Reverse Polarity Reductive Functionalization of Tertiary Amides *via* a Dual Iridium Catalyzed Hydrosilylation & SET Strategy

Tatiana Rogova, Pablo Gabriel[‡], Stamatia Zavitsanou[‡], Jamie A. Leitch[‡], Fernanda Duarte*, Darren J. Dixon*

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom

ABSTRACT: A new strategy for the mild generation of synthetically valuable α-amino radicals from robust tertiary amide building blocks has been developed. By combining Vaska's complex-catalyzed tertiary amide reductive activation and photochemical single electron reduction into a streamlined tandem process, metastable hemiaminal intermediates were successfully transformed into nucleophilic α-amino free radical species. This umpolung approach to such reactive intermediates was exemplified through coupling with an electrophilic dehydroalanine acceptor, resulting in the synthesis of an array of α-functionalized tertiary amine derivatives, previously inaccessible from the amide starting materials. The utility of the strategy was expanded to include secondary amide substrates, intramolecular variants and late stage functionalization of an active pharmaceutical ingredient. DFT analyses were used to establish the reaction mechanism and elements of the chemical system that were responsible for the reaction's efficiency.

INTRODUCTION

α-Functionalized amines and their derivatives are an integral part of a vast array of natural products, pharmaceutical agents and agrochemicals.[1] Traditionally, these valuable structures are accessed through C–N bond forming strategies and numerous protocols have been developed for this purpose.[2] Alternatively, C–C bond formation provides a complementary avenue towards these biologically-relevant architectures.[3]
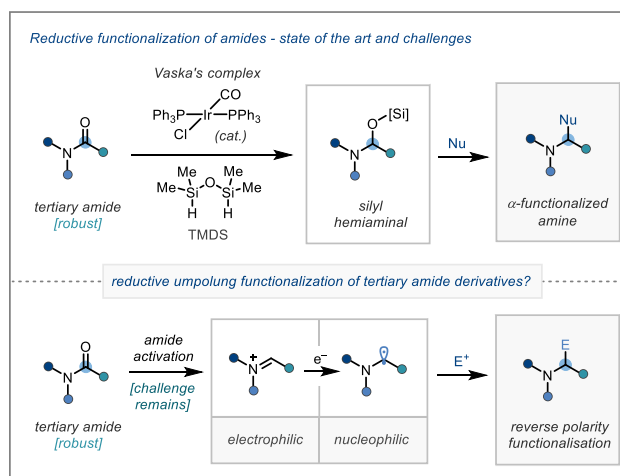
Within the scope of the latter approach, the reductive functionalization of ubiquitous amides is a powerful access point towards decorated α-branched amines. It is equally applicable for the elaboration of simple building blocks into valuable products as well as expediting natural product synthesis.[4-11] To this end, Vaska's complex (IrCl(CO)(PPh₃)₂), in conjunction with TMDS (1,1,3,3-tetramethyldisiloxane) as terminal reductant, has come to the fore as an effective system for generating iminium ions in situ, via the hydrosilylation of tertiary amide and lactam reactants (Scheme 1).[12] The mild reaction conditions, exquisite chemoselectivity, and broad functional group tolerance of this approach have contributed to its growing application as a synthetic strategy in the elaboration of simple building blocks and in late stage functionalization of complex molecular architectures including alkaloid natural products.[13]

Nevertheless, and without exception, all Vaska's complex catalysed amide activation methods that enable functionalization at the α-position[14] exploit the electrophilicity of iminium ion intermediates, generated in situ by ionization of the silyl hemiaminal. To date, despite its untapped synthetic potential, reductive functionalization of tertiary amides by reversing their natural polarity (umpolung) remains unreported.
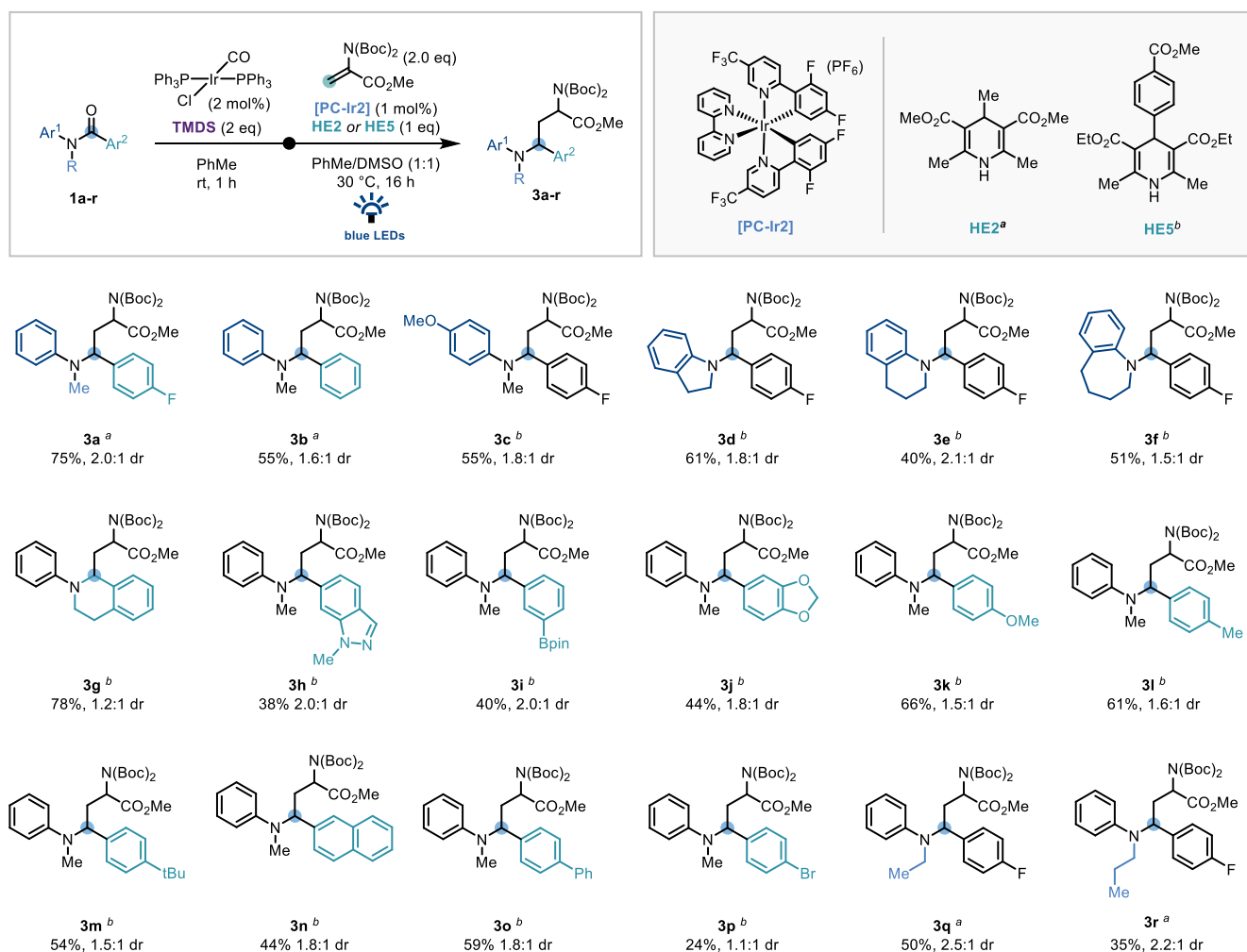
To this end, we reasoned that if single electron transfer (SET) to the metastable silylated hemiaminal or iminium ion could be realized, entry to the nucleophilic α-amino radical and therefore umpolung reactivity would be enabled (Scheme 2). Of the techniques available for such a single electron reduction, photoredox catalysis has emerged as the most versatile, and in related works,[15] the resulting free radical species have been shown to engage in a range of transformations, including reaction with electrophilic species such as Michael acceptors.[16]

Scheme 1. α-Functionalization strategies for amine synthesis from tertiary amides

Scheme 2. Proposed concept for accessing α-amino radicals *via* reverse polarity amide activation. Red= reductant

Concept design - reductive reverse polarity functionalization of amides

Accordingly, we reasoned that if both reductive processes could be streamlined into an effective one-pot, tandem process, the nucleophilic α-amino radical species could indeed be generated and therefore access to new chemical space for the abundant tertiary amide would be granted. Herein we wish to report our findings.

RESULTS & DISCUSSION

Optimization Studies. Our initial investigation focused on sequentially establishing a general set of experimental conditions for both the tertiary amide hydrosilylation and the photocatalytic reductive coupling. For this purpose, the fluorinated N-methyl anilide (**1a**) was chosen as a model tertiary amide substrate and protected dehydroalanine (DHA) derivative (**2**) was chosen as a suitably reactive nucleophilic radical acceptor that would ultimately afford medicinally relevant amino acid products (**3a**) (Scheme **3**).[16f, 17]

Following exploration of reduction conditions commonly utilized with Vaska's complex, smooth hydrosilylation of the tertiary amide (**1a**) to the hemiaminal species (**1aa**) was achieved in under an hour using the addition of 2 mol% of Vaska's complex, and 2 equivalents of TMDS in anhydrous toluene[18] (Scheme **3A**, Table 1, entry 2; see *Supporting Information* for further details). Following the full consumption of the starting material, it was found that addition of dimethylsulfoxide not only quenched the catalytic activity of the Vaska's complex, thereby suppressing over-reduction of **1aa** to the amine side-product (**3ac**), but also served as a suitable co-solvent for the subsequent photocatalytic step.[16b,f,m]

Scheme 3. Optimization studies for (A) Vaska's catalyzed amide hydrosilylation. (B) The photocatalytic reductive coupling of the silyl hemiaminal intermediate with DHA derivative.

A | *Hydrosilylation optimization*

entry	solvent	Vaska (mol%)	TMDS (eq)	time (h)	1aa (%)[a]
1	CH₂Cl₂	2	2	2.5	43
2	**PhMe**	**2**	**2**	**1.0**	**100**
3	PhMe	2	1.5	1.0	73
4	PhMe	1	2	1.0	81

Table 1: Iridium-catalyzed tertiary amide hydrosilylation. General conditions: **1a** (0.1 mmol), IrCl(CO)(PPh₃)₂ (x mol%), 1,1,3,3-tetramethyldisiloxane (y eq), solvent (0.5 mL), under a nitrogen atmoshere [a] Calculated using ¹⁹F{¹H} NMR analysis of the crude reaction mixture.

R¹ = *t*Bu: [PC-Ir1]
R¹ = H: [PC-Ir2]

Hantzsch ester

HE	R²	R³
HE1	H	Et
HE2	Me	Me
HE3	Cy	Me
HE4	Ph	Et
HE5	4-CO₂MePh	Et

B | *Photocatalytic coupling optimization*

entry	photocatalyst [PC]	HE	3a (%)[a]	dr[b]	3ab (%)[a]	3ac (%)[a]
1	[PC-Ir1]	HE1	25 (17)[c]	2.0:1	44	32
2	[PC-Ir2]	HE1	42	1.8:1	49	9
3	*fac*-Ir(ppy)₃	HE1	38	1.9:1	57	5
4	4-CzIPN	HE1	20	1.8:1	31	38
5[d]	**[PC-Ir2]**	**HE2**	**75 (75)[c]**	**1.8:1**	**24**	**1**
6[d,e]	[PC-Ir2]	HE3	81 (75)[c,f]	2.0:1	7	7
7[d,e]	[PC-Ir2]	HE4	54	1.6:1	42	3
8[d,e]	[PC-Ir2]	HE5	56	1.8:1	25	19
	change from entry 5					
9	*no photocatalyst*		0[g]	-	-	-
10	*no light*		0[g]	-	-	-
11	*1a (amide) as starting material*		0[h]	-	-	-

Table 2: Photocatalytic coupling of hemiaminal species. Ar = 4-fluorophenyl. General conditions: **1aa** (from hydrosilylation step, ~0.1 mmol), **2** (0.4 mmol), photocatalyst (PC, 0.001 mmol, 1 mol%), Hantzsch ester (0.15 mmol), DMSO/PhMe (1 mL, 1:1), 16 h, under a nitrogen atmosphere under blue light irradiation using 18 W LED lamp. [a] Calculated by ¹⁹F{¹H} NMR analysis of the crude reaction mixture. [b] Calculated by ¹H NMR analysis of the crude reaction mixture. [c] Isolated yield after silica gel column chromatography. [d] DHA (0.2 mmol, 2 eq) was used. [e] Hantzsch ester (0.1 mmol, 1 eq) used. [f] Difficult chromatographic separation. [g] 4-fluorobenzaldehyde was formed as the sole product. [h] No conversion from amide **1a** was observed.

Scheme 4. Substrate scope of the reductive photocatalytic functionalization of tertiary amides. [a] HE2 used as the terminal reductant. [b] HE5 used as the terminal reductant
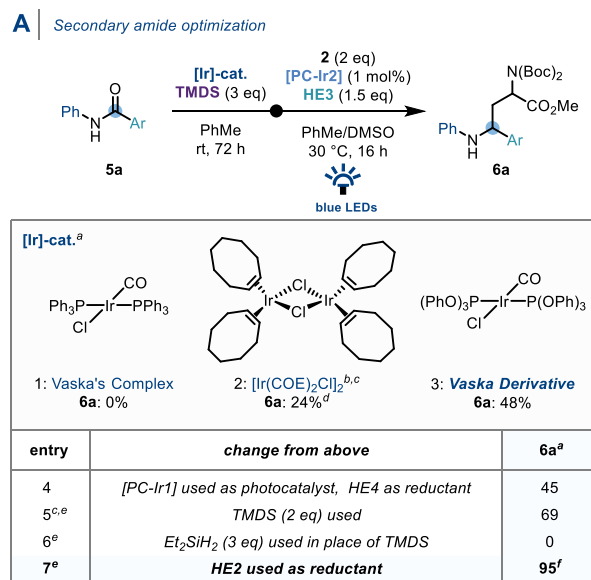

A survey of compatible photocatalysts gave a promising lead result of 17% yield of **3a** as a mixture of diastereomers when a system of [Ir(dF(CF₃)(ppy)₂(dtbbpy)]PF6 and commercially-available Hantzsch ester (HE1) terminal reductant under blue LED irradiation was employed. The desired product was however accompanied by significant quantities of undesired secondary alcohol coupled product (**3ab**) and over-reduction by-products (**3ac**) (Scheme **3B**, Table **2**, entry 1). Minimization of these background processes was achieved through fine-tuning of the reaction conditions by employing structurally modified photocatalysts and 4-substituted Hantzsch esters. After extensive screening, it was found that the combination of [Ir(dF(CF₃)(ppy)₂(bpy)](PF6) [PC-Ir] with methyl-substituted HE2 (Scheme **3B**, Table **2** entry 5) gave the 1,3-diamine product in a 75% isolated yield. The addition of other Hantzsch-based reductants (HE3 and HE5, Scheme **3B**, Table **2**, entries 6 and 8) produced similarly high-yielding results and allowed for greater flexibility in the choice of reductant in further substrate scope development. Importantly, deletion experiments demonstrated that the reaction did not proceed in the absence of photocatalyst, or light, or from the unactivated amide (entries 9-11).

Scope Development. With optimal reaction conditions in hand, the scope of the new method with respect to the aniline portion of the tertiary amides was investigated (Scheme **4**). Anisidine-derived amides (**3c**) were shown to be applicable to this methodology, as well as heterocyclic indoline (**3d**), tetrahydroquinoline (**3e**), and benzazepane (**3f**) structures, affording the decorated tertiary amine products in good yields. Notably in these cases, **HE5** outperformed the previous optimal reductant (**HE2**). Through diversification of the acyl unit on the amide, it was identified that tetrahydroisoquinoline derivative was an excellent substrate in this methodology delivering C–C coupled product **3g** in 78% yield. Furthermore, challenging architectures such as indazole (**3h**), and Ar-BPin (**3i**) motifs were well-tolerated. In addition, a variety of substituted arenes were explored under the reaction conditions (**3j-3p**). These studies revealed that electron donating substituents including alkoxy, alkyl, and aryl substituents were most effective in this transformation, forming the tertiary amine products in good yields, whereas electron-withdrawing substrates (**3p**) showed a reduction in efficacy. The length of the alkyl chain on nitrogen was then studied, and we were pleased to observe that ethyl and propyl sub-

stituted structures delivered tertiary amine products, although a steric increase vs. reaction efficiency trend was observed.[19]

Intramolecular Cyclization. We recognized the opportunity that this tandem amide activation protocol – through tethering an alkene acceptor to the alkyl chain of the amide starting material – could be suitably leveraged towards the synthesis of complex heterocyclic amine frameworks. Accordingly, model substrates bearing a pendant α,β-unsaturated ester (**1s-1t**) were prepared, but initial studies demonstrated that these motifs did not readily undergo hydrosilylation using Vaska's catalyst (only around 80% conversion was achieved after 8 hours of reaction time), and furthermore significant quantities of over reduction side-product were isolated following the photocatalytic step.[20] Nevertheless, these initial challenges were circumvented when a derivative of Vaska's complex bearing triphenylphosphite ligands – previously reported by Nagashima[21] – was employed in the hydrosilylation step instead (Scheme 5). Pleasingly, clean conversion to a stable silyl hemiaminal species was achieved within one hour, and subsequent subjection to the optimized photoredox conditions delivered the desired cyclic pyrrolidine (**4s**) and piperidine (**4t**) products in good yields.

Scheme 5. Extension of the Vaska-photoredox system for reductive cyclization of tertiary amides

Secondary Amide Activation. Recent endeavors by Chida and Sato, and Huang have demonstrated the utility of [Ir(COE)₂Cl]₂ complex in conjunction with Et₂SiH₂ reductant for the nucleophilic reductive functionalization of secondary amide building blocks, affording the corresponding α-branched secondary amine products.[4e,f]

Scheme 6. Reverse polarity, photocatalytic reductive functionalization of secondary amides. (A) Optimization of the reaction conditions. (B) Scope of the secondary amide activation protocol.

A | Secondary amide optimization

[Ir]-cat.[a]

1: Vaska's Complex
6a: 0%

2: [Ir(COE)₂Cl]₂[b,c]
6a: 24%[d]

3: *Vaska Derivative*
6a: 48%

entry	change from above	6a[a]
4	[PC-Ir1] used as photocatalyst, HE4 as reductant	45
5[c,e]	TMDS (2 eq) used	69
6[e]	Et₂SiH₂ (3 eq) used in place of TMDS	0
7[e]	HE2 used as reductant	95[f]

Table 3: Ar = 4-fluorophenyl. [a] Yield of **6a** measured using ¹⁹F{¹H} NMR analysis of the crude reaction mixture. [b] CH₂Cl₂ used as solvent and Et₂SiH₂ (3 eq) used as reductant in 1st step. [c] **HE5** used as reductant. [d] Mass balance is unreacted **5a**. [e] [PC-Ir-tBu] used as photocatalyst. [f] Isolated yield after silica gel column chromatography.

HE	R²	R³
HE2	Me	Me
HE3	Cy	Me
HE4	Ph	Et
HE5	4-CO₂MePh	Et

Hantzsch ester

R¹ = tBu: [PC-Ir1]
R¹ = H: [PC-Ir2]

B | Secondary amide scope

6a
95%, 1.8:1 dr

6b
70%, 1.1:1 dr

6c
51% 1:1 dr

6d
41%, 1.1:1 dr

6e*
50% ● 14:1 dr ● >20:1 dr

EPPTB
[inverse TAAR1 agonist]

6f
66%, 1.4:1 dr
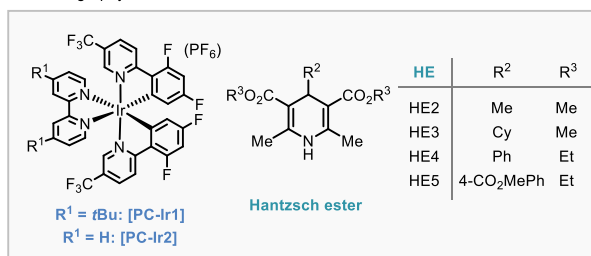
* benzyl (S)-2-(tert-butyl)-4-methylene-5-oxo-oxazolidine-3-carboxylate used as coupling partner

Accordingly, we envisioned that – drawing on their seminal work – our tandem reductive protocol could be applied to the reverse polarity functionalization of secondary amides (Scheme **6**).   Initial studies demonstrated that the Vaska/TMDS system was – as expected – ineffective in the reductive activation of secondary amides (Table 3, entry 1). Pleasingly, the [Ir(COE)$_2$Cl]$_2$ /Et$_2$SiH$_2$ system – when coupled with our photocatalytic step – formed the desired α-branched amine product (**6a**), albeit in low yields (entry 2). Unfortunately this protocol suffered from reproducibility issues attributed to the poor aerobic stability of the [Ir(COE)$_2$Cl]$_2$ complex.[22] Nevertheless, this challenge was circumvented when the phosphite derivative of Vaska's complex enabled more efficient hydrosilylation and subsequent formation of the C–C coupled product in increased yields (entry 3).

A subtle modification to the photoredox step, through exchange of photocatalyst and Hantzsch ester, gave the secondary amine structure (**6a**) in an excellent yield of 95%. This tandem secondary amide activation protocol was then applied to a varied subset of secondary amide substrates. Naphthalene (**6b**), furan (**6c**), and notably cyclohexyl (**6d**) substituted amides afforded C–C coupled products with good efficiency. Furthermore, greater diastereocontrol was imposed with the use of a modified DHA coupling partner (**6e**), with a substantial improvement in diastereoselectivity to 14:1 at the α-secondary amine position (blue). Most importantly, this reductive amide activation protocol was showcased as a late stage functionalization strategy in the transformation of the drug molecule EPPTB (**6f**) into its α-functionalized tertiary amine analogue in an excellent yield of 66%. This result illustrates the advantages of using tertiary or secondary amides as masked "iminium ion or imine" moieties that could be feasibly accessed under mild conditions in the presence of other sensitive functional groups.

MECHANISTIC INVESTIGATIONS

Control experiments. Control studies were carried out in order to probe the mechanistic pathway for the formation of the α-functionalized tertiary amine. Firstly, reactivity arising from the over-reduced amine **3ac** was investigated (Scheme **7A**). Under the tandem reductive functionalization conditions negligible quantities of the C–C coupled product were formed, and therefore the over-reduced amine was discounted as a source of the α-amino radical under these reaction conditions. Secondly, a mechanism involving direct condensation of the secondary amine and aldehyde precursors was probed. However, under the reaction conditions, only the alcohol adduct (**3ab**) was observed, demonstrating that in this system, such direct reactivity from the aldehyde moiety – and the resulting α-oxy radical – outcompetes any productive formation of an amine product (**3a**). It also highlights the importance of an amide-derived iminium ion in order to achieve .the desired reactivity.

DFT reaction pathway modelling. To further investigate the mechanistic pathway involved in the tandem hydrosilylation/photocatalytic approach, we turned to computational analysis. The reaction free energy profile for the addition of α-amino radical (**1ar**) into the DHA acceptor (**2**) was modelled at the SMD(DMSO)-ωB97X-D/6-311++G(d,p)//SMD(DMSO)-ωB97X-D/6-31+G(d,p) level of theory (Scheme **7B**). A slight out-of-plane twist in the geometry of the free radical species, resulted in a small energetic discrimination between the two potential facial orientations for the Giese-type addition.

Scheme 7. (A) Control experiments with amine and/or aldehyde starting points (B) Gibbs free energy profile for the addition of α-amino radical species into 2a.

HE= Hantzsch ester, HP= Hantzsch pyridine. Geometry optimization was completed at SMD(DMSO)/ωB97X-D/6 311++G(d,p)//SMD(DMSO)/ωB97X-D/6-31+G(d,p). Ar = 4-fluorophenyl. Blue colored and red colored electron density represent the alpha and beta spin respectively.
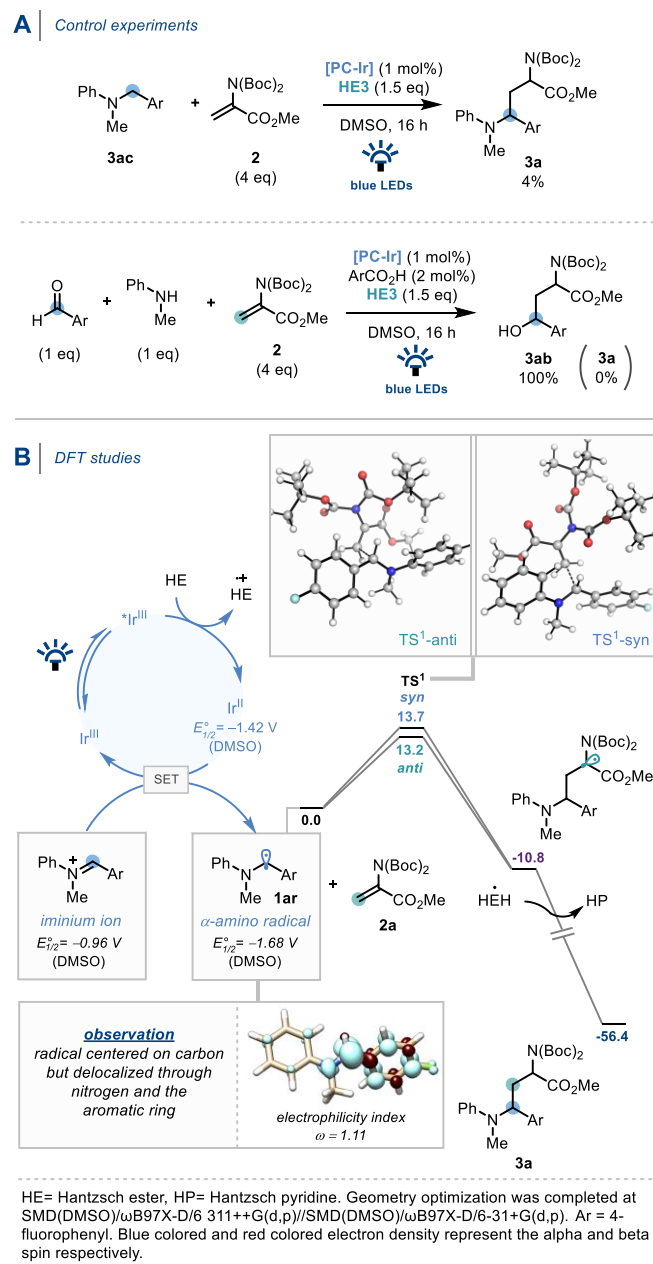
As a result, the labelled *anti* arrangement of the transition state is favored by 0.5 kcal mol⁻¹ (13.2 vs 13.7 kcal mol⁻¹ for the *syn* TS). However, it is acknowledged that ultimate diastereoselective control is established in the final HAT/protonation termination step. A similar behavior was observed for other representative substrates (see *Supporting Information* for further details). Moreover, the calculated reduction potential for the iminium species ($E^{red}_{1/2}$ = –0.96 V in DMSO) revealed that the substrate is compatible with the photocatalytic system and is unlikely to undergo two electron transfer events given the lower reduction potential of the corresponding α-amino radical ($E^{red}_{1/2}$ = –1.68 V in DMSO). Analysis of spin density for the free radical intermediates confirms the primary concentration of the electron at the α-carbon position, with additional stabilization achieved through delocalization into the adjacent nitrogen center and aromatic ring (Scheme **7B**). The combined evidence from activation energies, reduction potentials and spin densities conclude that the Giese type addition of the α-amino radical species is thermodynamically favorable.

Additionally, similar results were produced for other scope examples, suggesting that substituents on the aromatic rings did not have a significant impact on the radical's reactivity (see *Supporting Information*). To evaluate the degree to which these α-amino radicals behave as nucleophiles the global electrophilicity scale (ω), introduced by Parr, were employed.[23] Values of ω can vary from 0 to 4.00, with small values indicating a more nucleophilic species.[24] For the canonical radical species **1ar**, ω = 1.11 was obtained, which characterises it as a moderate nucleophile. A slightly smaller value was observed for radical precursors with electron donating substituents (e.g for **3k** ω = 0.97), whilst extended aromatic systems were found to be slightly

more "electrophilic" (**3o** *(ω = 1.28) and* **3p** *(ω = 1.25)*, albeit still within the acceptable range for nucleophiles. No clear trend was observed between these values and the activation energy calculated for these compounds. This further supports the idea that the variability in the electronic properties of the substrate's aromatic rings should not affect the favorability of final reductive coupling.

Yield-determining factors. Throughout this work, the efficiency of the tertiary amide components in the coupling methodology was found to be reasonably substrate-specific, with few obvious characteristics of a "good substrate". The interplay and balance between various factors – including electronic and redox properties – that favor the formation and reactivity of the two key reactive intermediates (iminium ion and α-amino radical), as well as their overall effect on the yield were subjected to deeper exploration using Density Functional Theory (DFT) methods. We initially turned to multilinear regression analysis, employing several electronic and steric parameters, such as ω indexes, reduction potentials, NBO charges, Sterimol[25] values and hydrolytic stability. Despite initial models not resulting in a comprehensive predictive model, (Scheme **8**, see *Supporting Information* for further details), an interesting correlation was observed when comparing the iminium ion stability and its corresponding reduction potential; represented as a two-dimensional heat map in Scheme **8B**. These results showed that an increased stability of the iminium ion and a lowered reduction potential enhance reaction yield. However, optimizing both parameters simultaneously is experimentally challenging to attain, given their inverse relationship. For example, while electron-withdrawing groups lower the reduction potentials, they also lead to destabilization of the iminium ion.

Scheme 8 (A). Identification of possible yield-determining parameters. (B) Heatmap correlating the reduction potential of iminium ions and their hydrolytic stability with the yield of the transformation
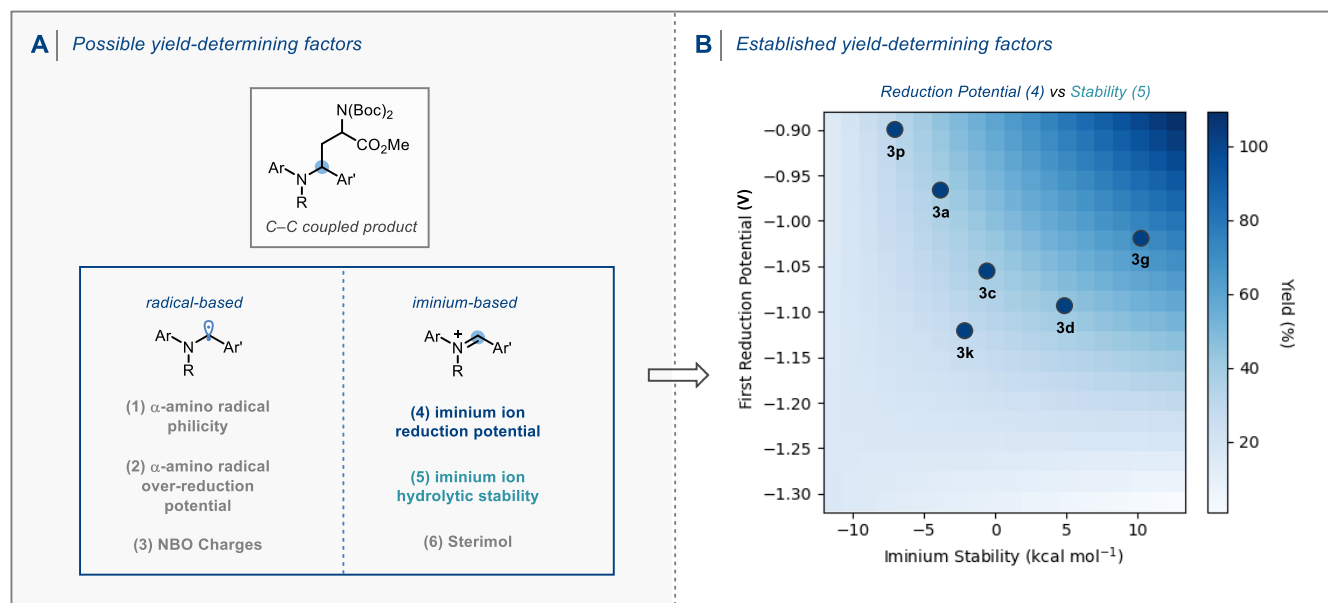
This can be illustrated with **3p**; ($E^{red}_{1/2}$ = −0.88 V; $\Delta G_{hydrolysis}$ = -4.0 kcal mol^{-1}), which despite having an accessible reduction potential, was isolated with only a 24% yield. On the other hand, electron-donating groups provide additional stability to the cationic intermediate; however, they are challenging to reduce. In agreement with this observation, no improvement in the reaction output was observed for electron rich substrates (**3d/3k**) ($E^{red}_{1/2}$ = −1.07/ −1.13 V ; $\Delta G_{hydrolysis}$ = +5.4/ -2.2 kcal mol^{-1}).

The model compound **3a** seems to provide the best compromise between these two properties ($E^{red}_{1/2}$ = −0.96 V; $\Delta G_{hydrolysis}$ = -3.8 kcal mol^{-1}). Interestingly, it was found that substrates that achieve iminium stability through geometrical constraints, without the presence of additional electron density, such as (**3g**), ($\Delta G_{hydrolysis}$ = +13.3 kcal mol^{-1} ; $E^{red}_{1/2}$ = −1.00 V), have the highest experimental and predicted yields. This predictive model indicates that the stability and accessible redox properties of the iminium ion were crucial for the successful tandem operation of the two iridium catalytic cycles.

CONCLUSION

In conclusion, a synthetic strategy that provides access to α-amino radicals from robust tertiary amide building blocks has been successfully developed. Selective tertiary amide reductive hydrosilylation using Vaska's complex, revealed a reactive iminium ion intermediate which upon photocatalytic single electron transfer afforded the desired α-amino radical in a one-pot procedure. The synthetic utility of this open-shell intermediate was exemplified in the coupling with DHA derivatives, resulting in the synthesis of 18 examples of α-functionalized tertiary amine architectures, inaccessible using conventional reductive methodologies from tertiary amides. Furthermore, the utility of our approach was showcased by adapting the method to apply to intramolecular examples and secondary amides, which we highlighted in the late stage functionalization of an API. DFT studies established that the energetic balance between hydrolytic stability of the iminium ion and an accessible reduction potential were key for the successful transition of the reactive intermediate between the hydrosilylation and photocatalytic reductive processes.

AUTHOR INFORMATION

‡ These authors contributed equally to the work.

Corresponding Author

* Fernanda Duarte (for computational correspondence): fernanda.duartegonzalez@chem.ox.ac.uk
* Darren J. Dixon (for synthetic correspondence): darren.dixon@chem.ox.ac.uk

ACKNOWLEDGMENT

REFERENCES

(1) Lemke, T. L., *Review of Organic Functional Groups: Introduction to Medicinal Organic Chemistry*, 4th ed.; Lippincott Williams & Williams: Baltimore, **2003**.

(2) For select discussions of various C-H amination strategies see: (a) *Amino Group Chemistry: From Synthesis to the Life Sciences*, Ricci, A. Ed. Wiley VCH: Weinheim, **2008**; (b) Bariwal, J.; d. Eycken, E. V. C-N Bond Forming Cross-Coupling Reactions: an Overview. *Chem. Soc. Rev.* **2013**, *42*, 9283-9303; (c) Hartwing, J. F., Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides. *Acc. Chem. Res.* **2008**, *41*, 1534-1544; (d) Surry, D. S.; Buchwald, S. L. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338-6361; (e) Heinz, C.; Lutz, J. P.; Summons, E. M.; Miller, M. M.; Ewing, W. R.; Doyle, A. G. Ni-Catalyzed Carbon-Carbon Bond-Forming Reductive Amination. *J. Am. Chem. Soc.* **2018**, *140*, 2292-2300; (f) Ruffoni, A.; Julia, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. Practical and Regioselective Amination of Arenes Using Alkyl Amines. *Nat. Chem.* **2019**, *11*, 426-433.

(3) Examples include Petasis-Mannich reaction: (a) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction. *Chem. Rev.* **2010**, *110*, 6169-6193. Amine lithiation/functionalization: (b) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanayan, S. Regioselective, Diastereoselective, and Enantioselective Lithiation-Substitution Sequences: Reaction Pathways and Synthetic Applications. *Acc. Chem. Res.* **1996**, *29*, 552-560; (c) Hoppe, D.; Hense, T. Enantioselective Synthesis with Lithium/(-)-Sparteine Carbanion Pairs. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282-2316; (d) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. Direct α-Functionalization of Saturated Cyclic Amines. *Chem.-Eur. J.* **2012**, *18*, 10092-10142. *Direct α-C-H functionalisation:* (e) Beatty, J. W.; Stephenson, C. R. J. Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1474-1484; (f) Shi, L.; Xia, W. Photoredox Functionalization of C-H Bonds Adjacent to a Nitrogen Atom. *Chem. Soc. Rev.* **2012**, *41*, 7687-7697; (g) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective sp³ C-H Alkylation via Polarity-Match-Based Cross-Coupling. *Nature* **2017**, *547*, 79-83; (h) Ratnikov, M. O.; Xu, X.; Doyle, M. P. Simple and Sustainable Iron-Catalyzed Aerobic C-H Functionalization of N,N-Dialkylanilines. *J. Am. Chem. Soc.* **2013**, *135*, 9475-9479; (i) Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; de Gombert, A.; Dixon, D. J. Primary α-Tertiary Amine Synthesis via α-C-H Functionalization. *Chem. Sci.* **2019**, *10*, 3401-3407; (j) He, J.; Hamann, L G.; Davies, H. M. L.; Beckwith, R. E. J. Late-Stage C-H Functionalization of Complex Alkaloids and Drug Molecules via Intermolecular Rhodium-Carbenoid Insertion. *Nat. Commun.* **2015**, *6*, 5943-5952; (k) Thullen, S. M.; Rovis, T. A Mild Hydroaminoalkylation of Conjugated Dienes Using a Unified Cobalt and Photoredox Catalytic System. *J. Am. Chem. Soc.* **2017**, *139*, 15504-15508; (l) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α-Amino C-H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114-1117.

(4) For reductive activation of secondary amides using catalytic methods see: (a) Ohta, T.; Kamiya, M.; Nobutomo, M.; Kusui, K.; Furukawa, I. Reduction of Carboxylic Acid Derivatives Using Diphenylsilane in the Presence of a Rh-PPh₃ Complex. *Bull Chem. Soc. Jpn.* **2005**, *78*, 1856-1861; (b) Hanada, S.; Ishida, T.; Motoyama, Y.; Nagashima, H. The Ruthenium-Catalyzed Reduction and Reductive N-Alkylation of Secondary Amides with Hydrosilanes:

Practical Synthesis of Secondary and Tertiary Amines by Judicious Choice of Hydrosilanes. *J. Org. Chem.* **2007**, *72*, 7551-7559; (d) Cheng, C.; Brookhart, M. Iridium-Catalyzed Reduction of Secondary Amides to Secondary Amines and Imines by Diethylsilane. *J. Am. Chem. Soc.* **2012**, *134*, 11304-11307; (e) Ou, W.; Han, F.; Hu, X. N.; Chen, H.; Huang, P.-Q. Iridium-Catalyzed Reductive Alkylations of Secondary Amides. *Angew. Chem. Int. Ed.* **2018**, *57*, 5705-5708; (f) Takahashi, Y.; Yoshii, R.; Sato, T.; Chida, N. Iridium-Catalyzed Reductive Nucleophilic Addition to Secondary Amides. *Org. Lett.* **2018**, *20*, 5705-5708. For non-catalytic methods see: (g) Xiao, K.-J.; Wang, A. E.; Huang, P.-Q. Direct Transformation of Secondary Amides into Secondary Amines: Triflic Anhydride Activated Reductive Alkylation. *Angew. Chem. Int. Ed.* **2012**, *51*, 8314-8317; (h) Zheng, J. F.; Qian, X. -Y.; Huang, P. -Q. Direct Transformations of Amides: a One-Pot Reductive Ugi-Type Three-Component Reaction of Secondary Amides. *Org. Chem. Front.* **2015**, *2*, 927-935; (i) Huang, P.-Q.; Huang, Y. -H.; Xiao, K.-J.; Wang, Y.; Xia, X. -E. A General Method for the One-Pot Reductive Functionalization of Secondary Amides. *J. Org. Chem.* **2015**, *80*, 2861-2868; (j) Huang, P.-Q.; Lang, Q.-W.; Hu, X. -N. One-Pot Reductive 1,3-Dipolar Cycloadditiion of Secondary Amides: A Two-Step Transformation of Primary Amides. *J. Org. Chem.* **2016**, *81*, 10227-10235; (k) Chen, H.; Ye, J. -L.; Huang, P.-Q. Chemoselective Direct Reductive Trifluoromethylation of Amides: a Flexible Access to Functionalized α-Trifluoromethylamines. *Org. Chem. Front.* **2018**, *5*, 943-947; (l) Wang, A. E.; Yu, C.-C.; Chen, T.-T.; Liu, Y.-P.; Huang, P.-Q. Enamines as Surrogates of Alkene Carbanions for the Reductive Alkenylation of Secondary Amides: an Approach to Allylamines. *Org. Lett.* **2018**, *20*, 999-1002.

(5) For reviews on tertiary amide activation see: (a) Seebach, D. Generation of Secondary, Tertiary and Quaternary Centers by Geminal Disubstitution of Carbonyl Oxygens. *Angew. Chem. Int. Ed.* **2011**, *50*, 96-101; (b) Addis, D.; Das, S.; Junge, K.; Beller, M. Selective Reduction of Carboxylic Acid Derivatives by Catalytic Hydrosilylation. *Angew. Chem. Int. Ed.* **2011**, *50*, 6004-6011; (c) Pace, V.; Holzer, W. Chemoselective Activation Strategies of Amidic Carbonyls Towards Nucleophilic Reagents. *Aust. J. Chem.* **2013**, *66*, 507-510; (d) Pace, V.; Holzer, W.; Olofsson, B. Increasing the Reactivity of Amides Towards Organometallic Reagents: An Overview. *Adv. Synth. Catal.* **2014**, *356*, 3697-3736; (e) Sato,T.; Chida, N. Nucleophilic Addition to N-Alkoxyamides. *Org. Biomol. Chem.* **2014**, *12*, 3147-3150; (f) Sato, T.; Yoritate, M.; Tajima, H.; Chida, N. Total Synthesis of Complex Alkaloids by Nucleophilic Addition to Amides. *Org. Biomol. Chem.* **2018**, *16*, 3864-3875; (g) Kaiser, D.; Bauer, A.; Lemmerer, M; Maulide, N. Amide Activation: an Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899-7925.

(6) Amide activation using triflic anhydride: (a) Xiao, K. J.; Luo J. M.; Ye, K. Y.; Wang, Y; Huang, P. -Q. Direct, One-pot Sequential Reductive Alkylation of Lactams/Amides with Grignard and Organolithium Reagents through Lactam/Amide Activation. *Angew. Chem. Int. Ed.* **2010**, *49*, 3037-3040; (b) Mewald, M.; Medley, J. W.; Movassaghi, M. Concise and Enantioselective Total Synthesis of (-)-Mehranine, (-)-Methylenebismehranine, and Related Aspidosperma Alkaloids. *Angew. Chem. Int. Ed.* **2014**, *53*, 11634-11639; (c) Romanens, A.; Belanger, G. Preparation of Conformationally Restricted β²,²- and β²,³-Amino Esters and Derivatives Containing All All-Carbon Quaternary Center. *Org. Lett.* **2015**, *17*, 322-325; (d) White, K. L.; Mewald, M.; Movassaghi, M. Direct Observation of Intermediates Involved in the Interruption of the Bischler-Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403-7411; (e) Kaiser, D.; Maulide, N. Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides. *J. Org. Chem.* **2016**, *81*, 4421-4428; (f) Lindemann, C.; Schneider, C. Quinolizidine-Based Alkaloids: A General Catalytic, Highly Enantio- and Diastereoselective Synthetic Approach. *Synthesis* **2016**, *48*, 828-844; (g) Gawali, V. S.; Simeonov, S.; Drescher, M.; Thomas, K.;

Olaf, S.; Kudolo, J.; Hanspeter, K.; Ulla, H.; Roller, A.; Todt, H.; Maulide, N. C2-Modified Sparteine Derivatives Are a New Class of Potentially Long-Acting Sodium Channel Blockers. *ChemMedChem* **2017**, *12*, 1819-1822.

(7) Amide activation using titanium reagents: (a) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. A Mild General Procedure for the One-Pot Conversion of Amides to Aldehydes. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1515-1516; (b) Laval, S.; Dayoub, W.; Favre-Reguillon, A.; Demonchaux, P.; Mignani, G.; Lemaire, M. A Mild Titanium-Based System for the Reduction of Amides to Aldehydes. *Tetrahedron. Lett.* **2010**, *51*, 2092-2094. (c) Jacubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. Total Synthesis of Manzamine A and Related Alkaloids. *J. Am. Chem. Soc.* **2012**, *134*, 17842-17485.

(8) Amide activation using Schwartz Reagent: (a) Oda, Y.; Sato, T.; Chida, N. Direct Chemoselective Allylation of Inert Amide Carbonyls. *Org. Lett.* **2012**, *14*, 950-953; (b) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. Total Synthesis of (±)-Gephrotoxin by Amide-Selective Reductive Nucleophilic Addition. *Angew. Chem. Int. Ed.* **2014**, *53*, 512-516; (c) Yoritate, M.; Meguro, T.; Matsuo, N.; Shirokane, K.; Sato, T.; Chida, N. Two-Step Synthesis of Multi-Substituted Amindes by Using an N-Methoxy Group as a Reactivity Control Element. *Chem. Eur. J.* **2014**, *20*, 8210-8216; (d) Nakajima, M.; Oda, Y.; Wada, T.; Minamikawa, R.; Shirokane, K.; Sato, T.; Chida, N. Chemoselective Reductive Nucleophilic Addition to Tertiary Amides, Secondary Amides, and N-Methoxyamides. *Chem. Eur. J.* **2014**, *20*, 17565-17571; (e) Shirokane, K.; Tanaka, Y.; Yoritate, M.; Takayama, N.; Sato, T.; Chida, N. Total Syntheses of (±)-Gephyrotoxin and (±)-Perhydrogephyrotoxin. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 522-537.

(9) Amide activation using stoichiometric metal reductants: (a) Shirokane, K.; Kurosai, Y.; Sato, T.; Chida, N. A Direct Entry to Substituted N-Methoxyamines from N-Methoxyamides via N-Oxyiminium Ions. *Angew. Chem. Int. Ed.* **2010**, *49*, 6369-6372; (b) Ong, D. Y.; Fan, D.; Dixon, D. J.; Chiba, S. Transition-Metal Free Reductive Functionalization of Tertiary Carboxamides and Lactams for α-Branched Amine Synthesis. *Angew. Chem. Int. Ed.* **2020**, *59*, 1-6.

(10) Amide activation using molybdenum catalysts: (a) Volkov, A.; Tinnis, F.; Slagbrand, T.; Pershagen, I.; Adolfsson, H. Mo(CO)₆ Catalysed Chemoselective Hydrosilylation of α,β-Unsaturated Amides for the Formation of Allylamines. *Chem. Commun.* **2014**, *50*, 14508-14511; (b) Tinnis, F.; Volkov, A.; Slagbrand, T.; Adolfsson, H. Chemoselective Reduction of Tertiary Amide under Thermal Control: Formation of Either Aldehydes or Amines. *Angew. Chem. Int. Ed.* **2016**, *55*, 4562-4566; (c) Trillo, P.; Slagbrand, T.; Tinnis, F.; Adolfsson, H. Facile Preparation of Pyrimidinediones and Thioacrylamides via Reductive Functionalization of Amides. *Chem. Commun.* **2017**, *53*, 9159-9162; (d) Slagbrand, T.; Kervefors, G.; Tinnis, F.; Adolfsson, H. An Efficient One-Pot Procedure for the Direct Preparation of 4,5-Dihydroisoxazoles from Amides. *Adv. Synth. Catal.* **2017**, *359*, 1990-1995; (e) Slagbrand, T.; Volkov, A.; Trillo, P.; Tinnis, F.; Adolfsson, H. Transformation of Amides into Highly Functionalized Triazolines. *ACS Catal.* **2017**, *7*, 1771-1775.

(11) Other transition metal catalysed amide activation methods include: Zinc (a) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. Zinc-Cataltzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance. *J. Am. Chem. Soc.* **2010**, *132*, 1770-1771; (b) Das, S.; Addis, D.; Junge, K.; Beller, M. Zinc-Catalyzed Chemoselective Reduction of Tertiary and Secondary Amides to Amines. *Chem. Eur. J.* **2011**, *17*, 12186-12192. Iron (c) Sunada, Y.; Kawakami, H.; Imaoka, T.; Motoyama, Y.; Nagashima, H. Hydrosilane Reduction of Tertiary Carboxamides by Iron Carbonyl Catalysts. *Angew. Chem. Int. Ed.* **2009**, *48*, 9511-9514; (d) Zhou, S.; Junge, K.; Addis, D.; Das, S.; Beller, M. A Convenient

and General Iron-Catalyzed Reduction of Amides to Amines. *Angew. Chem. Int. Ed.* **2009**, *48*, 9507-9510. Gold nanoparticles (e) Mikami, Y.; Noujima, A.; Misudome, T.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. Highly Efficient Gold Nanoparticle Catalyzed Deoxygenation of Amides, Sulfoxides, and Pyridine N-Oxides. *Chem. Eur. J.* **2011**, *17*, 1768-1772. Platinum (f) Hanada, S.; Tsutsumi, E.; Motoyama, Y.; Nagashima, H. Practical Access to Amines by Platinum-Catalyzed Reduction of Carboxamides with Hydrosilanes: Synergy of Dual Si-H Groups Leads to High Efficiency and Selectivity. *J. Am. Chem. Soc.* **2009**, *131*, 15032-15040. Ruthenium/Osmium (g) Motoyama, H.; Mitsui, K.; Ishida, T.; Nagashima, H. Self-Encapsulation of Homogenous Catalyst Species into Polymer Gel Leading to a Facile and Efficient Separation System of Amine Products in the Ru-Catalyzed Reduction of Carboxamides with Polymethylhydrosiloxane (PMHS). *J. Am. Chem. Soc.* **2005**, *127*, 13150-13151; (h) Igarashi, M.; Fuchikami, T. Transition-Metal Complex-Catalyzed Reduction of Amides With Hydrosilanes: a Facile Transformation of Amides to Amines. *Tetrahedron. Lett.* **2001**, *42*, 1945-1947. Rhodium (i) Kuwano, R.; Takahashi, M.; Ito, Y. Reduction of Amides to Amines via Catalytic Hydrosilylation by a Rhodium Complex. *Tetrahedron. Lett.* **1998**, *39*, 1017-1020. Iridium (j) Park, S.; Brookart, M. J. Development and Mechanistic Investigation of a Highly Efficient Iridium(V) Silyl Complex for the Reduction of Tertiary Amides to Amines. *J. Am. Chem. Soc.* **2012**, *134*, 640-653.

(12)   (a) Motoyama, Y.; Aoki, M.; Takaoka, N.; Aoto, R.; Nagashima, H. Highly Efficient Synthesis of Aldenamines from Carboxamides by Iridium-Catalyzed Silane Reduction/Dehydration Under Mild Conditions. *Chem. Commun.* **2009**, 1574-1576; (b) Gregory, A. W.; Chambers, A.; Hawkins, A.; Jakubec, P.; Dixon, D.J. Iridium-Catalyzed Reductive Nitro-Mannich Cyclization. *Chem. Eur. J.* **2015**, *21*, 111-114; (c) Nakajima, M.; Sato, T.; Chida, N. Iridium-Catalyzed Chemoselective Reductive Nucleophilic Addition to N-Methoxyamides. *Org. Lett.* **2015**, *17*, 1696-1699; (d) Huang, P. -Q.; Ou, W.; Han, F. Chemoselective Reductive Alkynylation of Tertiary Amides by Ir and Cu(I) Bis-Metal Sequential Catalysis. *Chem. Commun.* **2016**, *52*, 11967-11970; (e) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from N-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138*, 5246-5249; (f) Xie, L. G.; Dixon, D. J. Tertiary Amine Synthesis via Reductive Coupling of Amides with Grignard Reagents. *Chem. Sci.* **2017**, *8*, 7492-7497; (g) Fuentes de Arriba, A. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation. *Angew. Chem. Int. Ed.* **2017**, *56*, 3655-3659; (h) Xie, L.G.; Dixon, D.J. Iridium-Catalyzed Reductive Ugi-Type Reactions of Tertiary Amides. *Nat. Commun.* **2018**, *9*, 2841-2849.; (i) Takahashi, Y.; Sato, T.; Chida, N. Iridium-Catalyzed Reductive Nucleophilic Addition to Tertiary Amides. *Chem. Lett.* **2019**, *48*, 1138-1141; (j) Une, Y.; Tahara, A.; Miyamoto, Y.; Sunada, Y.; Nagashima, H. Iridium-PPh₃ Catalysts for Conversion of Amides to Enamines. *Organometallics,* **2019**, *38*, 852-862; (k) Gabriel, P.; Gregory, A. W.; Dixon, D. J. Iridium-Catalyzed Aza-Spirocyclization of Indole-Tethered Amides: An Interrupted Pictet-Spengler Reaction. *Org. Lett.* **2019**, *21*, 6658-6662; (l) Gabriel, P.; Xie, L. G.; Dixon, D. J. Iridium-Catalyzed Reductive Coupling of Grignard Reagents and Tertiary Amides. *Org. Synth.* **2019**, *96*, 511-527.

(13)   (a) Tan, P. W.; Seayad, J.; Dixon, D. J. Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates. *Angew. Chem. Int. Ed.* **2016**, *55*, 13436-13440; (b) Nakayama, Y.; Maeda, Y.; Kotatsu, M.; Sekiya, R.; Ichiki, M.; Sato, T.; Chida, N. Enantioselective Total Synthesis of (+)-Neostenine. *Chem. Eur. J.* **2016**, *22*, 3300-3303; (c) Yoritate, M.; Takahashi, Y.; Tajima, H.; Ogihara, C.; Yokoyama, T.; Soda, Y.; Oishi, T.; Sato, T.; Chida, N. Unified Total Synthesis of Stemoamide-Type Alkaloids by Chemoselective Assembly of Five Membered Building Blocks. *J. Am. Chem. Soc.* **2017**, *139*, 18386-18391; (d) Gammack, G. A. D.; Dixon, D. J. Enantioselective Synthesis of the ABCDE Pentacyclic Core of the Strychnos Alkaloids. *Org. Lett.* **2017**, *19*, 1894-1897; (e) Yamamoto, S.; Komiya, Y.; Kobayashi, A.; Minakawa, R.; Oishi, T.; Sato, T.; Chida, N. Asymmetric Total Synthesis of Fasicularin by Chiral N-Alkoxyamide Strategy. *Org. Lett.* **2019**, *21*, 1868-1871; (f) Wood, M. D.; Klosowski, D. W.; Martin, S. F. Stereoselective Total Syntheses of (±)-Alstoscholarisine E. *Org. Lett.* **2020**, *22*, 786-790.

(14)   For nucleophilic reactivity at the β-position from a hemi-aminal-derived enamine, see ref 13a.

(15)   For reviews see: (a) Leitch, J. A.; Rossolini, T.; Rogova, T.; Maitland, J. A. P.; Dixon, D. J. α-Amino Radicals via Photocatalytic Single-Electron Reduction of Imine Derivatives. *ACS Catal.* **2020**, *10*, 2009-2025; (b) Garrido-Castro, A. F.; Maesto, M. C.; Alemán, J. α-Functionalization of Imines via Visible Light Photoredox Catalysis. *Catalysts,* **2020**, *10*, 562; (c) Lee, K. N.; Ngai, M.-Y. Recent Development in Transition-Metal Photoredox-Catalyzed Reactions of Carbonyl Derivatives. *Chem. Commun.* **2017**, *53*, 13093-13112.

(16)   For select examples refer to: (a) Qi, L.; Chen, Y. Polarity-Reversed Allylations of Aldehydes, Ketones, and Imines Enables by Hantzsch Ester in Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 13312-13315; (b) Fuentes de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. Umpolung Synthesis of Branched α-Functionalized Amines From Imines via Photocatalytic Three-Component Reductive Coupling Reactions. *Chem. Commun.* **2016**, *52*, 14434-14437; (c) Lee, K.N.; Lei, Z.; Ngai, M.-Y. β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis Acid/Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 5003-5006; (d) Leitch, J. A.; Fuentes de Arriba, A. L.; Tan, J.; Hoff, O.; Martinez, C. M.; Dixon, D. J. Photocatalytic Reverse Polarity Povarov Reaction. *Chem. Sci.,* **2018**, *9*, 6653-6658; (e) Trowbridge, A.; Reich, D.; Gaunt, M. J. Multicomponent Synthesis of Tertiary Alkylamines by Photocatalytic Olefin-Hydroaminoalkylation. *Nature* **2018**, *561*, 522-527; (f) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett.* **2018**, *20*, 6794-6798; (g) Floden, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt M. J. Streamlines Synthesis of C(sp³)-Rich N-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426-8430; (h) Cao, K.; Tan, S. M.; Lee, R.; Yang, S.; Jia, H.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Enantioselective Addition of Prochiral Radicals to Vinylpyridines. *J. Am. Chem. Soc.* **2019**, *141*, 5437-5443; (i) Wang, R.; Ma, M.; Gong, X.; Fan, X.; Walsh, P. J. Reductive Cross-Coupling of Aldehydes and Imines Mediated by Visible Light Photoredox Catalysis. *Org. Lett.* **2019**, *21*, 27-31; (j) Reich, D.; Trowbridge, A.; Gaunt, M. J. Rapid Syntheses of (-)-FR901483 and (+)-TAN1251C Enables by Complexity-Generating Photocatalytic Hydroaminoalkylation. *Angew. Chem. Int. Ed.* **2020**, *59*, 2256-2261; (k) Kumar, R.; Floden, N.; Whitehurst, W. G.; Gaunt, M. J. A General Carbonyl Alkylative Amination for Tertiary Amine Synthesis. *Nature* **2020**, *581*, 415-420; (l) Leitch, J. A.; Rogova, T.; Duarte, F.; Dixon, D. J. Dearomative Photocatalytic Construction of Bridged 1,3-Diazepanes. *Angew. Chem. Int. Ed.* **2020**, *59*, 4121-4130; (m) Leng, L.; Fu, Y.; Peng, L.; Ready, J. M. Regioselective, Photocatalytic α-Functionalizatoin of Amines. *J. Am. Chem. Soc.* **2020**, *142*, 11972-11977.

(17)   (a) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A Pratical and Scalable System for Heteroaryl Amino Acid Synthesis. *Chem. Sci.* **2017**, *8*, 7998-8003; (b) Aycock, R. A.; Pratt, C. J.; Jui, N. T. Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. *ACS. Catal.* **2018**, *8*, 9115-9119; (c) Seath, C. P.; Jui, N. T. Intermolecular Reactions of Pyridyl Radicals with Olefins via Photoredox Catalysis. *Synlett* **2019**, *30*, 1607-1614.

(18) Anhydrous conditions were essential to prevent iminium ion hydrolysis. Toluene was degassed and stored over 4 Å molecular sieves in an AcrosSeal® bottle.

(19) Dialkyl and benzyl-substituted amides were found to be incompatible with these reaction conditions (see supporting information).

(20) The propensity for over-reduction is unclear, but a potential intramolecular [1,4]-HAT event from the α-amino radical instead of Giese addition could be responsible.

(21) Tahara, A.; Miyamoto, Y.; Aoto, R.; Shigeta, K.; Une, Y.; Sunada, Y.; Motoyama, Y.; Nagashima, H. Catalyst Design of Vaska-Type Iridium Complexes for Highly Efficient Synthesis of π-Conjugated Enamines. *Organometallics* **2015**, *34*, 4895-4907.

(22) Herde, J. L.; Lambert, J. C.; Senoff, C. V. *Inorganic Syntheses*; Parshall, G. W. Ed. McGraw-Hill, **1974**; Vol. 15, 18-20.

(23) Parr, R. G.; v. Szentpaly, L.; Liu, S. Electrophilicity Index. *J. Am. Chem. Soc.* **1999**, *121*, 1922-1924.

(24) De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. Electrophilicity and Nucleophilicity Index for Radicals. *Org. Lett.* **2007**, *9*, 2721-2724.

(25) Brethome, A. V.; Fletcher, S. P.; Paton, R. S. Conformational Effects on Physical-Organic Descriptors: The Case of Sterimol Steric Parameters. *ACS Catal.* **2019**, *9*, 2313-2323.