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Visible-Light-Mediated Remote γ-C(sp^3)−H Functionalization of Alkylimidates: Synthesis of 4-Iodo-3,4-dihydropyrrole Derivatives

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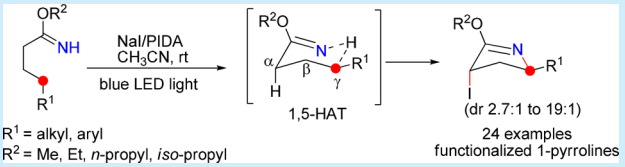
Supporting Information

ABSTRACT: An efficient and environmentally friendly synthetic approach toward functionalized dihydropyrrole derivatives is reported. The developed protocol proceeds via chemoselective intramolecular N−C bond formation of alkylimidates through 1,5-hydrogen atom transfer from *in situ* generated imidate *N*-radicals. The major advantage of this designed strategy lies in the choice of starting materials, mild reaction conditions, high chemo- and diastereoselectivity, clean source of energy, and good functional group tolerance. Further, 4-iododihydropyrroles could be easily transformed into a variety of useful derivatives.



The design of sustainable and efficient synthetic strategies that utilize ubiquitous and readily available starting materials and satisfy the parameters of green chemistry is a highly desirable and continuous effort in contemporary organic synthesis. Functionalized *N*-heterocycles are important and key structural motifs that are present in many natural products and high-value synthons for pharmaceutical industries.[1,2] The function of nitrogen-containing compounds critically depends on their characteristic structures, so the late-stage functionalization of these molecules is of high research priority in drug discovery.[1−3] *N*-Heterocycles containing a five-membered nucleus, for example, pyrroles[4] and dihydropyrroles,[5] are privileged scaffolds and play important roles across various fields of science. As a result, numerous elegant synthetic strategies have been designed for their synthesis.[4,5] Most of the developed protocols extensively use oxime derivatives as key precursors under either metal-catalyzed conditions or photochemical conditions (Figure 1).[6]

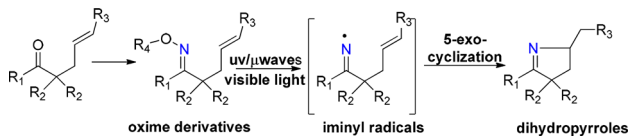


Figure 1. General scheme for the synthesis of dihydropyrrole derivatives.

Despite several well-decorated methods available in the literature, the major challenges associated with these reported protocols are (a) the need of elaborated steps to access starting materials and (b) the need for a metal-based-catalyst or photocatalyst (difficult to remove from the reaction mixtures and eventually responsible for toxicity). Considering these facts, there is a need to develop a convenient, efficient, and cost-effective method for the synthesis of functionalized dihydropyrroles from readily available starting materials under mild reaction conditions.

In the recent past, a photochemical approach has emerged as a powerful, clean, alternative technique for making C−C and C−X (where X = N, O, S) bonds. In particular, visible-light-mediated late-stage functionalization of unreactive (γ or δ) C(sp^3)−H bonds through chemoselective 1,5-hydrogen-atom-transfer (HAT) is an attractive research priority for the chemical industries.[7−13] Recently, several research groups, e.g., Leonori,[9] Studer,[10] Nevado,[11] and Muniz,[12] have designed very effective protocols for the functionalization of unreactive C(sp^3)−H distal bonds *viz.* the generation of iminyl or amidyl radicals under a single-electron-transfer (SET) approach using photoredox catalysts.[7−14] A major obstacle in these strategies is the cost of the overall reactions and limited availability of photoredox catalysts. Hence, a photochemical reaction without any costly additional metal-based-photocatalyst is a significant research field in organic chemistry. Very recently, the groups of Nagib[13b] and He[15] have reported methods for the synthesis of valuable 1,2-amino alcohols via radical-mediated intramolecular β-N−C bond formation of alkylimidate derivatives (Scheme 1A,B).

Taking inspiration from their pioneering works and our research interest in the development of new synthetic protocols for important heterocyclic molecules,[16] we envisaged that appropriately functionalized alkylimidates could ideally serve as a source of imidate *N*-radicals under visible-light conditions, which would eventually activate remote γ-C(sp^3)−H bonds selectively via a thermodynamically favorable 1,5-HAT leading to a variety of functionalized dihydropyrrole derivatives. Herein, we report the development of novel, transition-metal-free, visible-light induced, chemoselective intramolecular γ-C(sp^3)−H amidation reactions of alkylimi-

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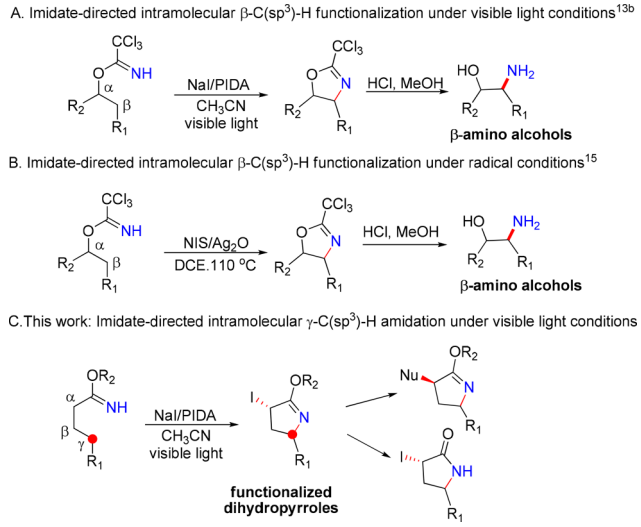
Scheme 1. Imidate Radical-Directed Intramolecular Chemoselective Distal N−C Bond Formation

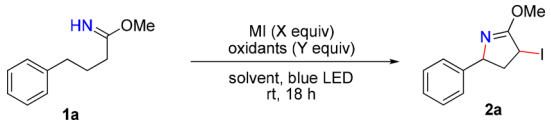


dates, including an unexpected C−I bond formation (Scheme 1C). To the best of our knowledge, use of alkylimidates as a key precursor for the straightforward synthesis of functionalized dihydropyrroles by intramolecular γ-N−C bond formation has not been reported to date.

At the outset, we selected 4-phenylbutylimidate **1a** as a model substrate as it possesses a benzylic C−H bond at the γ-position to the imidate (−NH) group. To generate an imidate *N*-radical, a combination of NaI/PIDA (*in situ* generation of triiodide, Nagib protocol)[13] was employed to form an N−I bond, and blue LED light (λ_{max} = 455 nm) was used to dissociate the N−I bond. Under these selected conditions, when the reaction was carried out in CH_3CN for 18 h, unexpectedly, we obtained 4-iododihydropyrrole **2a** in 64% yield with moderate diastereoselectivity (dr 3.2:1, entry 1, Table 1). The outcome of this reaction was quite interesting because it not only enables chemoselective N−C bond formation but also allows the formation of a C−I bond. Hence, several reaction parameters were optimized to increase the overall efficiency of this designed protocol, and the results are tabulated in Table 1 (for detailed optimization studies, see the Supporting Information (SI)).[17] After careful optimization, the reaction conditions described in Table 1, entry 11, were selected for the further exploration. Notably, in the absence of light, NaI, and PIDA, no product formation was observed, which further demonstrates their importance in this cascade reaction (entries 12−14).

With these optimized reaction conditions in hand, we next evaluated the scope of this transformation via visible-light-mediated remote γ-C(sp^3)−H activation. Alkylimidates containing different *O*-alkyl groups in the alkoxy group, for instance, trifluoroethyl, trichloroethyl, ethyl, *n*-propyl, and isopropyl groups (**1b−f**, Scheme 2) instead of the methyl moiety, were also employed under the optimized reaction conditions, and the corresponding 4-iodo-3,4-dihydropyrroles (**2b−f**) were isolated in moderate yields (54 to 61%). In general, we observed that the reaction proceeds very well with methyl- and trifluoroethyl-substituted butylimidates (**1a** and **1b**). Interestingly, when the reactions were carried out with ethyl-, *n*-propyl-, and isopropyl-substituted alkylimidates (**1d−f**), which contain two possible sites of γ-C−H functionalization

Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	MI (*X* equiv)	oxidants (*Y* equiv)	solvent	yield of **2a**[b] (%)
1	NaI (3.0)	PIDA (3.0)	CH_3CN	64
2	KI (3.0)	PIDA (3.0)	CH_3CN	48
3	NH_4I (3.0)	PIDA (3.0)	CH_3CN	0
4	NaI (3.0)	PIFA(3.0)	CH_3CN	0
5	NaI (3.0)	PIDA (3.0)	CH_2Cl_2	trace
6	NaI (3.0)	PIDA (3.0)	1,4-dioxane	46
7	NaI (4.0)	PIDA (4.0)	CH_3CN	71
8	NaI (5.0)	PIDA (5.0)	CH_3CN	62
9[c]	NaI (4.0)	PIDA (4.0)	CH_3CN	54
10[d]	NaI (4.0)	PIDA (4.0)	CH_3CN	30
11[e]	NaI (4.0)	PIDA (4.0)	CH_3CN	75
12[f]	NaI (4.0)	PIDA (4.0)	CH_3CN	0
13		PIDA (4.0)	CH_3CN	0
14	NaI (4.0)		CH_3CN	0

[a]Reaction conditions: imidate **1a** (0.3 mmol), MI (*X* equiv), oxidant (*Y* equiv), and solvent (3.0 mL) were irradiated under degassed conditions at rt using 12 W blue LED for 18 h. [b]Isolated yield of the product **2a**. [c]Reaction was performed with 12 W white LED. [d]Reaction was performed with 12W green LED. [e]Reaction was performed with 12 W(×2) blue LED. [f]Reaction was performed in the dark.

via 1,5-HAT, the chemoselective products were formed along with some unidentified compounds. The observed chemoselectivity could be explained on the basis of the C−H BDE (BDE: bond dissociation energy) for the benzyl over the methyl or ethyl groups. This high-level selectivity is an attractive feature of this developed method. Indeed, when the reaction was carried out with 1 mmol of **1a** under the standard reaction conditions, the desired product **2a** was obtained in 58% yield along with some uncharacterized compounds. Further, 4-arylbutylimidates **1g−k** containing electron-donating groups (EDGs), such as methyl, ethyl, *tert*-butyl, and methoxy, at the *meta* and *para* positions of the phenyl ring reacted well under the standard conditions and gave the corresponding products in moderate to good yields (50−70%, Scheme 2, entries **2g−k**) with excellent diastereoselectivity (dr 19:1).

The 2,4-*trans* diastereoselectivity was unambiguously confirmed by NMR techniques. The NOESY spectrum of **2a** shows no correlations between peaks of H-2 and H-4 protons; however, a strong correlation was observed between signals of H-2′ and H-4′ protons of other diastereomers, confirming the stereochemical relationship between two functional groups (for details, see the SI).[17] Similarly, 4-arylbutylimidates (**1n** and **1o**) bearing a halo functional group such as fluoro at the *para* position of the aromatic ring gave the desired products in moderate yields (49−56%, entries **2n** and **2o**). The substituents on the aryl ring had no apparent effect on the outcome of the reaction. In addition, the substrate scope of this protocol was further extended for the synthesis of the heteroaryl derivative, which was procured in a low yield of 36% (entry **2p**). Having demonstrated the generality of the developed protocol with alkylimidates containing benzylic C−H bonds, we next turned our attention to more challenging and unbiased substrates, for instance, long-chain aliphatic

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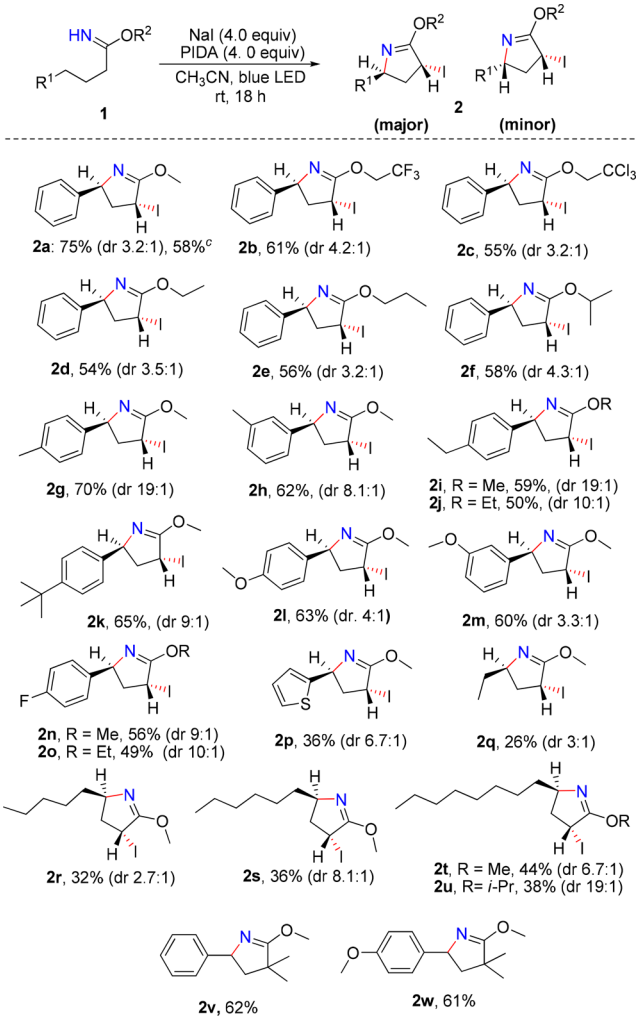
Scheme 2. Substrate Scope for 4-Iodo-3,4-dihydropyrrole Derivatives[a,b]

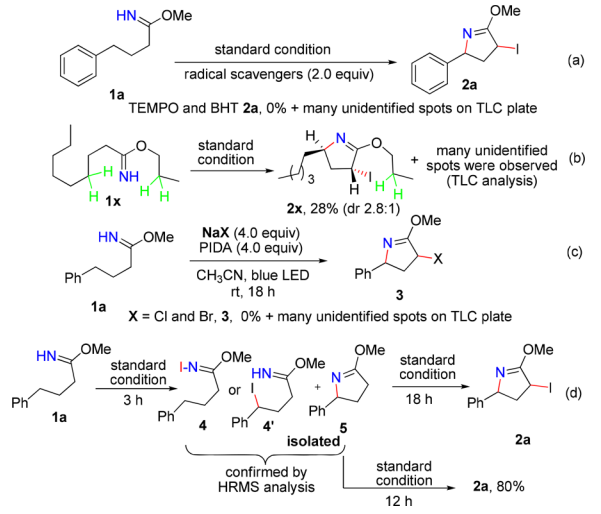


[a]For reaction conditions, see entry 11 of Table 1. [b]Isolated yields of the products. The diastereomeric ratios (dr) were determined by ^{1}H NMR analysis of reaction mixtures and are given in parentheses. [c]Reaction was carried out on a 1.0 mmol scale.

imidates containing stronger C−H bonds (BDE: benzylic 90 kcal/mol vs aliphatic 97 kcal/mol).[13b,18] The imidates containing unbiased secondary γ-C−H bonds (**1q**−**u**), when subjected to similar reaction conditions, gratifyingly provided the desired dihydropyrroles, albeit in low yields (26 to 44%, entries **2q**−**u**) with high diastereoselectivity. Subsequently, the substrate scopes of this protocol were further extended with sterically hindered alkylimidates. The reaction works equally well for α-disubstituted imidates (**1v**−**w**) and afforded the desired products in good yields (61−62%, entries **2v**−**w**).

To investigate the mechanistic aspects of this reaction, a few additional control experiments were carried out, and the results are summarized in Scheme 3. When the reaction of alkylimidate **1a** was carried out in the presence of a stoichiometric amount of radical scavengers such as TEMPO and BHT, the desired transformation was completely inhibited (Scheme 3a). This observation suggests that the reaction probably proceeds by the radical pathway. In order to check the chemoselectivity in this transformation, a suitable imidate **1x** containing two methylene (−CH_2) groups at the γ-position

Scheme 3. Control Experiments



to the imidate (−NH) was subjected to optimize conditions. Impressively, only one of the methylene groups was activated to form the desired product **2x** (28%) along with many uncharacterized products (Scheme 3b). This result illustrates that the γ-C−H bond of the nitrile sides of the imidate (−NH) group could be selectively activated over the alcohol domain. In addition, when the reactions were performed with other sodium halide salts such as NaCl and NaBr in place of NaI under the standard conditions, no desired product was obtained (Scheme 3c), and a complex reaction mixture was observed on a TLC plate. Next, we attempted to detect the reaction intermediates by using ^{1}H NMR and HRMS analysis (Scheme 3d, for details, see the SI).[17] Specifically, when **1a** was subjected to the standard conditions for 3 h, intermediates **4** or **4′** and **5** were detected ($[M + H]^+$ ion peaks at m/z = 304.0183 and 176.1066, respectively) by mass spectrometry, which eventually corresponds to either *N*-iodobutylimidate **4** or 4-iodophenylbutanimidate **4′** and 1-pyrroline **5**. Furthermore, it was possible to isolate the key intermediate **5** from the reaction mixture and unambiguously characterize it by NMR and HRMS measurements (for details, see the SI).[17] Moreover, when isolated intermediate **5** was further subjected to similar conditions, we obtained the C-4 halogenated 1-pyrroline **2a** in 80% yield. These additional control experiments implied that *in situ* generated IOAc (from NaI and PIDA) plays a dual role in this reaction to form the weak N−I bond (BDE: N−I = 38.0 kcal/mol)[13c,19] that is broken under these mild reaction conditions and to be the source of electrophilic iodonium ion. To the best of our knowledge, this is the first example that showcases the dual ability of iodine monoacetate in visible-light-mediated γ-C−H amidation.

On the basis of the above control experiments and previous literature reports,[7−13] a plausible reaction mechanism is proposed in Scheme 4. First, the imidate group (−NH) of **1a** reacts with NaI/PIDA via *in situ* generated IOAc[13c,20] (confirmed by ^{1}H NMR measurements, see the SI)[17] to give *N*-iodobutylimidate **4**, which undergoes *N*-I homolytic cleavage under visible-light conditions to afford imidate *N*-radical **A**. Subsequently, 1,5-HAT from the γ-C−H bond to the imidate radical **A** provides carbon radical **B**. This species **B** abstracts an iodine atom from **4** via a radical-chain reaction to generate iodinated intermediate **4′**. Intramolecular nucleophilic attack of the imidate (−*NH*) group onto the C−I bond

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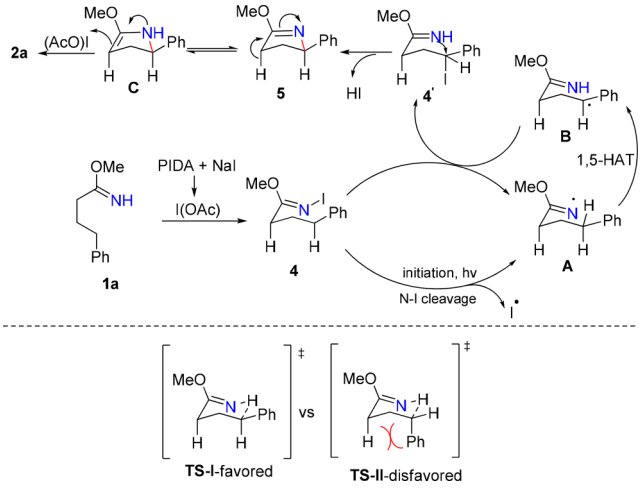
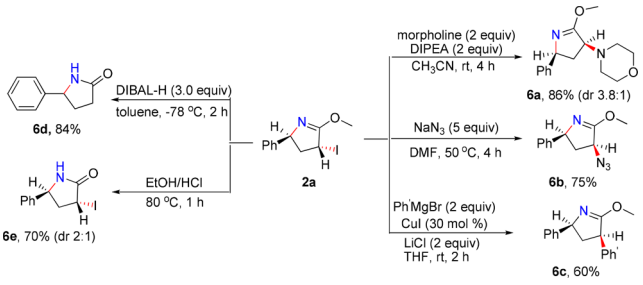
Scheme 4. Proposed Reaction Mechanism



leads to the five-membered key intermediate 1-pyrroline **5**. Subsequently, pyrroline **5** will give the desired 4-iodo-3,4-dihydropyrrole product **2a** via tautomerization of **5** to **C**, followed by the nucleophilic attack of enamine species **C** to the iodine monoaceate (IOAc). Notably, the observed high *trans* selectivity could be explained from the proposed transition state **TS-I** and **TS-II**. Minimization of the steric interaction between the hydrogen and phenyl moiety leads to thermodynamically favored **TS-I** over **TS-II**.

Apparently, the presence of an iodo or alkoxy moiety in the dihydropyrrole products makes venerable synthetic precursors that are well suited for further manipulation. Hence, we selected 4-iodo-2,3-dihydropyrrole **2a** to transform it into various useful products (Scheme 5). Nucleophilic substitution

Scheme 5. Synthetic Manipulations of 4-Iodo-3,4-dihydro-2*H*-pyrrole



(S_N2) of the iodide in **2a** with the nucleophile such as morpholine, azide, and Grignard reagent afforded the corresponding products in good yields (60−83%, entries **6a−c**) and gave an alternative method to construct such structures. Reaction with DIBAL-H at −78 °C for 2 h gave 5-phenylpyrrolidin-2-one **6d** in 84% yield, where the iodide group was also substituted with a hydride group in addition to the imine reduction. Further, selective cleavage of the C−O bond was realized in different reaction conditions. For example, when dihydropyrrole **2a** was treated with hydrochloric acid in ethanol at 80 °C for 1 h, selective cleavage of the C−O bond was achieved, and the corresponding 3-iodo-5-phenylpyrrolidin-2-one **6e** was isolated in 70% yield (entry **6e**).

In summary, we have developed an effective and straightforward approach for the synthesis of functionalized chiral dihydropyrroles from alkylimidates by employing NaI/PIDA and blue LED visible light. The overall reaction proceeds via chemoselective intramolecular N−C bond formation through 1,5-hydrogen atom transfer followed by nucleophilic attack of enamine species to the iodine monoaceate. *In situ* generated imidate *N*-radical selectively activates remote γ-C(sp^3)−H bonds over the other C(sp^3)−H bonds. This strategy enables the formation of not only intramolecular N−C bonds but also intermolecular C−I bonds, which could be further functionalized into important, high-value derivatives. The synthetic application of this developed protocol is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02022.

Experimental procedure, ^{1}H NMR, ^{13}C {^{1}H}, COSY, HSQC, and NOESY NMR spectra of the products, and control experiment results (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on functionalized *N*-heterocycles, see: (a) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Visible light photoredox-controlled reactions of *N*-radicals and radical ions. *Chem. Soc. Rev.* **2016**, *45*, 2044−2056. (b) Shaikh, T. M.; Hong, F.-E. Recent developments in the preparation of N-heterocycles using Pd-catalysed C-H activation. *J. Organomet. Chem.* **2016**, *801*, 139−156. (c) Feng, J.-J.; Zhang, J. Synthesis of Unsaturated *N*-Heterocycles by Cycloadditions of Aziridines and Alkynes. *ACS Catal.* **2016**, *6*, 6651−6661. (d) Huang, H.; Cai, J.; Deng, G.-J. O-Acyl oximes: versatile building blocks for *N*-heterocycle formation in recent transition metal catalysis. *Org. Biomol. Chem.* **2016**, *14*, 1519−1530. (e) Qiu, G.; Wu, J. Generation of *N*-Heterocycles via Tandem Reactions of *N*′-(2-Alkynyl benzyl idene)hydrazides. *Chem. Rec.* **2016**, *16*, 19−34. (f) Vo, C.-V. T.; Bode, J. W. Synthesis of Saturated *N*-Heterocycles. *J. Org. Chem.* **2014**, *79*, 2809−2815. (g) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Aromaticity as a Cornerstone of Heterocyclic Chemistry. *Chem. Rev.* **2004**, *104*, 2777−2812.

(2) For selected examples on functionalized *N*-heterocycles, see: (a) Ye, L.; Lo, K.-Y.; Gu, Q.; Yang, D. Pd-Catalyzed Intramolecular Aminoalkylation of Unactivated Alkenes: Access to Diverse *N*-Heterocycles. *Org. Lett.* **2017**, *19*, 308−311. (b) Zhao, H.-B.; Hou, Z.-W.; Liu, Z.-J.; Zhou, Z.-F.; Song, J.; Xu, H.-C. Amidinyl Radical Formation through Anodic N-H Bond Cleavage and Its Application in Aromatic C-H Bond Functionalization. *Angew. Chem., Int. Ed.* **2017**, *56*, 587−590. (c) Wang, H.; Lorion, M. M.; Ackermann, L.

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Org. Lett. XXXX, XXX, XXX−XXX

Overcoming the Limitations of C-H Activation with Strongly Coordinating *N*-Heterocycles by Cobalt Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 10386−10390. (d) Nicolle, S. M.; Lewis, W.; Hayes, C. J.; Moody, C. J. Stereoselective Synthesis of Functionalized Pyrrolidines by the Diverted N-H Insertion Reaction of Metallocarbenes with β-Aminoketone Derivatives. *Angew. Chem., Int. Ed.* **2016**, *55*, 3749−3753. (e) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. Electrochemical C-H/N-H Functionalization for the Synthesis of Highly Functionalized (Aza)-indoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 9168−9172. (f) Mahato, S.; Haldar, S.; Jana, C. K. Diastereoselective α-C−H functionalization of aliphatic N-heterocycles: an efficient route to ring fused oxazines. *Chem. Commun.* **2014**, *50*, 332−334. (g) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. Copper-Catalyzed Intramolecular Dehydrogenative Amino oxygenation: Direct Access to Formyl-Substituted Aromatic *N*-Heterocycles. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678−5681.

(3) Martins, P.; Jesus, J.; Santos, S.; Raposo, L.; Roma-Rodrigues, C.; Baptista, P.; Fernandes, A. Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift towards the Use of Nanomedicine's Tool Box. *Molecules* **2015**, *20*, 16852−16891.

(4) For selected examples on pyrroles, see: (a) Guchhait, S. K.; Sisodiya, S.; Saini, M.; Shah, Y. V.; Kumar, G.; Daniel, D. P.; Hura, N.; Chaudhary, V. Synthesis of Polyfunctionalized Pyrroles *via* a Tandem Reaction of Michael Addition and Intramolecular Cyanide-Mediated Nitrile-to-Nitrile Condensation. *J. Org. Chem.* **2018**, *83*, 5807−5815. (b) Qiu, G.; Wang, Q.; Zhu, J. Palladium-Catalyzed Three-Component Reaction of Propargyl Carbonates, Isocyanides, and Alcohols or Water: Switchable Synthesis of Pyrroles and Its Bicyclic Analogues. *Org. Lett.* **2017**, *19*, 270−273. (c) Gao, P.; Wang, J.; Bai, Z.-J.; Shen, L.; Yan, Y.-Y.; Yang, D.-S.; Fan, M.-J.; Guan, Z.-H. Synthesis of Polycarbonyl Pyrroles *via* $K_2S_2O_8$-Mediated Oxidative Cyclization of Enamines. *Org. Lett.* **2016**, *18*, 6074−6077.

(5) For selected examples on dihydropyrroles, see: (a) Zeng, J.-C.; Xu, H.; Huang, R.-L.; Yu, F.; Zhang, Z. Facile synthesis of polysubstituted 2,3-dihydropyrroles and pyrroles from $Mn(OAc)_3$-promoted oxidative cyclization of alkenes with amines/alkyne esters or enaminone esters. *Tetrahedron Lett.* **2018**, *59*, 1576−1580. (b) Wang, R.; OuYang, Y.; Xu, C.; Yi, N.; Jiang, J.; Deng, W.; Zeng, Z.; Xiang, J. Hypervalent iodine-triggered transformation of homopropargyl sulfonamides into dihalo-2,3-dihydropyrroles. *Org. Biomol. Chem.* **2017**, *15*, 796−800. (c) Majhail, M. K.; Ylioja, P. M.; Willis, M. C. Direct Synthesis of Highly Substituted Pyrroles and Dihydropyrroles Using Linear Selective Hydroacylation Reactions. *Chem. - Eur. J.* **2016**, *22*, 7879−7884. (d) Yoshida, M.; Kobayashi, A.; Nakayama, A.; Namba, K. Synthesis of functionalized 2,3-dihydropyrroles by oxidative radical cyclization of *N*-Sulfonyl β-enamino esters with alkenes. *Tetrahedron* **2016**, *72*, 2544−2551. (e) Li, Y.; Xu, H.; Xing, M.; Huang, F.; Jia, J.; Gao, J. Iodine-Promoted Construction of Polysubstituted 2,3-Dihydropyrroles from Chalcones and β-Enamine Ketones (Esters). *Org. Lett.* **2015**, *17*, 3690−3693. (f) Chen, J.; Li, J.; Wang, J.; Li, H.; Wang, W.; Guo, Y. Phosphine-Catalyzed Aza-MBH Reactions of Vinylpyridines: Efficient and Rapid Access to 2,3,5-Triarylsubstituted 3-Pyrrolines. *Org. Lett.* **2015**, *17*, 2214−2217. (g) Xiang, J.; Xie, H.; Li, Z.; Dang, Q.; Bai, X. Stereoselective Synthesis of 3-Carboxy-4,5-dihydropyrroles via an Intramolecular Iminium Ion Cyclization Reaction. *Org. Lett.* **2015**, *17*, 3818−3821. (h) Souto, J. A.; Becker, P.; Iglesias, Á.; Muñiz, K. Metal-Free Iodine(III)-Promoted Direct Intermolecular C−H Amination Reactions of Acetylenes. *J. Am. Chem. Soc.* **2012**, *134*, 15505−15511.

(6) For the generation of pyrroles and dihydropyrroles *via* oxime derivatives, see: (a) Xie, Y.; Li, Y.; Chen, X.; Liu, Y.; Zhang, W. Copper/amine-catalyzed formal regioselective [3 + 2] cycloaddition of an α,β-unsaturated O-acetyl oxime with enals. *Org. Chem. Front.* **2018**, *5*, 1698−1701. (b) Guo, K.; Zhang, H.; Cao, S.; Gu, C.; Zhou, H.; Li, J.; Zhu, Y. Copper-Catalyzed Domino Cyclization/Trifluoromethylthiolation of Unactivated Alkenes: Access to SCF_3-Containing Pyrrolines. *Org. Lett.* **2018**, *20*, 2261−2264. (c) Yang, H.-B.; Pathipati, S. R.; Selander, N. Nickel-Catalyzed 1,2-Aminoarylation of Oxime Ester-Tethered Alkenes with Boronic Acids. *ACS Catal.* **2017**, *7*, 8441−8445. (d) Walton, J. C. Synthetic Strategies for 5- and 6-Membered Ring Aza- heterocycles Facilitated by Iminyl Radicals. *Molecules* **2016**, *21*, 660. (e) Walton, J. C. The Oxime Portmanteau Motif: Released Heteroradicals Undergo Incisive EPR Interrogation and Deliver Diverse Heterocycles. *Acc. Chem. Res.* **2014**, *47*, 1406−1416. (f) Faulkner, A.; Scott, J. S.; Bower, J. F. Palladium catalyzed cyclizations of oxime esters with 1,1-disubstituted alkenes: synthesis of α, α-disubstituted dihydropyrroles and studies towards an asymmetric protocol. *Chem. Commun.* **2013**, *49*, 1521−1523. (g) Race, N. J.; Bower, J. F. Palladium Catalyzed Cyclizations of Oxime Esters with 1,2-Disubstituted Alkenes: Synthesis of Dihydropyrroles. *Org. Lett.* **2013**, *15*, 4616−4619.

(7) For selected recent reviews on 1,5-HAT, see: (a) Stateman, L. M.; Nakafuku, K. M.; Nagib, D. A. Remote C−H Functionalization *via* Selective Hydrogen Atom Transfer. *Synthesis* **2018**, *50*, 1569−1586. (b) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056−2071. (c) Hu, X.-Q.; Chen, J.-R.; Xiao, W.-J. Controllable Remote C-H Bond Functionalization by Visible-Light Photocatalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 1960−1962.

(8) For recent selected examples on 1,5-HAT, see: (a) Wu, X.; Wang, M.; Huan, L.; Wang, D.; Wang, J.; Zhu, C. Tertiary-Alcohol-Directed Functionalization of Remote $C(sp^3)$−H Bonds by Sequential Hydrogen Atom and Heteroaryl Migrations. *Angew. Chem., Int. Ed.* **2018**, *57*, 1640−1644. (b) Hu, A.; Guo, J.-J.; Pan, H.; Tang, H.; Gao, Z.; Zuo, Z. δ-Selective Functionalization of Alkanols Enabled by Visible-Light-Induced Ligand-to-Metal Charge Transfer. *J. Am. Chem. Soc.* **2018**, *140*, 1612−1616. (c) Ratushnyy, M.; Parasram, M.; Wang, Y.; Gevorgyan, V. Palladium-Catalyzed Atom-Transfer Radical Cyclization at Remote Unactivated $C(sp^3)$−H Sites: Hydrogen-Atom Transfer of Hybrid Vinyl Palladium Radical Intermediates. *Angew. Chem., Int. Ed.* **2018**, *57*, 2712−2715. (d) Chen, D.-F.; Chu, J. C. K.; Rovis, T. Directed γ-$C(sp^3)$−H Alkylation of Carboxylic Acid Derivatives through Visible Light Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 14897−14900. (e) Chen, J.-Q.; Wei, Y.-L.; Xu, G.-Q.; Liang, Y.-M.; Xu, P.-F. Intramolecular 1,5-H transfer reaction of aryl iodides through visible-light photoredox catalysis: a concise method for the synthesis of natural product scaffolds. *Chem. Commun.* **2016**, *52*, 6455−6458. (f) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic alkylation of remote C−H bonds enabled by proton-coupled electron transfer. *Nature* **2016**, *539*, 268−271. (g) Chu, J. C. K.; Rovis, T. Amide-directed photoredox-catalysed C−C bond formation at unactivated sp^3 C−H bonds. *Nature* **2016**, *539*, 272−275.

(9) For recent examples on 1,5-HAT by the Leonori group, see: (a) Dauncey, E. M.; Morcillo, S. P.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Photoinduced Remote Functionalisations by Iminyl Radical Promoted C−C and C−H Bond Cleavage Cascades. *Angew. Chem., Int. Ed.* **2018**, *57*, 744−748. (b) Davies, J.; Sheikh, N. S.; Leonori, D. Photoredox Imino Functionalizations of Olefins. *Angew. Chem., Int. Ed.* **2017**, *56*, 13361−13365. (c) Reina, D. F.; Dauncey, E. M.; Morcillo, S. P.; Svejstrup, T. D.; Popescu, M. V.; Douglas, J. J.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated 5-exo-dig Cyclizations of Amidyl Radicals. *Eur. J. Org. Chem.* **2017**, *2017*, 2108−2111. (d) Davies, J.; Svejstrup, T. D.; Fernandez Reina, D.; Sheikh, N. S.; Leonori, D. Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition-Metal-Free Hydroamination and *N*-Arylation Reactions. *J. Am. Chem. Soc.* **2016**, *138*, 8092−8095. (e) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A.; Leonori, D. Visible-Light-Mediated Generation of Nitrogen-Centered Radicals: Metal-Free Hydroimination and Iminohydroxylation Cyclization Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017−14021.

(10) For recent examples on 1,5-HAT by the Studer group, see: (a) Jiang, H.; Studer, A. α-Aminoxy-Acid-Auxiliary-Enabled Intermolecular Radical γ-$C(sp^3)$−H Functionalization of Ketones. *Angew. Chem., Int. Ed.* **2018**, *57*, 1692−1696. (b) Jiang, H.; Studer, A. Iminyl-Radicals by Oxidation of α-Imino-oxy Acids: Photoredox Neutral

DOI: 10.1021/acs.orglett.8b02022
Org. Lett. XXXX, XXX, XXX−XXX

Alkene Carboimination for the Synthesis of Pyrrolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 12273−12276.
(11) For recent examples on 1,5-HAT by the Nevado group, see: (a) Shu, W.; Nevado, C. Visible-Light-Mediated Remote Aliphatic C-H Functionalizations through a 1,5-Hydrogen Transfer Cascade. *Angew. Chem., Int. Ed.* **2017**, *56*, 1881−1884. (b) Shu, W.; Genoux, A.; Li, Z.; Nevado, C. γ-Functionalizations of Amines through Visible-Light-Mediated, Redox-Neutral C-C Bond Cleavage. *Angew. Chem., Int. Ed.* **2017**, *56*, 10521−10524.
(12) For recent examples on 1,5-HAT by the Muñiz group, see: (a) Duhamel, T.; Stein, C. J.; Martínez, C.; Reiher, M.; Muñiz, K. Engineering Molecular Iodine Catalysis for Alkyl−Nitrogen Bond Formation. *ACS Catal.* **2018**, *8*, 3918−3925. (b) Becker, P.; Duhamel, T.; Martínez, C.; Muñiz, K. Designing Homogeneous Bromine Redox Catalysis for Selective Aliphatic C−H Bond Functionalization. *Angew. Chem., Int. Ed.* **2018**, *57*, 5166−5170. (c) Becker, P.; Duhamel, T.; Stein, C. J.; Reiher, M.; Muñiz, K. Cooperative Light-Activated Iodine and Photoredox Catalysis for the Amination of C-H Bonds. *Angew. Chem., Int. Ed.* **2017**, *56*, 8004−8008. (d) O'Broin, C. Q.; Fernández, P.; Martínez, C.; Muñiz, K. *N*-Iodosuccinimide-Promoted Hofmann−Löffler Reactions of Sulfonimides under Visible Light. *Org. Lett.* **2016**, *18*, 436−439. (e) Martínez, C.; Muñiz, K. An Iodine-Catalyzed Hofmann−Löffler Reaction. *Angew. Chem., Int. Ed.* **2015**, *54*, 8287−8291.
(13) For recent examples on 1,5-HAT by the Nagib group, see: (a) Wappes, E. A.; Vanitcha, A.; Nagib, D. A. β C-H di-halogenation via iterative hydrogen atom transfer. *Chem. Sci.* **2018**, *9*, 4500−4504. (b) Wappes, E. A.; Nakafuku, K. M.; Nagib, D. A. Directed β C-H Amination of Alcohols via Radical Relay Chaperones. *J. Am. Chem. Soc.* **2017**, *139*, 10204−10207. (c) Wappes, E. A.; Fosu, S. C.; Chopko, T. C.; Nagib, D. A. Triiodide-Mediated δ-Amination of Secondary C−H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 9974−9978.
(14) For recent examples on *N*-centered radicals, see: (a) An, X.-D.; Yu, S. Photoredox-catalyzed C(sp^2)−N coupling reactions. *Tetrahedron Lett.* **2018**, *59*, 1605−1613. (b) Zhao, Y.; Xia, W. Recent advances in radical-based C−N bond formation *via* photo-/electrochemistry. *Chem. Soc. Rev.* **2018**, *47*, 2591−2608. (c) Zhang, H.; Muñiz, K. Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C(sp^3)−H Amination under Visible Light. *ACS Catal.* **2017**, *7*, 4122−4125. (d) Kärkäs, M. D. Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications. *ACS Catal.* **2017**, *7*, 4999−5022. (e) Martínez, C.; Bosnidou, A. E.; Allmendinger, S.; Muñiz, K. Towards Uniform Iodine Catalysis: Intramolecular C-H Amination of Arenes under Visible Light. *Chem. - Eur. J.* **2016**, *22*, 9929−9932. (f) Zard, S. Z. Recent progress in the generation and use of nitrogen-centered radicals. *Chem. Soc. Rev.* **2008**, *37*, 1603−1618.
(15) Mou, X.-Q.; Chen, X.-Y.; Chen, G.; He, G. Radical-mediated intramolecular β-C(sp^3)-H amidation of alkylimidates: facile synthesis of 1,2-amino alcohols. *Chem. Commun.* **2018**, *54*, 515−518.
(16) (a) Jaiswal, Y.; Kumar, Y.; Pal, J.; Subramanian, R.; Kumar, A. Rapid Synthesis of Polysubstituted Phenanthridines from Simple Aliphatic/Aromatic Nitriles and Iodo Arenes *via* Pd(II) Catalyzed Domino C-C/C-C/C-N Bonds Formation. *Chem. Commun.* **2018**, *54*, 7207−7210. (b) Jaiswal, Y.; Kumar, Y.; Kumar, A. Palladium-Catalyzed Regioselective C−H Alkenylation of Arylacetamides *via* Distal Weakly Coordinating Primary Amides as Directing Groups. *J. Org. Chem.* **2018**, *83*, 1223−1231. (c) Kumar, Y.; Jaiswal, Y.; Kumar, A. Copper(II)-Catalyzed Benzylic C(sp^3)−H Aerobic Oxidation of (Hetero)Aryl Acetimidates: Synthesis of Aryl-α-ketoesters. *J. Org. Chem.* **2016**, *81*, 12247−12257. (d) Kumar, Y.; Shaw, M.; Thakur, R.; Kumar, A. Copper(II)-Mediated Aerobic Oxidation of Benzylimidates: Synthesis of Primary α-Ketoamides. *J. Org. Chem.* **2016**, *81*, 6617−6625. (e) Kumar, Y.; Jaiswal, Y.; Shaw, M.; Kumar, A. Metal-Free Catalyst-Controlled Chemoselective Synthesis of Aryl α-Ketoesters and Primary α-Ketoamides from Aryl Acetimidates. *ChemistrySelect* **2017**, *2*, 6143−6148.
(17) See the Supporting Information for complete details of the experiment.
(18) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255−263.
(19) Dean, J. A.; Lange, N. A. *Lange's Handbook of Chemistry*, 15th ed.; McGraw Hill, Inc.: New York, 1999.
(20) Courtneidge, J. L.; Lusztyk, J.; Pagé, D. Alkoxyl radicals from alcohols. Spectroscopic detection of intermediate alkyl and acyl hypoiodites in the Suárez and Beebe reactions. *Tetrahedron Lett.* **1994**, *35*, 1003−1006.

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Org. Lett. XXXX, XXX, XXX−XXX