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PCET-Enabled Olefin Hydroamidation Reactions with *N*-Alkyl Amides

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Abstract

Olefin aminations are important synthetic technologies for the construction of aliphatic C–N bonds. Here we report a catalytic protocol for olefin hydroamidation that proceeds through transient amidyl radical intermediates that are formed via proton-coupled electron transfer (PCET) activation of the strong N–H bonds in *N*-alkyl amides by an excited-state iridium photocatalyst and a dialkyl phosphate base. This method exhibits a broad substrate scope, high functional group tolerance, and amenability to use in cascade polycyclization reactions. The feasibility of this PCET protocol in enabling the intermolecular anti-Markovnikov hydroamidation reactions of unactivated olefins is also demonstrated.

Graphical Abstract

Olefin Hydroamidation Enabled by PCET Activation of *N*-Alkyl Amides

Keywords

hydroamidation; proton-coupled electron transfer; hydrogen atom transfer; amidyl radicals; photoredox catalysis

Oxidative proton-coupled electron transfer (PCET) has emerged as a promising technology for catalytic radical generation, enabling formal H• abstraction from strong E–H bonds found in many common protic functional groups.¹ In this context, numerous light-driven PCET methods for olefin amination have been reported in recent years that utilize *N*-radical intermediates derived from the homolytic activation of the N–H bonds in anilides and sulfonamides.² However, analogous PCET-based olefin aminations with *N*-alkyl amides have proven more challenging to develop. This stems in part from the unusually strong N–H

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bonds in these amide derivatives (N–H bond dissociation free energies (BDFEs) ~ 110 kcal/mol)³, which makes them difficult substrates for PCET activation (Figure 1a). Moreover, as suggested by their high BDFEs, this class of amidyls is highly reactive and capable of engaging in numerous non-productive pathways that can compete kinetically with olefin addition.^{2f, 2g, 4} We recently addressed the thermodynamic constraints associated with *N*-alkyl amide activation in the development of a catalytic PCET method for amidyl-directed C–H alkylation (Figure 1b).⁵ Building on this work, we report here a PCET-based protocol for catalytic olefin hydroamidation reactions of *N*-alkyl amides for the preparation of γ -lactams and cyclic *N*-acyl amine derivatives (Figure 1b).^{4b, 6} The optimization, substrate scope studies, and preliminary mechanistic evaluation of this process are presented herein.

To begin, we focused on the conversion of amide **1** to lactam **2** by adapting the PCET conditions previously reported for amide-directed C–H alkylation (Table 1).^{5a} Specifically, blue light irradiation of a solution containing **1** with 3 mol% of photocatalyst [Ir(dF(CF₃)ppy)₂(5,5'-d(CF₃)bpy)]PF₆⁷ (**A**), 25 mol% of tetrabutylphosphonium dibutylphosphate base, and 40 mol% of hydrogen atom transfer (HAT) catalyst 2,4,6-triisopropyl thiophenol (TRIP thiol) at room temperature in fluorobenzene furnished the desired lactam product **2** in 44% yield (entry 1). Using less oxidizing photocatalysts [Ir(dF(CF₃)ppy)₂(4,4'-d(CF₃)bpy)]PF₆ (**B**) and [Ir(dF(CF₃)ppy)₂(bpy)]PF₆ (**C**)⁸ diminished the reaction yields significantly (entries 2, 3), consistent with a less favorable driving force for the PCET event. Investigation of numerous thiols revealed that TRIP thiol was the optimal co-catalyst for this transformation (entries 4–6). However, we observed that the use of 10 mol% of 2,4,6-triisopropyl diphenyldisulfide (TRIP disulfide)⁹ in addition to 40 mol% of the corresponding thiol dramatically improved the yield to 95% (entry 7). Alternative conditions employing either 60 mol% of TRIP thiol or 30 mol% of TRIP disulfide proved less effective (entries 12, 13). Evaluation of the reaction efficiency in numerous solvents revealed that fluorobenzene was optimal (entries 8–11). Lowering phosphate base loading while doubling reaction concentration maintained the reactivity, enhancing the practicality for preparative-scale reactions (entries 14–16). Control experiments confirmed that visible light, photocatalyst **A**, phosphate base, and HAT co-catalyst are all required to achieve the observed reactivity (entries 17–20).

With these optimized conditions established, we next evaluated the scope of the method with respect to the formation of both lactams and cyclic *N*-acyl amines (Table 2). In the lactam series, hydroamidation of a substrate bearing a terminal olefin provided **3** in 97% isolated yield. For 1,2-disubstituted olefins, both *cis* and *trans* isomers were processed with high efficiency (**4**, **5**). Cyclization onto a 1,1-disubstituted olefin to form a tertiary carbinamine center was also realized to form **6** in 92% yield. Moreover, the reaction can accommodate steric bulk adjacent to the site of C–N bond formation as evidenced by the formation of *gem*-dimethyl product **7** in 89% yield. With respect to the *N*-alkyl group, we found that branched *N*-cyclohexyl and *N*-tetrahydropyranyl substrates provided lactams **8** and **9**, respectively, in good yields. We also observed that silyl ethers and acetals were tolerated under these reaction conditions, providing lactams **10** and **11**. More complex polycyclic lactams were also accessible using this protocol (**12–14**). In addition to amides, urea and S-thiocarbamate substrates could be cyclized efficiently to furnish imidazolidinone (**15**) and

thiazolidinone (**16**) products. This method could further be employed for the functionalization of the muscle relaxant Baclofen to afford **17** in 73% yield. Similarly, a leelamine-derived substrate was successfully hydroamidated to furnish lactam **18** in 67% yield as a 1.3:1 mixture of diastereoisomers.

With respect to the formation of cyclic *N*-acyl amines, the hydroamidation reaction proceeded smoothly with various olefin substitution patterns (**19–21**). Notably, a substrate bearing a 1,1-disubstituted olefin acceptor underwent 6-*endo* cyclization at a faster rate than 5-*exo* to form a 2:1 mixture of piperidine- and pyrrolidine-derived amides (**20**).¹⁰ The amidation also tolerated alkyl fluoride and Boc-protected amine substrates to afford products **22** and **23** in good yields. Spirocycle **24** and bridged bicyclic amide **25** were also obtained in excellent yields using this protocol. A urea substrate cyclized smoothly to furnish **26** in 71% yield. Lastly, hydroamidation of a peracetylated cholic acid derivative was accomplished to provide **27** in 91% yield.

This hydroamidation method also proved efficient in the synthesis of cyclic carbamates, though optimization was more challenging due to the unfavorable conformational preferences of these substrates.¹¹ More specifically, carbamates derived from allylic alcohols are known to favor (*Z*)-configurations, orienting the reactive amidyl distal to the olefin and rendering it unable to engage in C–N bond formation. Together, these factors suggest that both non-productive HAT^{4b} from the thiol and back electron transfer (BET)¹² between *N*-radical and the reduced Ir(II) state of the photocatalyst may compete favorably with the desired isomerization and cyclization pathway. Accordingly, we found that decreasing reaction concentration and utilizing 30 mol% of TRIP disulfide to minimize the concentration of free thiol in solution gave markedly improved results, delivering cyclic carbamate **28** in 89% yield, as compared to 33% under the standard conditions from Table 1. Other olefin substitution patterns were also accommodated (**29–32**). It is worth noting that substrates bearing stereogenic centers adjacent to the olefin acceptors were amidated with high levels of diastereoselectivity (**33, 34**). Distal olefin functionality is also well tolerated in this protocol, as illustrated by the isolation of the spirocycle **35**.

We next questioned whether this method could be extended to cascade processes, wherein the alkyl radical formed upon *N*-radical cyclization can engage in a second C–C bond forming event with a pendant alkene prior to HAT from the thiol to form a polycyclic product (Scheme 1a–c).¹³ Upon subjecting amide **36** to the standard hydroamidation conditions described above, monocyclized product **38** and a mixture of diastereomeric bicycles **39** and **40** were observed in 20% and 54% yield, respectively (Table S.1). Gratifyingly, this observation implies that the rate of the second cyclization step from intermediate **37** is kinetically competitive with bimolecular HAT from thiophenol ($\sim 10^8 \text{ M}^{-1}\text{s}^{-1}$).^{4a} In order to further suppress the formation of undersired **38**, TRIP thiol was replaced with 30 mol% of TRIP disulfide, providing a ~ 4 :1 mixture of **39** and **40** in 83% isolated yield (Scheme 1a). Similarly, structurally complex tricyclic lactams (**42, 43**) could be successfully synthesized in 69% yield from simple amide **41** using the modified conditions (Scheme 1b). Polycyclization of cyclohexene-derived amide **44** was also accomplished, affording a 1.4:1 isomeric mixture of lactams **45** and **46** in 76% combined

yield (Scheme 1c). These results demonstrate that this PCET method is amenable to the direct construction of valuable indolizidine and pyrrolizidine cores from simple linear precursors.

Lastly, preliminary results suggest that this methodology can be extended to intermolecular hydroamidation reactions of primary amides (Scheme 1d).^{2c, 9a, 14} We initially questioned whether the bimolecular addition of these amidyl radicals to olefins would be fast enough to outcompete BET and non-productive HAT from the thiol co-catalyst. In addition, PCET activation of the secondary amide product might lead to product inhibition or undesired side-reactions. Using standard conditions from Table 1, the intermolecular hydroamidation of 4-methoxybenzamide **47** and diisobutylene afforded the desired product **48** in 17% yield. Gratifyingly, further optimization of the reaction provided **48** in 67% isolated yield as a single regioisomer. Notably, to the best of our knowledge, this reaction represents the first reported example of a catalytic intermolecular anti-Markovnikov hydroamidation reaction^{2c,9a,15} between primary amides and unactivated alkyl olefins.

As previously noted, the addition of TRIP disulfide was found to dramatically improve the reaction efficiency compared with the use of TRIP thiol alone. Initially, we attributed this observation to disulfide-mediated oxidation of any photocatalyst that is captured in the reduced Ir(II) state following an undesired side reaction of the amidyl. From cyclic voltammetry measurements, reduction potentials of TRIP disulfide and Ir(III)/(II) couple of **A** were found to be -2.16 V and -1.07 V^{5a} (vs. Fc^+/Fc in MeCN), respectively, suggesting that direct electron transfer between the two compounds is unlikely to occur. However, it is known that aryl disulfides can be homolyzed under blue-light irradiation to afford aryl thiyl radicals ($E_{\text{p}2} = -0.22$ V vs. Fc^+/Fc in MeCN),^{2c} which are capable of oxidizing the Ir(II) complex to form thiolate and regenerate the ground-state Ir(III) photocatalyst.

Nocera and coworkers recently put forward an alternative explanation for the beneficial role of disulfides in their detailed kinetic study of PCET-based olefin hydroamidation reactions of *N*-aryl amides.¹⁶ These authors found that, while excited-state PCET is relatively efficient, BET between the amidyl radical and the reduced Ir(II) state of the photocatalyst is faster than cyclization, which in turn greatly diminishes the quantum yield. They observed that reversible trapping of the amidyl radical occurs through reaction with an aryl disulfide (which forms in equilibrium with free thiol under the reaction conditions), forming a stable *N*-thioamide intermediate. This adduct serves as an off-cycle resting state for the amidyl radical and can eventually be converted back to the reactive *N*-radical, leading to productive C–N bond formation and significantly improved quantum efficiencies. This work inspired us to consider whether the beneficial role of disulfides in these reactions of *N*-alkyl amides could be attributed to a similar cause. DFT calculations (U ω B97XD/6–311G++(2d,3p)//UB3LYP/6–31+G(d,p)) indicated that the reaction of an *N*-alkyl amidyl radical with TRIP disulfide to form a *N*-thioamide adduct and thiyl radical is energetically favorable ($\Delta G_{\text{calc.}} = -4.3$ kcal/mol) (See SI). Moreover, trace amounts of *N*-thioamide adduct **49** could be detected via MS analysis of the crude reaction mixture from an incomplete hydroamidation of model amide **1**. Lastly, irradiation of independently synthesized **49** under standard conditions in the presence of Ir(III) photocatalyst **A**, phosphate base, and TRIP thiol provided lactam **2** in 86% yield (Scheme 2). As such, the viability of **49** as an intermediate

in these reactions is plausible and likely plays a role in suppressing non-productive charge recombination, in line with Nocera's findings.

In conclusion, we have developed a catalytic protocol for direct homolysis of the strong N–H bonds in unactivated *N*-alkyl amide derivatives using excited-state PCET. The resulting amidyl radicals can engage successfully in a wide range of olefin hydroamidation reactions to provide valuable lactams and cyclic *N*-acyl amines from simple linear starting materials. Moreover, this methodology can be adapted to enable both the cascade polycyclization reactions of polyunsaturated amides, as well as the first example of an anti-Markovnikov intermolecular hydroamidation with primary amides. We are optimistic that these results can be further adapted to enable challenging aliphatic C–N bond constructions in a wide variety of synthetic contexts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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a) BDFEs of N-H bonds in common amine derivatives

b) Catalytic reactions of N-alkyl amidyl radicals enabled by PCET

Figure 1.
(a) BDFEs of N-H bonds in amine derivatives. (b) PCET-enabled generation of amidyl radicals for C-C and C-N bonds formation reactions.

All reactions were performed on 0.5 mmol scale. Reported yields are for isolated and purified material and represent the average of two experiments. Diastereomeric ratios and ratios of regioisomers were determined by ^1H -NMR analysis of the crude reaction mixtures. ^aYield was determined by ^1H -NMR analysis of the crude reaction mixtures.

Scheme 1.

Polycyclization cascade and intermolecular anti-Markovnikov hydroamidation reaction.

Scheme 2.
Olefin hydroamidation with *N*-thioamide

Table 1.

Reaction Optimization^a

Entry	Solvent	PC	H-Atom Donor	Additive	Yield (%) ^b
1	PhF	A	TRIP thiol	-	44
2	PhF	B	TRIP thiol	-	26
3	PhF	C	TRIP thiol	-	10
4	PhF	A	thiophenol	-	32
5	PhF	A	tri(<i>t</i> Bu) thiophenol	-	33
6	PhF	A	<i>n</i> Dodecanethiol	-	8
7	PhF	A	TRIP thiol	TRIP disulfide	95
8	PhMe	A	TRIP thiol	TRIP disulfide	46
9	PhCF ₃	A	TRIP thiol	TRIP disulfide	73
10	CH ₂ Cl ₂	A	TRIP thiol	TRIP disulfide	51
11	CHCl ₃	A	TRIP thiol	TRIP disulfide	62
<i>Change from entry 7</i>					
12			60 mol% TRIP thiol, no TRIP disulfide		58
13			no TRIP thiol, 30 mol% TRIP disulfide		81
14			5 mol% phosphate base		80
15			0.1 M PhF		85
16			5 mol% phosphate base and 0.1 M PhF		97
17			no light		0
18			no photocatalyst		0
19			no phosphate base		0
20			no TRIP thiol and/or TRIP disulfide		0

^aOptimization reactions were performed on 0.05 mmol scale.

^bYields were determined by ¹H-NMR analysis of crude reaction mixtures relative to an internal standard.

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Table 2.

Substrate Scope^a

^a Reactions were performed on 0.5 mmol scale. Reported yields are for isolated and purified material and represent the average of two experiments. Diastereomeric ratios were determined by ¹H-NMR analysis of the crude reaction mixtures.

^b Starting material was a *trans* olefin.

^c Starting material was a *cis* olefin.

^d Changes from the original conditions included 20 mol% PBu₄OP(O)(OBu)₂ and 80 mol% TRIP thiol.

^e Yields were reported from ¹H-NMR analysis of the crude reaction mixture.

^f Changes from the original conditions included 25 mol% PBu₄OP(O)(OBu)₂, 80 mol% TRIP thiol, and a concentration of 0.05 M.

^g Reactions were performed on a 0.2 mmol scale; changes from the original conditions included 20 mol% NBu₄OP(O)(OPh)₂, 30 mol% TRIP disulfide, and a concentration of 0.02 M.

^h Reactions were performed on a 0.2 mmol scale; changes from the original conditions included 20 mol% NBu₄OP(O)(OPh)₂, 40 mol% TRIP disulfide, and a concentration of 0.02 M.