Catalytic Alkene Carboaminations Enabled by Oxidative Proton-Coupled Electron Transfer

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Supporting Information Placeholder

ABSTRACT: Here we describe a dual catalyst system comprised of an iridium photocatalyst and weak phosphate base that is capable of both selectively homolyzing the N-H bonds of *N*-aryl amides (BDFEs ~ 100 kcal/mol) via concerted proton-coupled electron transfer (PCET) and mediating efficient carboamination reactions of the resulting amidyl radicals. This manner of PCET activation, which finds its basis in numerous biological redox processes, enables the formal homolysis of a stronger amide N-H bond in the presence of weaker allylic C-H bonds, a selectivity that is uncommon in conventional molecular H-atom acceptors. Moreover, this transformation affords access to a broad range of structurally complex heterocycles from simple amide starting materials. The design, synthetic scope and mechanistic evaluation of the PCET process are described.

Hydrogen atom transfer (HAT) is a powerful mechanism for homolytic bond activation that plays a central role in organic free radical chemistry. However, in HAT reactions involving conventional acceptors, such as main group radicals and highvalent metal oxo complexes, the rates of abstraction are highly correlated with the strengths of the bonds being broken.¹ In turn, this has limited the development of catalytic HAT methods that enable the selective homolysis of strong E-H bonds found in many common organic functional groups, such as alcohols and amides, in preference to weaker C-H bonds present in the same substrates.²

We recently questioned whether proton-coupled electron transfer (PCET) could serve as an alternative mechanism for homolytic bond activation that addresses this limitation.³ In PCET oxidations, an electron and proton originating from a single donor are transferred to two independent acceptors - a Brønsted base and a one-electron oxidant - in a concerted elementary step. While these exchanges constitute a formal loss of H• and furnish a neutral free radical product in a manner similar to HAT, the chemoselectivities and energetic characteristics of PCET reactions are distinct. First, multisite PCET oxidations require the formation of a hydrogen bond between the transferring proton and the Brønsted base prior to electron transfer.⁴ As typical C-H bonds are poor H-bond partners, we postulated that PCET might enable the homolytic activation of stronger O-H and N-H bonds selectively via the formation of more favorable non-covalent complexes. Moreover, these hydrogen bonding interactions should significantly decrease the potential requirements for the electron transfer process, enabling the use of comparatively mild one-electron

Oxidative PCET Activation of Amide N-H Bonds



N-H BDFE for N-aryl amide ~100 kcal/mol PCET 'BDFE' (kcal/mol) = 1.37 $pK_a(H-B)$ + 23.06 $E(M^n)$ + C_{solv}



Figure 1. PCET activation of amide N-H bonds and application to the development of a catalytic protocol for alkene carboamination.

oxidants.⁵ Lastly, the driving force for the PCET step can be rationally modulated over a wide range of energies by independently varying the pK_a of the proton acceptor and the reduction potential of the oxidant (*vide infra*).⁶ Taken together, these attributes provide a basis for the rational identification oxidant/base combinations that are thermodynamically competent to selectively homolyze strong E-H bonds with BDFEs in excess of 100 kcal/mol.

In line with the ideas above, we report here a dual oxidant/base catalyst system for the oxidative PCET activation of the strong N-H bonds in N-aryl amide derivatives (N-H BDFEs ~ 100 kcal/mol) and utilization of the resulting amidyl radicals in a new catalytic protocol for alkene carboamination (Figure 1).⁷ These reactions, which install vicinal C-N and C-C bonds across an unactivated alkene in a single transformation, are complementary in scope to many established catalytic carboamination technologies and have the potential to simplify the synthesis of a range of complex heterocyclic compounds. Moreover, while most state of the art technologies in synthetic amidyl chemistry rely on radical generation via either N-functionalized substrates⁸ or the use of strong stoichiometric oxidants,9 the reaction described here constitutes a rare example of catalytic amidyl generation via direct homolysis of the N-H bond in a simple amide precursor.¹⁰ The design, scope and mechanistic evaluation of the PCET process are described herein.

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Scheme 1. Proposed catalytic cycle



Reaction design Our initial efforts focused on identifying combinations of Brønsted bases and excited state oxidants that, while incapable of reacting with the amide substrates individually, are thermodynamically competent in combination to effect PCET homolysis of the N-H bond in model amide 1 (Scheme 1). In these reactions, we envisioned that the Brønsted base would first form a hydrogen bond complex with the secondary amide substrate, modulating its oxidation potential to facilitate PCET with the excited state of the photoredox catalyst. The nascent amidyl radical intermediate would then cyclize onto the pendant olefin to form a new C-N bond and an adjacent carbon-centered radical. This radical would in turn undergo intermolecular addition to an acrylate acceptor to form a new C-C bond and an α -carbonyl radical that would accept an electron from the reduced state of the photocatalyst to furnish an enolate. Favorable proton transfer between the enolate and the conjugate acid produced in the PCET event would furnish the desired carboamination product and regenerate the catalytically active forms of the oxidant/base pair.

To identify effective catalyst combinations for N-H homolysis, we made use of a simple thermodynamic formalism introduced by Mayer and coworkers that defines an effective bond strength ('BDFE') for any given base/oxidant pair as a function of the pK_a and redox potential of its constituents (Figure 1) and a constant term relating to the energetics of proton reduction.¹¹ In turn, these values enable the thermochemistry of any proposed PCET event to be estimated by comparing the effective BDFE of the chosen base/oxidant pair to the strength of the bond being homolyzed. Importantly, as these two key parameters are independent variables, the formal bond strength can be rationally varied with respect to the strength of the target bond. We tested the validity of this approach through combinatorial evaluation of five iridium photocatalysts and four Brønsted bases with effective bond strengths ranging from 80 to 108 kcal/mol in the carboamination of anilide 1 (N-H BDFE = 99 kcal/mol) (Table 1).^{12,13} In these experiments, we observed that combinations with 'BDFE' values significantly lower than the strength of the substrate N-H bond were not successful catalysts for carboamination (entries 1-9). However, all combinations with effective BDFEs approaching or exceeding the N-H BDFE of 1 resulted in catalytic generation of 2, though with varying deTable 1. Reaction optimization

Dh U	Me 3 mol% photocatalyst 25 mol% Brønsted base		O Ph		
	Me 3.0 equiv. methyl acrylate		VY.	✓ ^{CO₂Me}	
	1 Blue LE	Blue LEDs, rt, 12 hr		Me Me 2	
Entry	Photocatalyst	Base	'BDFE'a	Yield (%)	
1	Ir(ppy) ₂ (phen)PF ₆	NBu4OP(O)(OBu)2	80	0	
2	Ir(ppy) ₂ (phen)PF ₆	lutidine	82	0	
3	Ir(Fmppy)2(dtbbpy)PF6	NBu4OP(O)(OBu)2	82	0	
4	Ir(Fmppy)2(dtbbpy)PF6	lutidine	83	0	
5	Ir(Fmppy) ₂ (phen)PF ₆	NBu4OP(O)(OBu)2	83	trace	
6	Ir(Fmppy) ₂ (phen)PF ₆	lutidine	85	0	
7	Ir(ppy) ₂ (phen)(PF ₆)	DMAP	87	trace	
8	Ir(Fmppy)2(dtbbpy)PF6	DMAP	89	0	
9	Ir(Fmppy) ₂ (phen)PF ₆	DMAP	90	6	
10	Ir(ppy) ₂ (phen)PF ₆	NBu ₄ OBz	92	20	
11	Ir(dF(CF ₃)ppy) ₂ (dtbbpy)PF ₆	NBu4OP(O)(OBu)2	92	76	
12	Ir(dF(CF3)ppy)2(dtbbpy)PF6	lutidine	93	22	
13	Ir(Fmppy)2(dtbbpy)PF6	NBu ₄ OBz	93	56	
14	Ir(Fmppy) ₂ (phen)PF ₆	NBu ₄ OBz	95	35	
15	Ir(dF(CF3)ppy)2(bpy)PF6	NBu4OP(O)(OBu)2	97	92	
16	Ir(dF(CF3)ppy)2(bpy)PF6	lutidine	98	24	
17	Ir(dF(CF3)ppy)2(dtbbpy)PF6	DMAP	99	34	
18	Ir(dF(CF3)ppy)2(bpy)PF6	DMAP	103	16	
19	Ir(dF(CF ₃)ppy) ₂ (dtbbpy)PF ₆	NBu ₄ OBz	104	76	
20	$Ir(dF(CF_3)ppy)_2(bpy)PF_6$	NBu_4OBz	108	50	
Entry	Change from best conditions (entry 15)			Yield (%)	
21	no light			0	
22	no photocatalyst			0	
23	no NBu ₄ OP(O)(OBu) ₂			<5	
24	1 mol% $Ir(dF(CF_3)ppy)_2(bpy)PF_6$			76	
25	10 mol% NBu ₄ OP(O)(OBu) ₂			78	
26	1.1 equivalents of acrylate			68	
27	0.1 M in CH ₂ Cl ₂			80	

Optimization reactions performed at 0.05 mmol scale. Yields determined by ¹H-NMR analysis of the crude reaction mixture relative to an internal standard. ^a 'BDFE' values in kcal/mol calculated from pK_a and potential data in MeCN, with a C_{solv} value of 54.9 kcal/mol. Structures and potential data for all photocatalysts is included in the Supporting Information.

grees of efficiency (entries 10–20). Notably, all of the iridium complexes and bases evaluated proved active in at least one combination, including those with pK_{as} and potentials far removed from those of the amide substrate ($pK_{a} \sim 32$, $E_{p} = +1.2$ V vs. Fc/Fc⁺ in MeCN) (entry 10).^{12,13} Taken together, these results are consistent with a PCET mechanism of amidyl formation (*vide infra*) and support the notion that thermochemistry is a principal determinant in the kinetic viability of N-H activation. In addition, these studies highlight the ability of PCET to enable access to catalytically active H• acceptor systems with effective bond strengths higher than those attainable with any known molecular H-atom transfer catalysts (entry 20).

From the successful combinations tested, we elected to further study the $Ir(dF(CF_3)ppy)_2(bpy)PF_6/dibutyl phosphate pair$ (entry 15, 'BDFE' = 97 kcal/mol). Control reactions omitting either the Ir photocatalyst or visible light irradiation provided none of the desired carboamination product (entries 21,22). Similarly, reactions run in the absence of the phosphatebase resulted in <5% conversion of the amide starting material(entry 23). The carboamination reaction was also successful, 1

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Reactions performed at 0.5 mmol scale. Yields are for purified material and are the average of two experiments. Diastereomeric ratios determined by ¹H-NMR analysis of the crude reaction mixtures.

though lower yielding, when carried out at lower concentrations, with lower catalyst loadings, or with 1.1 equivalents of the acrylate acceptor (entries 24–27).

Substrate Scope Using the optimal conditions outlined above, we next examined the scope of this process. On preparative scale, carboamination of the model substrate 1 furnished amide 2 in 95% isolated yield after 18 hours of irradiation with blue LEDs at rt (Table 2). Carbamates were also excellent substrates, providing straightforward access to vicinal amino alcohols derivatives such as 3 from simple allylic alcohol starting materials. Structurally related urea and thiazolidinone products 4 and 5 could also be accessed in good yields. Notably, this method was also found to accommodate tetrasubstituted olefin substrates, providing access to products containing vicinal tertiary carbinamine and quaternary carbon centers, such as 6. This observation was extended to an endo-

cyclic tetrasubstituted olefin substrate, furnishing spirocycle 7 in good vield and with moderate diastereoselectivity. To the best of our knowledge, tetrasubstituted olefins are not substrates in any other reported catalytic carboamination technology. Fused bicyclic systems could also be generated using this method. For example, a cyclohexenol-derived carbamate was cyclized to furnish 8 in 86% yield as 8:1 mixture of diastereomers at the quaternary carbon center. Additionally, a protected glucal substrate was successfully carboaminated to provide carbohydrate derivate 9 with high levels of diastereoselectivity. A carbamate substrate derived from an acyclic chiral allylic alcohol cyclized to provide access to a trans-fused oxazolidinone 10 with excellent diastereoselectivity. Geminal substitution adjacent to the olefin is tolerated and enables the use of both monosubstituted and 1,2-disubstituted olefins substrates, with moderate diastereoselectivity observed in the latter case (11 and 12). Simple monosubstituted olefins could be also carboaminated efficiently when more activated olefin acceptors were employed (13).

With respect to the aryl amine component, numerous *para*substituted substrates were accommodated (14–17) including both electron-rich and electron-deficient examples. Similarly, substrates bearing both *meta-* and *ortho*-substituted arenes could be carboaminated in good yields (18 and 19). In addition, heterocyclic arenes, such as pyridine and benzothiazole could be incorporated into the amide moiety and cyclized with good efficiency (20 and 21). Notably, the potential required for direct ET oxidation of *p*-CN carbamates such as 15 is more than 600 mV more positive than that of the Ir(III) excited state ($E_{1/2} = +1.0$ V vs. Fc/Fc⁺ in MeCN), highlighting the ability of simple H-bonding interactions to facilitate otherwise challenging charge transfer events.^{14,15} Lastly, a variety of electrondeficient olefin partners were found to effectively couple, including methyl acrylate, methyl vinyl ketone, acrolein, acrylonitrile, and 2-vinylpyridine (20–23).

Mechanism of amidyl formation To assess the role of PCET in these reactions, we studied the mechanism of amidyl formation using luminescence quenching techniques and Nphenyl acetamide (26) as a model substrate. Stern-Volmer analysis revealed that 26 ($E_p = +1.2$ V vs. Fc/Fc⁺ in MeCN) does not quench the excited state of $Ir(dF(CF_3)ppy)_2(bpy)PF_6$ (* $E_{1/2}$ = +1.0 V vs. Fc/Fc⁺ in MeCN) in acetonitrile at 25 °C.¹⁴⁻ ¹⁶ However, solutions containing both amide **26** and tetrabutyl ammonium dibutyl phosphate resulted in a significant decrease in the observed emission intensity. Variation of the phosphate base and amide concentrations in these assays demonstrated that the rate law for the quenching process exhibits a first order kinetic dependence on the concentration of each component. Additionally, an isotope effect of 1.15 ± 0.04 was observed in independent experiments conducted with the N-H and N-D isotopologues of 26, consistent with the notion that the labeled bond plays a specific role in the quenching process.¹⁷ Notably, the phosphate base alone was also found to weakly quench the Ir excited state ($k_{sv} = 41 \text{ M}^{-1}$), but not sufficiently to account for the much greater degree of quenching observed when amide 26 was also present in solution (k_{sv} = 731 M⁻¹).

While the results above indicate that the excited state iridium complex does not oxidize the amide substrate directly, they are consistent in principle with either concerted PCET activation or rate-limiting deprotonation of the amide substrate by the phosphate base followed by fast oxidation of the resulting anilide anion. However, the large pK_a difference between the amide and the phosphate ($\Delta pK_a \sim 20$) suggests that the latter pathway would not be kinetically competitive with luminescent decay of the Ir excited state ($\tau = 2.3 \ \mu s$ in MeCN at rt).¹⁴ As the feasibility of both sequential transfer mechanisms can be discounted, the measured rate law and isotope effect are consistent with a concerted PCET mechanism of amidyl formation.¹⁸

In conclusion, we have developed a novel PCET-based protocol for alkene carboamination. Notably, these studies demonstrate that concerted multisite PCET is a viable mechanism for the direct homolytic activation of strong N-H bonds, providing catalytic access to amidyl radical intermediates from simple anilide starting materials. Differential H-bonding ability enables these PCET activations to be completely chemoselective for the N-H bond even when much weaker allylic C-H bonds are present in the same substrates. Additionally, the qualitative success of effective BDFEs in enabling catalyst selection suggests this simple metric will become an enabling tool in PCET reaction design.¹⁹ These results provide further support for the view that concerted PCET mechanisms can be successfully translated to small molecule catalysis platforms and enable the development of new synthetic methods.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(19) As pointed out by a reviewer, the thermochemical considerations reflected in the effective BDFE formalism are best viewed as a necessary but not a sufficient condition to ensure a given PCET activation.

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Selective Homolysis of Amide N-H Bonds via PCET