substituents. However, these groups will also necessarily diminish the reducing capacity of the conjugate base, and thus partially negate the bond weakening effect. Analogous arguments can be applied to the coupled oxidant/base properties of conventional H-atom abstractors.

Fortunately, the thermochemistry of multisite PCETs are not subject to the same compensatory constraints, and can be rationally varied over a much wider range of energies. This notion was elegantly expressed by Mayer, who noted that the thermodynamic capacity of any given oxidant/base (or reductant/acid) pair to serve as a formal H• acceptor (or donor) can be described using an identical thermochemical cycle (Figure 2b), wherein the free energy on the diagonal is referred to as an effective BDFE (denoted as ‘BDFE’ in this Account) and signifies the strength of a bond that can be formed or broken in a thermoneutral reaction using the prescribed catalyst pair.[17] As the pK_a and reduction potential are decoupled in this construct and can be varied independently, the range of accessible ‘BDFE’s extends far beyond what is possible using unimolecular HAT platforms, and in principle is limited only by the compatibility of the PCET reagents. In turn, this presents new opportunities to identify catalysts that are energetically competent to activate a range of functional groups that are not viable substrates for traditional H-atom transfer platforms. In addition, this effective BDFE formalism provides a simple criterion for identifying catalyst pairs that are thermochemically competent to activate a target bond – a powerful feature for the design of new PCET processes.

Multisite PCET also offers chemoselectivity that is orthogonal to that of conventional HAT mechanisms. While HAT selectivity is principally governed by reaction driving force, self-

exchange kinetics, and polar effects,[18,19] bond activation in PCET reactions requires the formation of a discrete hydrogen bond complex between the substrate and proton donor/acceptor prior to the electron transfer step (Figure 2c).[20] This constraint provides a pathway to selectively homolyze the stronger bonds to hydrogen found in polar protic functional groups, such as alcohols and amides, in the presence of weaker aliphatic C-H bonds that typically cannot form the requisite H-bonded complexes. In an analogous way, H-bond acceptor π-systems, such as ketones and imines, can be targeted selectively in the presence of less polar olefins despite a large thermochemical bias for C-H bond formation. Moreover, we reasoned that this critical H-bonding interaction would necessarily generate the nascent radical intermediates as catalyst-bound adducts. If these radical H-bonded complexes are sufficiently stabilizing and persistent, they present opportunities to direct the absolute stereoselectivity of the subsequent bond-forming events.

Lastly, the kinetic features of PCET are also advantageous, as the concerted transfer mechanisms are often significantly favored over the competing stepwise pathways (Figure 2d). In fact, the prevalence of PCET in enzymatic catalysis is often attributed to this feature, as it allows kinetically rapid redox events to occur in the absence of a significant overpotential. Moreover, the concerted pathways enable the cooperative use of oxidants and bases (or reductant and acids) with potentials and pK_a values far removed from those of the substrates they are activating. In turn, this enables radical generation under much milder reaction conditions than would be required to proceed through either sequential transfer pathway.

Taken altogether, these attributes suggest that concerted PCET might serve as a general mechanism for homolytic bond activation and provide a catalytic platform for the development of new synthetic methods. In the following sections we outline our recent progress toward this goal, and highlight the predictive role that simple thermochemical considerations can play in catalyst selection.

Catalytic Ketyl Generation Enabled by Reductive PCET

We first set out to develop PCET-based methods for the homolytic activation of ketones as a means to access neutral ketyl radicals. Ketyls are classical open-shell intermediates that have found extensive use in synthesis.[21] However, the strongly reducing conditions required to generate ketyls via outer sphere electron transfer (E = −2.48 V vs. Fc for acetophenone) has limited the development of catalytic and asymmetric variants.[22] Ketyl generation can formally be viewed as the addition of H• to a ketone π-system, though such a process would result in the formation of an exceptionally weak O-H bond (O-H BDFE = 26 kcal/mol for acetophenone ketyl). While no known molecular HAT catalyst is likely to successfully mediate such an exchange, the effective bond strength formalism suggests that such a value is easily accessible under the joint action of an independent one-electron reductant and Brønsted acid. Moreover, effective catalyst combinations could exhibit potentials and pK_a values energetically far removed from those of the ketone substrate, ensuring comparatively mild reactions conditions, so long as both partners function together in a concerted process.

These ideas were validated in the development of a new PCET-based method for the reductive coupling of ketones and electron-deficient olefins.[23] We envisioned a catalytic

cycle wherein initial electron transfer from a sacrificial amount of Hantzch dihydropyridine (HEH) to the excited state photocatalyst would lend a more reducing M^{n-1} ground state. Pre-equilibrium H-bonding between ketone **1** and the Brønsted acid catalyst could then facilitate electron transfer from the reduced photoredox catalyst to provide neutral ketyl intermediate **2** (Figure 3). This radical could then engage in C-C bond formation with an electrophilic olefin to produce a new radical intermediate **3** that could subsequently abstract a H-atom from the HEH to afford the desired carbocycle **4**. The resulting open-shell HEH species **5** could then undergo sequential one-electron oxidation and deprotonation with the excited state photocatalyst and conjugate base to close the catalytic cycle.

Upon evaluating a series of acid/reductant combinations with effective 'BDFE's ranging from 45 to 20 kcal/mol, we observed that effective bond strength considerations were uniformly successful in forecasting reaction outcomes (Table 1). Specifically, for any acid/reductant pair sufficiently close in energy to the strength of the ketyl O-H bond being formed in the process (26 kcal/mol), high yields of cyclized product were observed, consistent with efficient ketyl formation. However, no conversion was observed in combinations with effective BDFEs significantly above the 26 kcal/mol threshold. These results suggest that simple thermodynamic considerations could play a useful and predictive role in PCET catalysis, and serve as an enabling tool for rational catalyst selection.

Using $[Ru(bpy)_3](BAr_F)_2$ and diphenyl phosphoric acid ('BDFE' = 33 kcal/mol), we studied the scope of this process (Figure 4). These conditions were used to efficiently construct a variety of carbocyclic structures derived from aryl ketones and olefin acceptors (Figure 5). Interestingly, this reaction provides predominantly *cis*-fused products, in contrast to the *trans*-selectivity observed with SmI_2. Moreover, this PCET pair was competent to activate ketones with reduction potentials ~900mV more negative than the Ru(I) state of the photocatalyst ($E_{1/2}$ = -1.71V vs Fc), highlighting the ability of PCET to facilitate otherwise endergonic charge transfer steps. We also observed that use of 2-phenyl-dihydrobenzothaizoline (BT) as the stoichiometric reductant led to increased levels of *cis*-diastereoselectivity, suggesting that the C-C bond formation in these reactions is reversible and that the HAT steps play a direct role in stereoselection.

We also investigated the mechanism of ketyl formation in detail. Luminescence quenching experiments demonstrate that neither acetophenone nor diphenyl phosphoric acid were competent to quench the excited state of $Ir(ppy)_3$ ($E_{1/2}$ = -2.11V vs Fc), suggesting that direct electron transfer mechanisms are not operative. However, solutions containing both ketone and acid resulted in efficient quenching of the Ir(III) excited state, exhibiting a first-order dependence on the concentration of each component. In addition, an isotope effect of 1.22 ± 0.02 was observed upon using the deuterated isotopologue of the phosphoric acid, suggesting that the labeled bond plays a specific role in excited state deactivation.[24] Together, these findings are potentially consistent with either a rate-determining PT step or a concerted PCET. However, the former possibility could be discounted on energetic grounds, as the minimum free energy barrier for proton transfer (+17.9 kcal/mol) necessitates a maximum rate constant that is much too slow to be competitive with luminescent decay of the Ir(III) excited state lifetime (τ = 1.9 μs).

Enantioselective PCET Catalysis

Further consideration of the kinetic data above suggested that concerted PCET might also serve as an effective platform for asymmetric catalysis of radical reactions. Specifically, by coupling electron transfer to a pre-equilibrium hydrogen-bonding event, concerted PCET ensures that the radical intermediates will only be generated when they are pre-associated with the proton donor. If the successor H-bond complex formed between the conjugate base and the neutral ketyl following PCET is sufficiently stable to remain intact throughout the course of subsequent bond-forming events, we envisioned that use of a chiral Brønsted acid might render these reactions enantioselective.

We tested this hypothesis in the development of a catalytic asymmetric aza-pinacol cyclization.[25] The asymmetric coupling of ketones and imine derivatives is an attractive method to access enantioenriched amino alcohol scaffolds commonly found in pharmaceutical agents, ligand frameworks, and natural products. However, while such reductive couplings are well known in the radical literature, few catalytic or asymmetric variants had been reported previously. Subjecting ketohydrazones to conditions similar to the PCET-mediated ketyl-olefin coupling described above, we were able to access a wide variety of *cis*-amino alcohol products in generally excellent yields and enantioselectivities when chiral phosphoric acid **7** is utilized as the PT catalyst (Figure 5). These studies represent a rare example of a highly enantioselective bond-forming process mediated by a discrete hydrogen-bonding interaction between a chiral anion and a neutral free radical.[26]

Oxidative PCET

Based on the results above, we also sought to develop oxidative PCET processes for the homolytic activation of common protic functional groups that are not viable substrates for traditional H-atom transfer catalysts. To this end, we became interested in concerted PCET from simple amide N-H bonds as a direct means to access electrophilic amidyl radicals. Amidyls are versatile synthetic intermediates that participate in a variety of valuable olefin addition and C-H abstraction reactions.[27,28] However, traditional protocols for amidyl generation rely on the use of *N*-functionalized derivatives[29,30] or strongly oxidizing conditions[31] (Figure 6a). While serviceable, the requisite activating groups can be difficult to selectively install or carry through a multistep synthetic sequence, limiting the use of amidyl-based transforms in synthesis. Direct H-atom abstraction from an amide N-H bond represents a more attractive and potentially general approach. However, due to their exceptional homolytic stability (N-H BDFEs ~ 100–110 kcal/mol),[5] there are currently no reported molecular catalysts capable of abstracting H• from simple amide substrates.

Carboamination

We envisioned that concerted PCET might enable direct amidyl formation from native amide precursors via the dual action of a mild photo-oxidant and a weak Brønsted base (Figure 6b). Our initial efforts focused on the development of a catalytic method for alkene carboamination.[32] We imagined a catalytic cycle in which an appropriate oxidant/base combination would serve to homolyze the amide N-H bond in model anilide **8** to furnish a transient amidyl **9** (Figure 7). This resulting amidyl would then undergo C-N bond formation with a pendant olefin to form a new heterocycle and generate an alkyl radical intermediate

10. This nucleophilic carbon-centered radical could then be intercepted by an electrophilic acrylate acceptor to construct a new C-C bond and produce an α-carbonyl radical. Reduction of this radical via electron transfer from the reduced state of the photocatalyst and protonation of the resulting enolate by the conjugate acid of the catalytic base would furnish the desired carboamination product **12** and close the c cycle.

To aid in catalyst selection, we again made use Mayer's 'BDFE' formalism. Specifically, we anticipated photo-oxidant/base pairs with effective BDFE values similar in energy to the amide N-H bond being activated would be kinetically competent to mediate the desired oxidative PCET event. Combinatorial evaluation of five iridium photocatalysts and four Brønsted bases provided catalyst pairs with 'BDFE's ranging from 80 to 110 kcal/mol for the model carboamination reaction. While reactions that employed catalyst combinations with 'BDFEs' significantly less than the strength of the amide N-H bond being activated (BDFE ~ 98 kcal/mol) were ineffective, those pairs with 'BDFEs' approaching or exceeding this value all resulted in product formation (Figure 8). Moreover, each photocatalyst and base evaluated was a partner in at least one successful reaction, strongly suggesting that differences in reactivity are attributable to the ability of a given pair to activate the substrate N-H bond. These results further support the utility of the effective bond strength formalism as a guide for catalyst selection, and highlight the modularity and precise control of reaction energetics afforded by this approach.

From the oxidant/base pairs evaluated in this study, we elected to use the combination of $[Ir(dF(CF_3)\text{-}ppy)_2(bpy)]PF_6$ and dibutyl phosphate [$E_{1/2}$ ($*Ir^{III}/Ir^{II}$) = +1.0V vs Fc, pK_a ~13 in MeCN, 'BDFE' = 97) to evaluate the synthetic scope of the reaction (Figure 9). Carboamination of the model substrate **1** furnished amide **2** in 95% isolated yield after 18 hours of irradiation with blue LEDs. Carbamates and ureas were also excellent substrates, providing straightforward access to valuable amino alcohol and diamine derivatives from simple starting materials. This method was also found to accommodate a wide variety of olefinic partners, including substrates that furnish interesting bicyclic and spirocyclic products. The scope of aryl amine derivatives was also broad, and included electron-rich, electron-deficient, and heterocyclic examples, as well as substrates bearing *meta*- and *ortho*-substitutions. This protocol even enables oxidation of substrates with potentials up to 600 mV more positive than that of the Ir(III) excited state,[33] highlighting again the ability of simple H-bonding interactions to facilitate otherwise challenging charge transfer events.

To better understand the mechanism of amidyl formation, we again made use of luminescence quenching assays. Stern-Volmer analysis demonstrated that *N*-phenyl acetamide ($E_{1/2}$ = +1.2V vs. Fc) does not quench the excited state of $[Ir(dF(CF_3)\text{-}ppy)_2(bpy)]PF_6$, suggesting that direct electron transfer is not kinetically feasible. Next, we observed that while solutions of the dibutyl phosphate base alone exhibited modest quenching (K_{SV} = 41 M^{-1}), admixtures of phosphate and amide led to a marked increase in quenching efficiency (K_{SV} = 731 M^{-1}) and exhibited a first-order kinetic dependence on the concentration of each component. Deuterium labeling of the amide N-H bond resulted in a kinetic isotope effect of 1.15 ± 0.04, consistent with proton motion accompanying excited state deactivation.[23] These results are potentially consistent with either a PT or PCET mechanism, but the former can again be dismissed on thermochemical grounds. Specifically,

the large pKa difference between the anilide substrate and the dialkyl phosphate base (ΔG_{PT} = 27 kcal/mol) ensures that a rate-limiting proton transfer step would not be kinetically viable within the microsecond excited state lifetime of the Ir catalyst. These studies represent the first report of amide activation via concerted PCET, and suggest that other strong bond oxidations might also be feasible using similar design principles.

Hydroamidation

We next pursued the development of an amidyl-based method for alkene hydroamidation.[34] In this work, we imagined that the N-H PCET and C-N bond forming steps from the carboamination reaction could be retained. However, the resulting alkyl radical intermediate could instead be reduced by an appropriate H-atom donor catalyst to furnish a closed-shell hydroamidation product (Figure 10). The oxidized HAT catalyst could then undergo one-electron reduction and protonation by the reduced form of the photocatalyst and conjugate acid of the Brønsted base catalyst, respectively, to complete the catalytic cycle.

In considering this proposal, we were wary of whether the strong N-H amide bond could be selectively activated in the presence of a conventional H-atom donor that, by necessity, will exhibit a much weaker bond to hydrogen. Specifically, the H-atom donor could impede catalysis by either serving as a substrate for multisite PCET itself or via fast HAT reduction of key amidyl intermediate. In spite of these concerns, we conducted an evaluation of common H-atom donors for a model hydroamidation reaction, and were surprised to find that simple aryl thiols emerged as optimal catalysts for this process (Figure 10). Thiophenol is a known substrate for concerted PCET oxidation itself, and its S-H bond strength is nearly 20 kcal/mol weaker than the N-H bond of the amide substrate. To better understand the factors governing PCET selectivity in this reaction, we performed a series of competitive luminescence quenching experiments. These studies indicated that solutions containing only thiophenol or acetanilide did not affect the emission intensity of the Ir(III) excited state. However, addition of the phosphate base to these solutions led to linear excited-state quenching behavior, consistent with a PCET process. Next, we observed that varying the thiophenol concentration in the presence of constant acetanilide and phosphate produces no measurable concentration-dependent quenching. In contrast, when thiophenol and phosphate concentrations are kept constant and the amide concentration is varied, first-order quenching behavior is retained. These results suggest that when all the reaction components are present together in solution, contra-thermodynamic amide PCET is not only feasible, but is the kinetically dominant reaction pathway. A rationale for this surprising selectivity stems from the differential H-bond donor abilities of the amide and thiophenol (Figure 11). We reasoned that an aryl amide would form a much more favorable hydrogen-bonded complex with the phosphate base than thiophenol does. As pre-equilibrium H-bonding between the substrate and base is required prior to the electron transfer event, this more favorable complexation translates to a higher concentration of amide-phosphate complex in solution, providing a basis for the observed selectivity. This hypothesis was supported by DFT calculations (ωB97XD 6-31G++(2d,2p) CPCM = CH_2Cl_2), which indicated that the H-bonded amide is 5.2 kcal/mol more favorable than the H-bonded phosphate-thiol complex.

Bond Weakening Catalysis

In addition to the reactions described above, we have also become interested in a second PCET mechanism for strong bond activation based on complexation-induced bond weakening. Numerous reports describe the ability of redox-active transition metal complexes to destabilize the bonds in coordinated ligands.[35,36,37,38,39,40] These effects can be attributed to the favorable changes in metal oxidation state and ligand bond strengths that accompany H-atom abstraction from a coordinated substrate. The degree of destabilization can be marked, with select examples exhibiting weakening effects of more 60 than kcal/mol (Figure 12a). While this phenomenon has been observed for many different metals, bond types, and ligand platforms, the exploitation of homolytic bond weakening as a mechanism of substrate activation in catalysis has not been extensively explored.[41,42] We envisioned that this bond-weakening strategy might prove to be a general elementary step that could enable the 'soft homolysis' of normally strong bonds using comparably weak H-atom acceptors via PCET (Figure 12b). The synthetic value of such processes would stem from their ability to furnish metallated intermediates from simple E-H and C-H bond precursors in the absence of an identifiable Brønsted base.

To test these ideas, we elected to explore a catalytic conjugate amination reaction enabled by the 'soft homolysis' of amide N-H bonds (Figure 12b).[43] In this scheme coordination of the amide substrate to a redox-active metal would weaken the N-H bond sufficiently that it could be abstracted by a weak H-atom acceptor. If successful, this elementary step would furnish a metallated aza-enolate intermediate that could then undergo addition to an electron-deficient olefin acceptor. In considering potential metal catalysts, we were drawn to the work of Cuerva and later Gansauer, [44,45] who demonstrated that the strong O-H bond in water is weakened by nearly 60 kcal/mol upon coordination with a reduced titanocene complex, $Cp_2Ti(III)Cl$. We postulated that if ligation of amides to a Ti^{III} complex could produce a similar N-H weakening, then we could potentially perform hydrogen atom abstraction using a weak H-atom acceptor. This PCET event would result in a Ti(IV)-bound aza-enolate species competent to act as a nucleophile in subsequent bond formation.

With respect to the H-atom acceptor, the nitroxyl TEMPO was selected due to its commercial availability and ease of handling, as well as the strongly negative potentials required for its one-electron reduction ($E_{1/2}$ = −1.95V vs Fc). However, we were also cognizant of work from Waymouth and coworkers demonstrating that TEMPO can form stable covalent Ti(IV) complexes with Cp_2TiCl – albeit with a weak Ti-O bond (BDFE 25 kcal/mol).[46] These authors also demonstrated that the strength of this Ti-O bond could be diminished by increasing the steric bulk of the ancillary ligands on titanium. With this in mind, we hypothesized if the ligand set was sufficiently large, coordination to a bulky ligand such TEMPO might become unfavorable on steric grounds, while binding to smaller substrate molecules could still occur. Such a system would represent an interesting homolytic counterpart to "frustrated" Lewis pairs, as the two open-shell catalysts cannot directly bind with one another, but are able to function jointly to activate a bound substrate.[47]

We envisioned a catalytic cycle (Figure 13) wherein coordination of the model amide **13** to a bulky titanocene catalyst would induce a sufficient bond-weakening effect to enable the abstraction of this normally strong N-H bond (BDFE ~ 99 kcal/mol) by the persistent radical TEMPO (TEMPO-H O-H BDFE ~ 67 kcal/mol). This PCET event would produce TEMPO-H and a Ti^{IV} aza-enolate species **14** that could undergo addition to an electron-deficient olefin and isomerize to generate a new titanium enolate **15**. TEMPO-H could then protonate **15** to afford the desired product **16**, and furnish a highly reducing nitroxide anion that is thermochemically competent to reduce Ti(IV) to Ti(III) and close the catalytic cycle.

In accord with our design hypothesis, unsubstituted titanocene complexes such as Cp_2TiCl proved to be ineffective catalysts (Table 2, Entries 1-2). However, more sterically encumbered titanocenes, such as Cp^*_2TiCl or Cp*(Cp)TiCl worked well, furnishing the desired product **16** in excellent yields in the presence of a TEMPO co-catalyst (Table 2, Entries 3-4). This dual catalytic system was able to cyclize *N*-aryl amides, carbamates, ureas, and thiocarbonates with consistently high efficiencies and could even tolerate base-sensitive groups such Fmoc-protected acrylates. Related Ti(IV) complexes were found to be catalytically inactive.

Numerous experimental and theoretical studies support the proposed ‘soft homolysis’ mechanism of substrate activation. DFT calculations determined that coordination of *N*-phenyl propionamide to Cp^*_2TiCl decreased the strength of the N-H bond from 99 kcal/mol to 66 kcal/mol. This degree of weakening is sufficient to enable a thermoneutral H-atom exchange with TEMPO. In addition, we also confirmed that the Cp^*_2TiCl and TEMPO could exist together in solution. Specifically, EPR spectroscopy demonstrated that 1:1 admixtures of the nitroxyl and the bulky Ti(III) complex retained the spectral features of each component, suggesting that each was concurrently present in solution. In support of this finding, DFT calculations illustrated that the Ti-O BDFE in the complex between TEMPO is only ~2 kcal/mol.

Conclusions

We are hopeful that these collective studies not only demonstrate the feasibility and potential benefits of concerted PCET activation in synthesis, but also provide a framework for their subsequent expansion to include increasingly more challenging substrate classes and bond constructions. Prospectively, we anticipate that many other functional groups can also be activated via concerted PCET, and we are optimistic that these protocols will represent a valuable new area of synthetic research and development.

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References

1. Chen MS, White MC. Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. Science. 2010; 327:566–571. [PubMed: 20110502]

2. Liu W, Huang X, Cheng M-J, Nielsen RJ, Goddard WA III, Groves JT. Oxidative Aliphatic C-H Fluorination with Fluoride Ion Catalyzed by a Manganese Porphyrin. Science. 2012; 337:1322–1325. [PubMed: 22984066]
3. Smith DM, Pulling ME, Norton JR. Tin-Free and Catalytic Radical Cyclizations. J Am Chem Soc. 2007; 129:770–771. [PubMed: 17243807]
4. Iwasaki K, Wan KK, Oppedisano A, Crossley SWM, Shenvi RA. Simple, Chemoselective Hydrogenation with Thermodynamic Stereocontrol. J Am Chem Soc. 2014; 136:1300–1303. [PubMed: 24428640]
5. Luo, YR. Handbook of Bond Dissociation Free Energies in Organic Compounds. CRC Press; Boca Raton, FL: 2003.
6. Blanksby SJ, Ellison GB. Bond Dissociation Energies of Organic Molecules. Acc Chem Res. 2003; 36:255–263. [PubMed: 12693923]
7. Choi J, Pulling ME, Smith DM, Norton JR. Unusually Weak Metal-Hydrogen Bonds in HV(CO)4(P-P) and Their Effectiveness as H Donors. J Am Chem Soc. 2008; 130:4250–4252. [PubMed: 18335937]
8. Pannewitz A, Wenger OS. Proton-Coupled Electron Transfer from the Excited State of a Ruthenium(II) Pyridylimidazole Complex. Phys Chem Chem Phys. 2016; 18:11374–11382. [PubMed: 27094541]
9. Van der Eide EF, Helm ML, Walter ED, Bullock RM. Structural and Spectroscopic Characterization of 17- and 18-Electron Piano-Stool Complexes of Chromium. Thermochemical Analyses of Weak Cr-H Bonds. Inorg Chem. 2013; 52:1591–1603. [PubMed: 23343354]
10. Green MT, Dawson JH, Gray HB. Oxoiron(IV) in Chloroperoxidase Compound II is Basic: Implications for P450 Chemistry. Science. 2004; 304:1653–1656. [PubMed: 15192224]
11. Reece SY, Hodgkiss JM, Stubbe J, Nocera DG. Proton-Coupled Electron Transfer: the Mechanistic Underpinning for Radical Transport and Catalysis in Biology. Phil Trans R Soc, B. 2006; 361:1351–1364. [PubMed: 16873123]
12. Weinberg DR, Gagliardi CJ, Hull JF, Murphy CF, Kent CA, Westlake BC, Paul A, Ess DH, McCafferty DG, Meyer TJ. Proton-Coupled Electron Transfer. Chem Rev. 2012; 112:4016–4093. [PubMed: 22702235]
13. Hammes-Schiffer S. Theory of Proton-Coupled Electron Transfer in Energy Conversion Processes. Acc Chem Res. 2009; 42:1881–1889. [PubMed: 19807148]
14. Bordwell FG, Cheng J-P, Harrelson JA. Homolytic Bond Dissociation Energies in Solution from Equilibrium Acidity and Electrochemical Data. J Am Chem Soc. 1988; 110:1229–1231.
15. Breslow R, Chu W. Thermodynamic Determination of pK_a's of Weak Hydrocarbon Acids Using Electrochemical Reduction Data. J Am Chem Soc. 1973; 95:411–418.
16. Warren JJ, Tronic TA, Mayer JM. Thermochemistry of Proton-Coupled Electron Transfer Reagents and its Implications. Chem Rev. 2010; 110:6961–7001. [PubMed: 20925411]
17. Waidmann CR, Miller AJM, Ng C-WA, Scheuermann ML, Porter TR, Tronic TA, Mayer JM. Using Combinations of Oxidants and Bases as PCET Reactants: Thermochemical and Practical Considerations. Energy Environ Sci. 2012; 5:7771.
18. Warren JJ, Mayer JM. Predicting Organic Hydrogen Atom Transfer Rate Constants Using Marcus Cross Relation. Proc Natl Acad Sci USA. 2010; 107:5282. [PubMed: 20215463]
19. Roberts BP. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. Chem Soc Rev. 1999; 28:25–35.
20. Sjödin M, Irebo T, Utas JE, Lind J, Merényi G, Åkermark B, Hammarström L. Kinetic Effects of Hydrogen Bonds on Proton-Coupled Electron Transfer from Phenols. J Am Chem Soc. 2006; 128:13076–13083. [PubMed: 17017787]
21. Edmonds DJ, Johnston D, Procter DJ. Samarium(II)-Iodide-Mediated Cyclizations in Natural Product Synthesis. Chem Rev. 2004; 104:3371–3404. [PubMed: 15250745]
22. Fukuzumi S, Ishikawa K, Hironaka K, Tanaka T. Acid Catalysis in Thermal and Photoinduced Electron-Transfer Reactions. J Chem Soc Perkin Trans II. 1987:751–760.
23. Tarantino KT, Liu P, Knowles RR. Catalytic Ketyl-Olefin Cyclizations Enabled by Proton-Coupled Electron Transfer. J Am Chem Soc. 2013; 135:10022–10025. [PubMed: 23796403]

24. Edwards SJ, Soudackov AV, Hammes-Schiffer S. Analysis of Kinetic Isotope Effects for Proton-Coupled Electron Transfer Reactions. J Phys Chem A. 2009; 113:2117–2126. [PubMed: 19182970]
25. Rono LJ, Yayla HG, Wang DY, Knowles RR. Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. J Am Chem Soc. 2013; 135:17735–17738. [PubMed: 24215561]
26. Sibi MP, Manyem S, Zimmerman J. Enantioselective Radical Processes. Chem Rev. 2003; 103:3263–3296. [PubMed: 12914498]
27. Horner JH, Musa OM, Bouvier A, Newcomb M. Absolute Kinetics of Amidyl Radical Reactions. J Am Chem Soc. 1998; 120:7738–7748.
28. Li Z, Song L, Li C. Silver-Catalyzed Radical Aminofluorination of Unactivated Alkenes in Aqueous Media. J Am Chem Soc. 2013; 135:4640–4643. [PubMed: 23506151]
29. Schmidt VA, Quinn RK, Brusoe AT, Alexanian EJ. Site-Selective Aliphatic C-H Bromination Using *N*-Bromoamides and Visible Light. J Am Chem Soc. 2014; 136:14389–14392. [PubMed: 25232995]
30. Newcomb M, Esker JL. Facile Production and Cyclizations of Amidyl Radicals. Tetrahedron Lett. 1991; 32:1035–1038.
31. Nicolaou KC, Baran PS, Zhong Y-L, Barluenga S, Hunt KW, Kranich R, Vega JA. New Routes to Heterocyclic Compounds via *o*-Iodoxybenzoic Acid-Mediated Cyclizations: Generality, Scope, and Mechanism. J Am Chem Soc. 2002; 124:2233–2244. [PubMed: 11878977]
32. Choi GJ, Knowles RR. Catalytic Alkene Carboaminations Enabled by Oxidative Proton-Coupled Electron Transfer. J Am Chem Soc. 2015; 137:9226–9229. [PubMed: 26166022]
33. Hanss D, Freys JC, Bernardinelli G, Wenger OS. Cyclometalated Iridium(III) Complexes as Photosensitizers for Long-Range Electron Transfer: Occurrence of a Coulomb Barrier. Eur J Inorg Chem. 2009; 32:4850–4859.
34. Miller DC, Choi GJ, Orbe HS, Knowles RR. Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer. J Am Chem Soc. 2015; 137:13492–13495. [PubMed: 26439818]
35. Chciuk TV, Flowers RA II. Proton-Coupled Electron Transfer in the Reduction of Arenes by SmI_2-Water Complexes. J Am Chem Soc. 2015; 137:11526–11531. [PubMed: 26273964]
36. Mader EA, Manner VW, Markle TF, Wu A, Franz JA, Mayer JM. Trends in Ground-State Entropies for Transition Metal Based Hydrogen Atom Transfer Reactions. J Am Chem Soc. 2009; 131:4335–4345. [PubMed: 19275235]
37. Manner VW, Mayer JM. Concerted Proton-Electron Transfer in a Ruthenium Terpyridyl-Benzoate System with a Large Separation between the Redox and Basic Sites. J Am Chem Soc. 2009; 131:9874–9875. [PubMed: 19569636]
38. Pappas I, Chirik PJ. Ammonia Synthesis by Hydrogenolysis of Titanium-Nitrogen Bonds Using Proton-Coupled Electron Transfer. J Am Chem Soc. 2015; 137:3498–3501. [PubMed: 25719966]
39. Ribas X, Calle C, Poater A, Casitas A, Gómez L, Xifra R, Parella T, Benet-Buchholz J, Schweiger A, Mitrikas G, Solà M, Llobet A, Stack TDP. Facile C-H Bond Cleavage via a Proton-Coupled Electron Transfer Involving a C-H--Cu^{II} Interaction. J Am Chem Soc. 2010; 132:12299–12306. [PubMed: 20712320]
40. Estes DP, Grills DC, Norton JR. The Reaction of Cobaloximes with Hydrogen: Products and Thermodynamics. J Am Chem Soc. 2014; 136:17362–17365. [PubMed: 25427140]
41. Spiegel DA, Wiberg KB, Schacherer LN, Medeiros MR, Wood JL. Deoxygenation of Alcohols Employing Water as the Hydrogen Atom Source. J Am Chem Soc. 2005; 127:12513–12515. [PubMed: 16144398]
42. Pozzi D, Scanlan EM, Renaud P. A Mild Radical Procedure for the Reduction of *B*-Alkylcatecholboranes to Alkanes. J Am Chem Soc. 2005; 127:14204–14205. [PubMed: 16218613]
43. Tarantino KT, Miller DC, Callon TA, Knowles RR. Bond-Weakening Catalysis: Conjugate Aminations Enables by the Soft Homolysis of Strong N-H Bonds. J Am Chem Soc. 2015; 137:6440–6443. [PubMed: 25945955]
44. Paradas M, Campaña AG, Jiménez T, Robles R, Oltra JE, Buñuel E, Justicia J, Cárdenas DJ, Cuerva JM. Understanding the Exceptional Hydrogen-Atom Donor Characteristics of Water in

Ti^{III}-Mediated Free-Radical Chemistry. J Am Chem Soc. 2010; 132:12748–12756. [PubMed: 20722395]

45. Gansäuer A, Behlendorf M, Cangönül A, Kube C, Cuerva JM, Friedrich J, van Gastel M. H_2O Activation for Hydrogen-Atom Transfer: Correct Structures and Revised Mechanisms. Angew Chem Int Ed. 2012; 51:3266–3270.
46. Huang K-W, Han JH, Cole AP, Musgrave CB, Waymouth RM. Homolysis of Weak Ti-O Bonds: Experimental and Theoretical Studies of Titanium Oxygen Bonds Derived from Stable Nitroxyl Radicals. J Am chem Soc. 2005; 127:3807–3816. [PubMed: 15771515]
47. Stephan DW, Erker G. Frustrated Lewis Pair Chemistry: Development and Perspectives. Angew Chem Int Ed. 2015; 54:6400–6441.

Biographies

Robert Knowles received a B.S in chemistry from William and Mary in 2003 and his PhD from Caltech in 2008. Next he was an NIH postdoctoral fellow at Harvard University and is currently an assistant professor of chemistry at Princeton University.

Emily Gentry received a B.S in chemistry from UNC – Chapel Hill in 2013. She is currently a graduate student in the Knowles group.

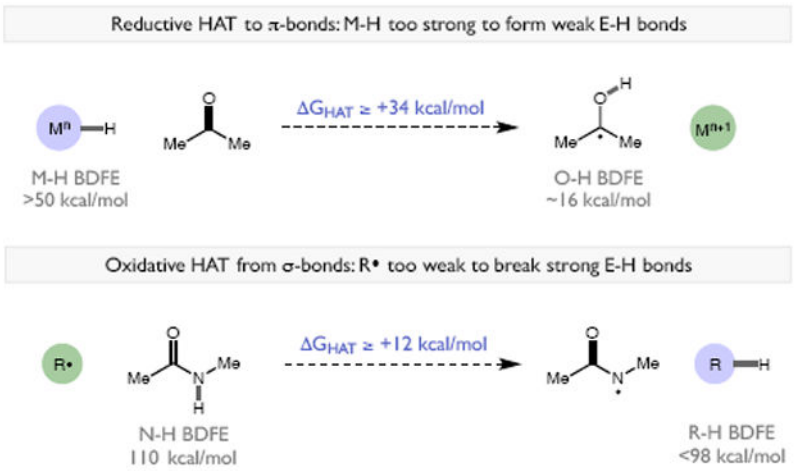


Figure 1.
Challenges of conventional HAT.

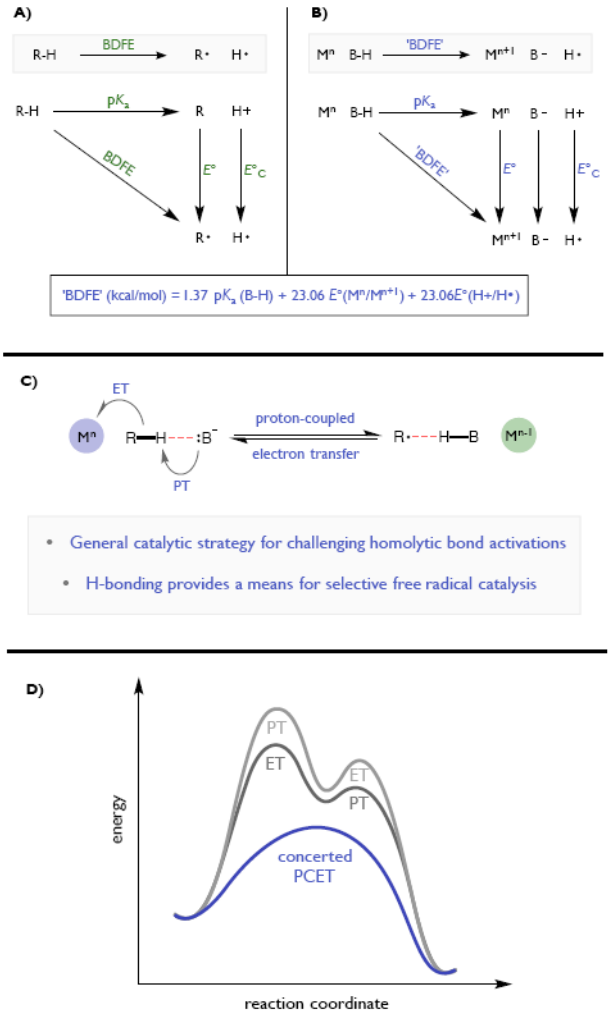


Figure 2.

(a) Thermodynamic cycle to determine BDFEs; (b) 'BDFE' formalism for PCET thermochemistry; (c) PCET mechanism (d) Kinetic advantages of PCET.

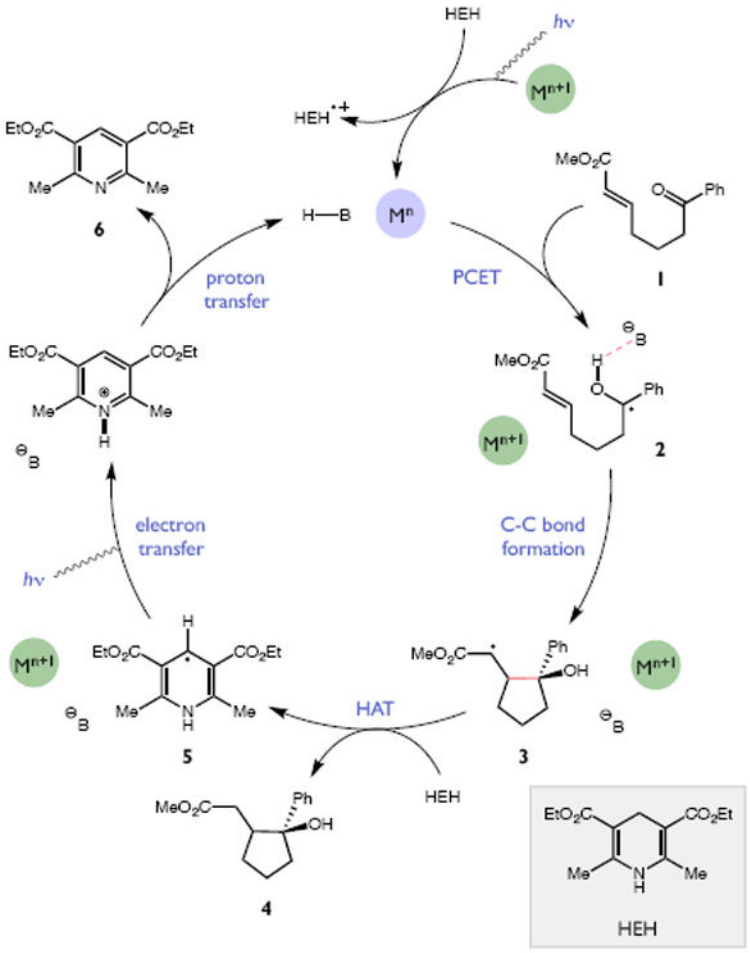


Figure 3.
Proposed catalytic cycle for ketyl-olefin coupling.

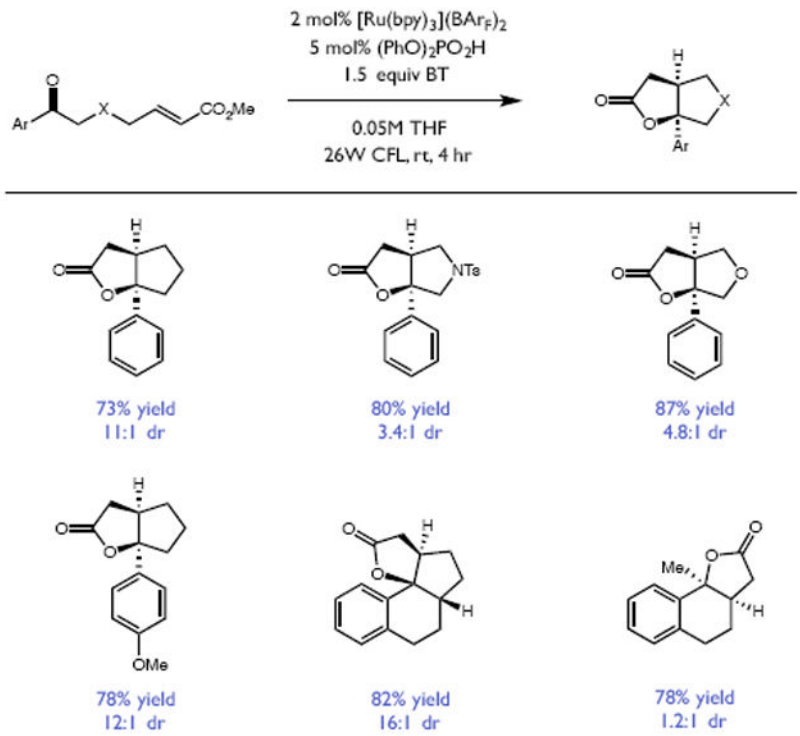


Figure 4.
Substrate scope for ketyl-olefin coupling.

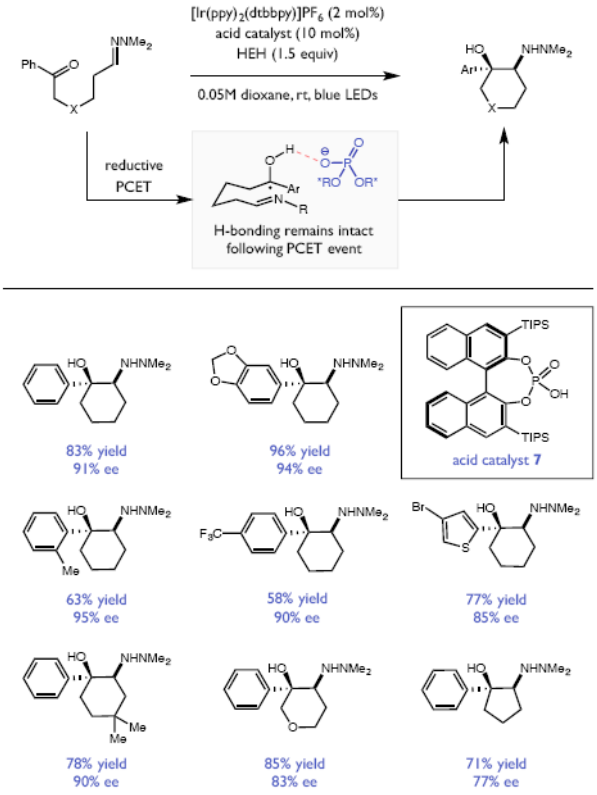


Figure 5.
Selected scope for the enantioselective aza-pinacol.

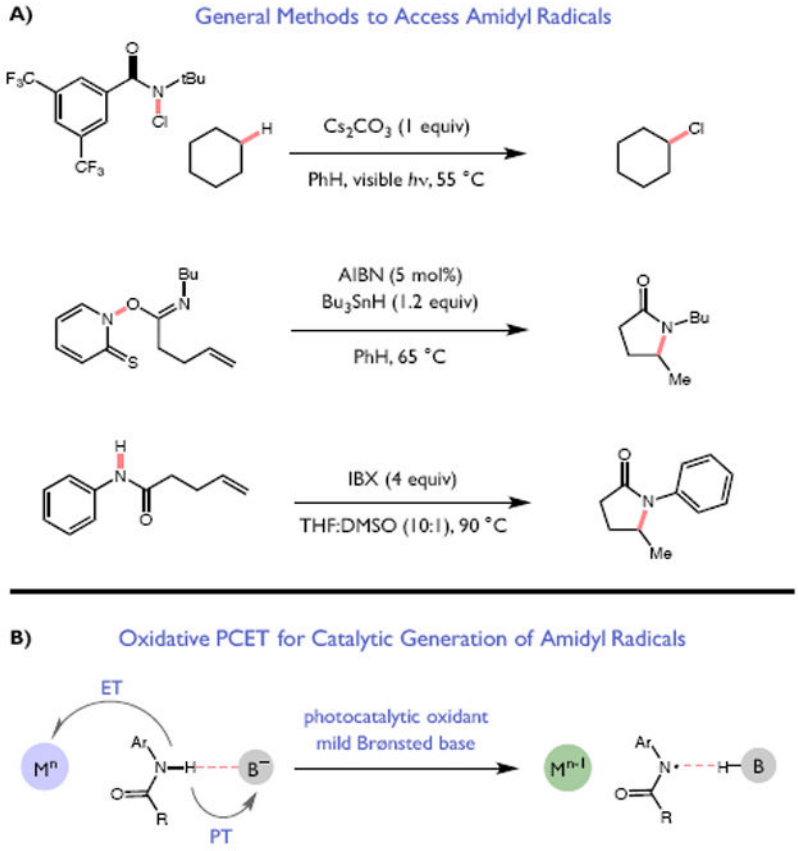


Figure 6.
Methods for amidyl generation.

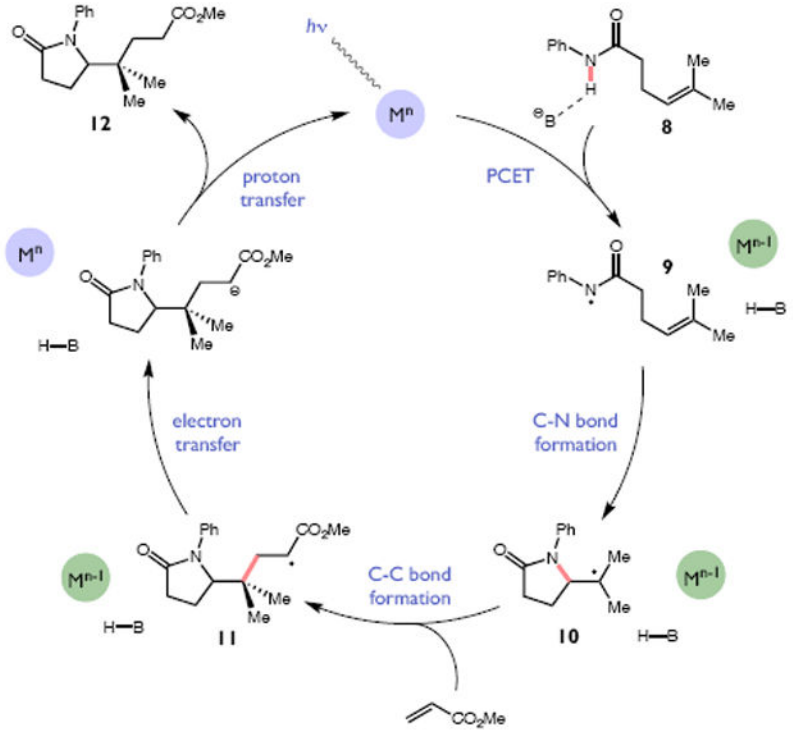


Figure 7.
Proposed catalytic cycle for carboamination.

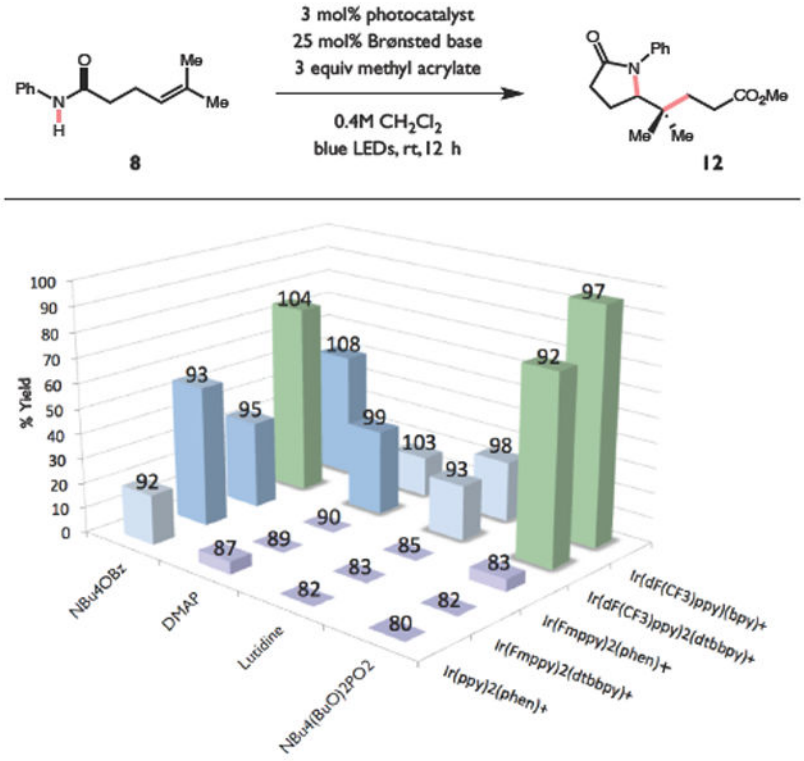


Figure 8.

'BDFE' correlation with reactivity in olefin carboamination. 'BDFE' values are represented by the number on top of the corresponding column. The oxidant in all combinations is the Ir(III) excited state.

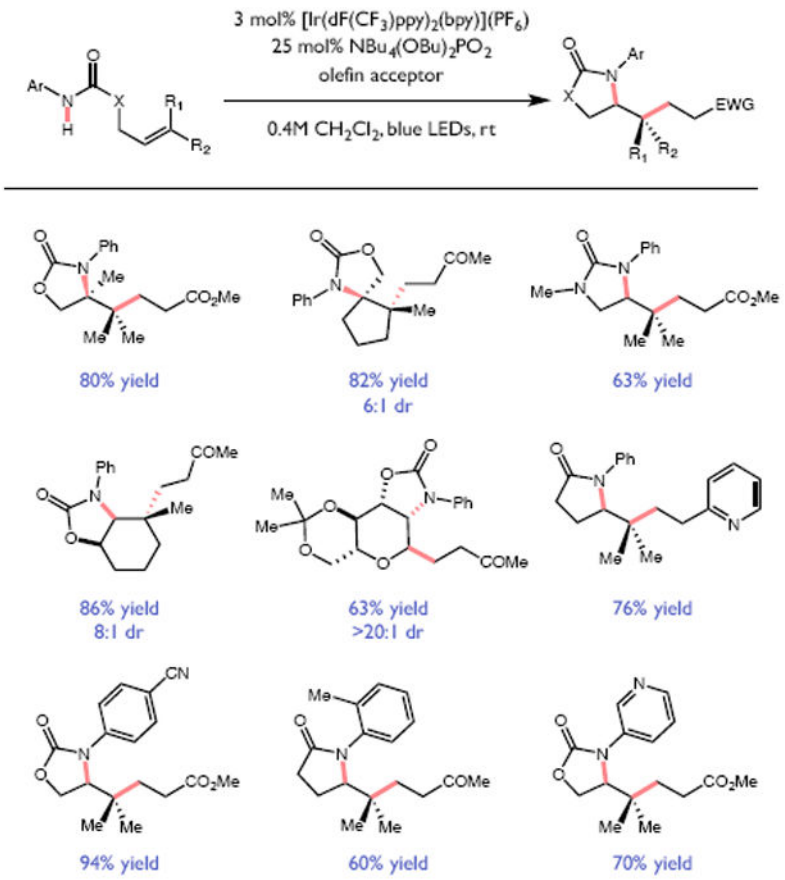


Figure 9.
Selected substrate scope for catalytic alkene carboamination.

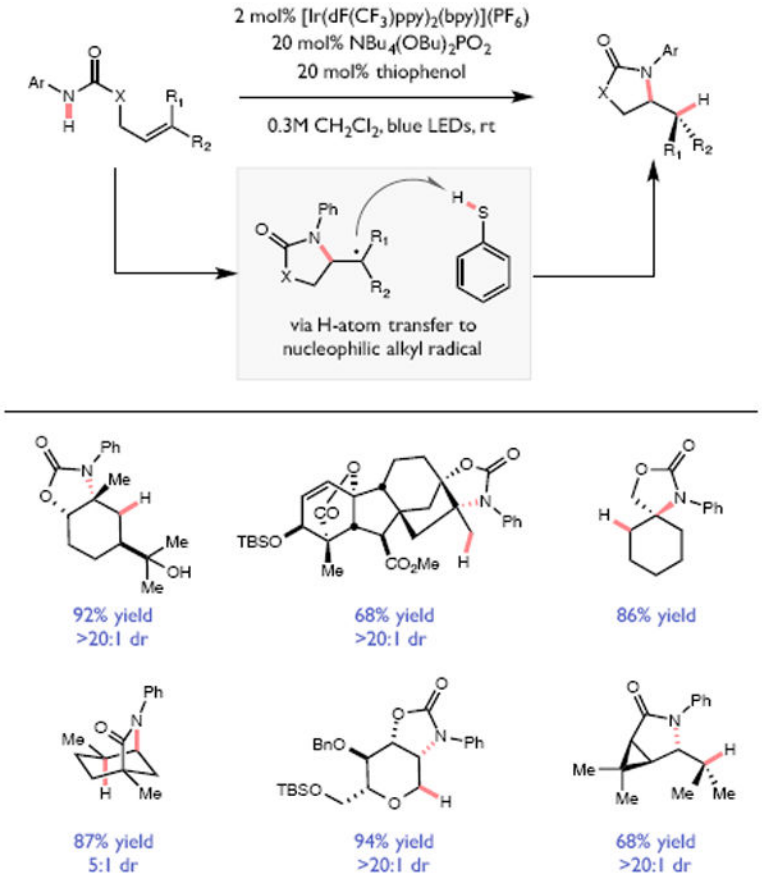


Figure 10.
Selected substrate scope for olefin hydroamination.

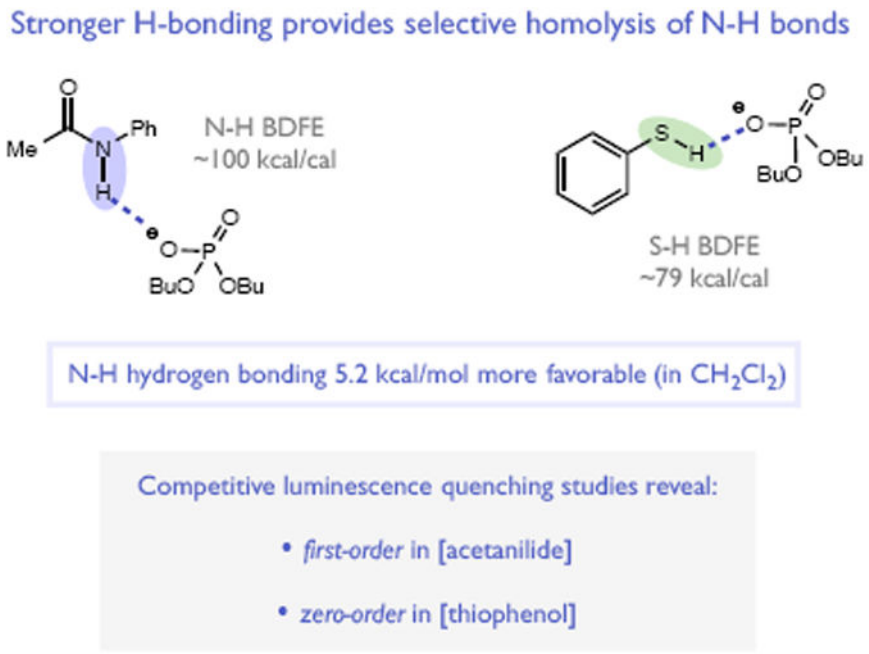


Figure 11.
Origins of selectivity in hydroamination.

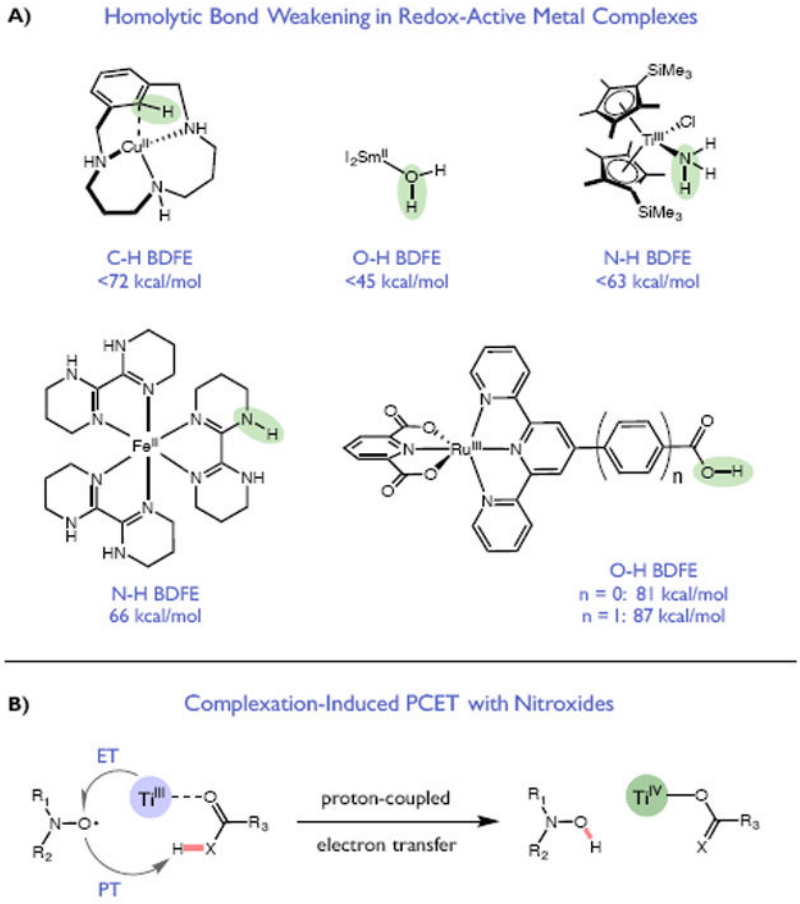


Figure 12.
Complexation-induced bond weakening.

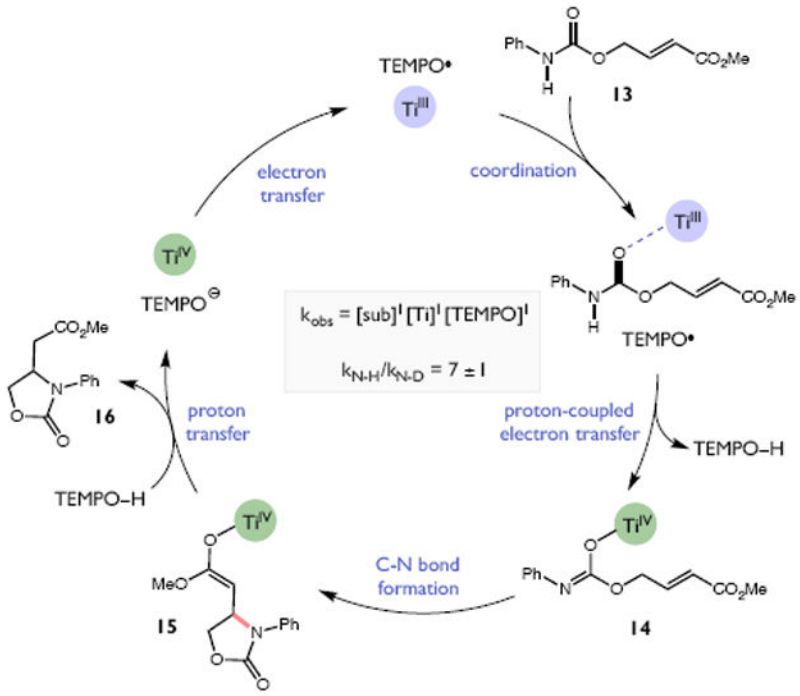
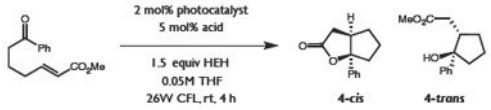


Figure 13.
Proposed catalytic cycle for conjugate amination.

Table 1

Reaction efficiency correlation with ‘BDFE’.



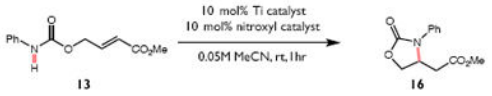
acid cat	redox cat	‘BDFE’[a]	% yield[b]
none	$[Ru(bpy)_3](BAr_F)_2$	--	0
BzOH	$[Ru(bpy)_3](BAr_F)_2$	45	0
$Et_3N•HBF_4$	$[Ru(bpy)_3](BAr_F)_2$	41	0
lutidine•HBF_4	$[Ru(bpy)_3](BAr_F)_2$	35	0
$(PhO)_2PO_2H$	$[Ru(bpy)_3](BAr_F)_2$	33	78
lutidine•HBF_4	$[Ir(ppy)_2(dtbbpy)](PF_6)$	31	74
$(PhO)_2PO_2H$	$[Ir(ppy)_2(dtbbpy)](PF_6)$	29	93
PTSA	$[Ru(bpy)_3](BAr_F)_2$	27	92
$(PhO)_2PO_2H$	$Ir(ppy)_3$	24	74

[a] Effective ‘BDFE’ values were calculated from the thermodynamic cycle illustrated in Figure 2a using pK_a and potential data in MeCN.

[b] Yields determined by GC analysis of crude reaction mixtures relative to internal standard. Isomeric ratios are ~5:1 in all cases, favoring the *cis* stereoisomer which spontaneously lactonizes to form product **4-*cis***.

Table 2

Optimization of conjugate amination.



Ti cat	nitroxyl cat	% yield
Cp_2TiCl	TEMPO	0
$(t\text{-BuCp})_2TiCl$	TEMPO	0
CpCp*TiCl	TEMPO	95
Cp^*_2TiCl	TEMPO	98
Cp^*_2TiCl	AZADO	96
--	TEMPO	0
Cp^*_2TiCl	--	0
$Cp^*_2TiCl_2$	TEMPO	0
Cp^*_2TiCl (1 mol%)	TEMPO (1 mol%)	95