OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

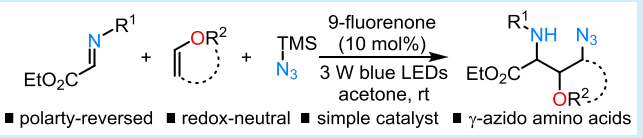
Polarity-Reversed Addition of Enol Ethers to Imines under Visible Light: Redox-Neutral Access to Azide-Containing Amino Acids

Sen Yang, Shuangyu Zhu, Dengfu Lu,* and Yuefa Gong

School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, 1037 Luoyu Road, Wuhan, Hubei 430074, China

Supporting Information

ABSTRACT: A three-component and polarity-reversed addition cascade with a glyoxylate-based imine, an enol ether, and $TMSN_3$ was established for the construction of γ-azido amino acids under visible light. This transformation features mild and redox-neutral conditions, affording a series of amino esters with excellent chemoselectivity. Preliminary mechanistic studies revealed that the addition of an oxyalkyl radical to imine is likely the rate-determining step. The obtained azido-containing amino esters could be successfully converted to various valuable building blocks.



Nonproteinogenic amino acids play important roles in molecular biology and medicinal chemistry,[1] not only serving as neurotransmitters[2] and toxins[3] but also acting as essential building units in protein engineering.[4] The synthesis of highly functionalized α-amino acids has drawn vast attention due to their increasing applications in recent years.[5] Especially, the incorporation of azide group into amino acids is a fascinating but challenging endeavor[6] because azide is by far the most useful linker in bioorthogonal chemistry.[7] Also, such structural motifs also widely occur in natural products and pharmaceuticals, such as mugineic acid,[8] caprazol,[9] and Nikkomycin Z (Figure 1).

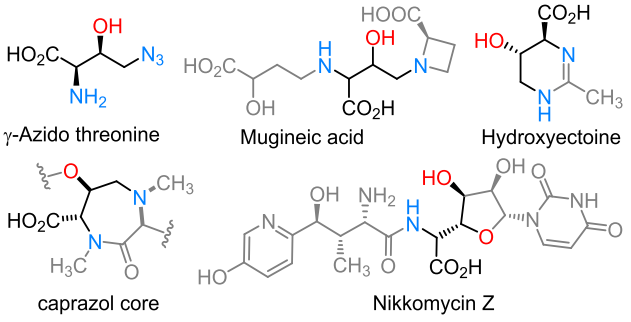
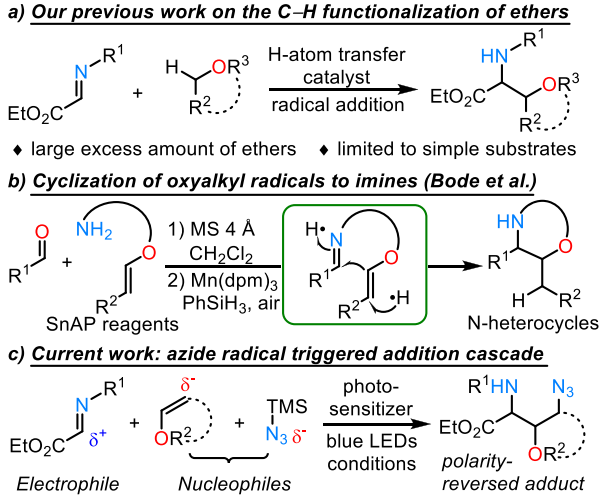


Figure 1. γ-Azidothreonine and its natural analogs.

The addition of oxyalkyl radicals to glyoxylate-based imines has been proven an efficient approach to threonine analogs.[10] For example, several α C−H functionalization methods of ethers/alcohols have been established by using H atom abstracting radicals,[11] including our own work (Scheme 1a).[12] However, this strategy faces inevitable downsides, such as the requirement of a large excess amount of substrate and limited scope. These drawbacks may be ascribed to the high barrier of the C−H abstraction, as well as the competitive participation of the product. Bode et al. have established an intramolecular strategy based on saturated *N*-heterocycle building blocks. The oxyalkyl radicals generated through either the homolysis of C−Sn[13] and C−Si[14] bonds or the hydride radical addition to enol ethers[15] rapidly cyclized with imine to afford corresponding cyclic amino ethers (Scheme 1b).

Owing to the versatile applications of organic azides,[16] the past few years have witnessed the renascence of olefin azidation via new approaches,[17] including single-electron redox metals,[18] electrochemistry,[19] and photoredox catalysis.[20] Based on these discoveries, we envisaged assembling azide-containing threonine derivatives via a polarity-reversed addition cascade among an enol ether, an anionic azide

Scheme 1. Redox-Neutral Oxyalkylation of Imines



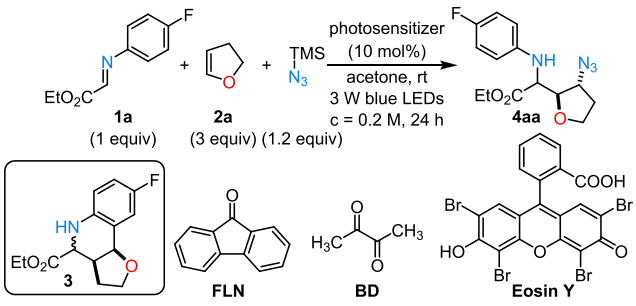
Received: September 13, 2019

DOI: 10.1021/acs.orglett.9b03238
Org. Lett. XXXX, XXX, XXX−XXX

source, and a glyoxylate imine as illustrated in Scheme 1c. Although similar sequences have been reported by Liu,[21] Chu,[20a] and Nagib[22] with heteroarenes as the final radical acceptors, intermolecular multicomponent radical additions to imines remained a challenge due to their complicate reactivity. On one hand, imines are easily attacked by enol ethers via ionic pathways, leading to Mannich, Povarov,[23] or Imino-ene[24] reactions. On the other hand, enol ethers are also sensitive to strong oxidants, generating radical cation species. Therefore, developing a non-Lewis acidic and mild catalytic system for the oxidative azide radical formation is pivotal to materialize our working hypothesis.

As a safe and easy to operate azide source,[25] $TMSN_3$ exhibits certain Lewis acidity that promotes polar reactions. Fortunately, *N*-aryl imine **1a** showed decent stability toward a cyclic enol ether **2a** in the presence of $TMSN_3$, while a Povarov product **3** was afforded in 72% yield with a stronger Lewis acid TMSOTf in 10 min.[26] **1a** and **2a** were therefore used as model substrates to commence our reaction discovery, and the conversion and yield were determined by quantitative ^{19}F NMR analysis. After extensive condition screening, fluorenone (FLN) was found to be the optimal photosensitizer and the polarity-reversed adduct **4aa** was selectively obtained in acetone (Table 1, entry 1, 89% yield, *dr* = 1.2:1). A few

Table 1. Optimization of Reaction Conditions[a]



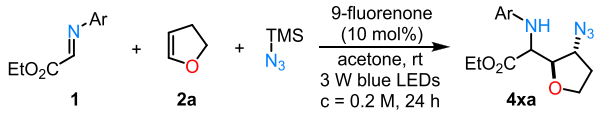
entry	catalysts and conditions	conv.[b] (%)	yield[c] (%)
1	**FLN**, standard cond.	>95	89
2	**BD**, standard cond.	>95	70
3	benzophenone, standard cond.	>95	65
4[d]	**Eosin Y**, standard cond.	>95	69
5	**FLN**, in CH_3CN	>95	87
6	**FLN**, in CH_2Cl_2	>95	78
7	**FLN**, DMF	>95	75
8	*c* = 0.1 M	93	80
9	**FLN**, in the dark	<5	<5
10	no catalyst, standard cond.	90	70

[a]Unless otherwise stated, the reaction was performed under N_2 with imine **1a** (0.2 mmol), dihydrofuran (0.6 mmol), and $TMSN_3$ (0.24 mmol) in the presence of a photosensitizer (0.02 mmol) with light irradiation (3 W blue LEDs). [b]Determined by quantitative ^{19}F NMR analysis with 4-fluoroiodobenzene as an internal standard. [c]Determined by NMR; **4aa** consists of a pair of diastereomers, *dr* ≈ 1.2:1. [d]2 mol % of Eosin Y was used.

other organic photosensitizers were then tested, and inferior yields were generally observed (entries 2−4). This cascade showed good compatibility in various solvents such as CH_2Cl_2, acetonitrile, or DMF, giving **4aa** in slightly diminished yields (entries 5−7). It is noteworthy that all the reactions were performed in regular solvents without drying, so the proton on the final product may come from moisture. Next, diluting the reaction to 0.1 M led to a noticeably decreased yield (entry 8). Importantly, no product was detected when the reaction was performed in darkness (entry 9). To our surprise, the reaction proceeded smoothly in the absence of a photosensitizer to afford **4aa** in moderate yield (entry 10). This result will be discussed later in the mechanistic section.

Although the reaction proceeded to a certain extent without a photosensitizer, in order to achieve good reproducibility and faster conversions, we decided to employ fluorenone as the catalyst to explore the substrate scope of this radical addition cascade (Table 2). First, a series of imines prepared from ethyl

Table 2. Scope of Imines[a]



entry	product	Ar	yield[b] (%)	*dr*[c]
1	**4aa**	4-F-Ph	86	1.2
2	**4ba**	Ph	81	1.2
3	**4ca**	4-Cl-Ph	86	1.3
4	**4da**	4-Br-Ph	86	1.2
5	**4ea**	4-CH_3-Ph	84	1.1
6	**4fa**	4-OMe-Ph	63	1.3
7	**4ga**	3-F-Ph	84	1.2
8	**4ha**	3-Cl-Ph	79	1.1
9	**4ia**	3-Br-Ph	81	1.1
10	**4ja**	3-CH_3-Ph	84	1.2

[a]Unless otherwise stated, the reaction was performed under N_2 with an imine **1** (0.2 mmol), dihydrofuran **2a** (0.6 mmol), and $TMSN_3$ (0.24 mmol) in the presence of a fluorenone (0.02 mmol) in acetone under light irradiation (3 W blue LEDs) for 24 h. [b]Isolated yield. [c]Determined by ^1H NMR.

glyoxalate and substituted anilines were applied with dihydrofuran **2a** and $TMSN_3$ under the optimized conditions, and the results are listed in Table 2. Product **4aa** was obtained in 86% yield after purification through a silica gel flash column. Imine **1b** with a simple *N*-phenyl ring exhibited comparable reactivity to produce **4ba** in 81% yield (entry 2). Several *para*-substituted imines are perfectly tolerated under the same conditions to provide the azide-containing amino esters **4ca**−**4ea** in satisfactory yields (entries 3−5). Notably, imine **1f** with a removable *para*-methoxyphenyl group (PMP) was also reactive under the standard conditions, furnishing **4fa** in a moderate yield (entry 6). In addition, an array of substrates with *meta*-substituents were also proved to be suitable for this transformation (entries 7−10).

Next, the scope of enol ethers was examined (Figure 2). Simple vinyl alkyl ethers are equally active under the standard conditions, providing γ-azido-threonine derivatives **4db** and **4dc** with good selectivity. Compound **4dd** bearing a silyl protected hydroxyl group was obtained with trimethylsilyl vinyl ether as a substrate. The tolerance of functionalities on the vinyl ethers was then assessed. Hydroxyl, ester, and tosylate groups all survived the transformation, affording product **4de**, **4df**, and **4dg**, respectively. In addition, with a common protecting group, benzyl vinyl ether displayed good compatibility with this method, giving compounds **4bh**, **4ch**, and **4dh**. It is noteworthy that a di-TBS protected glycal **2l** that is easily obtained from thymidine was successfully ligated with imine

DOI: 10.1021/acs.orglett.9b03238
Org. Lett. XXXX, XXX, XXX−XXX

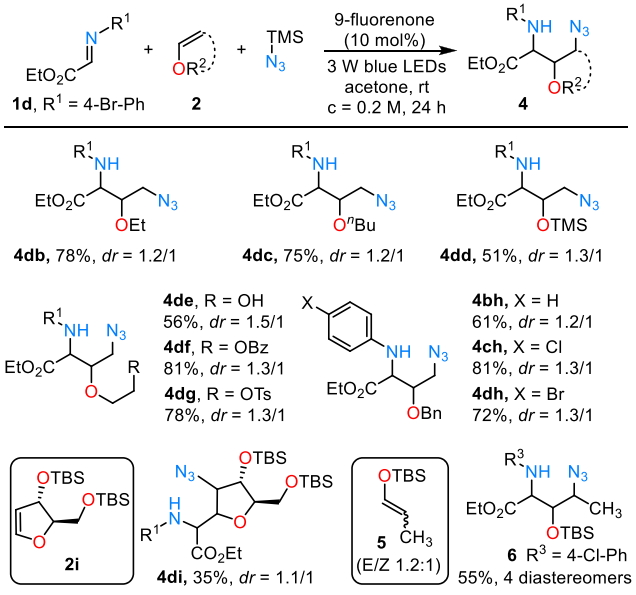
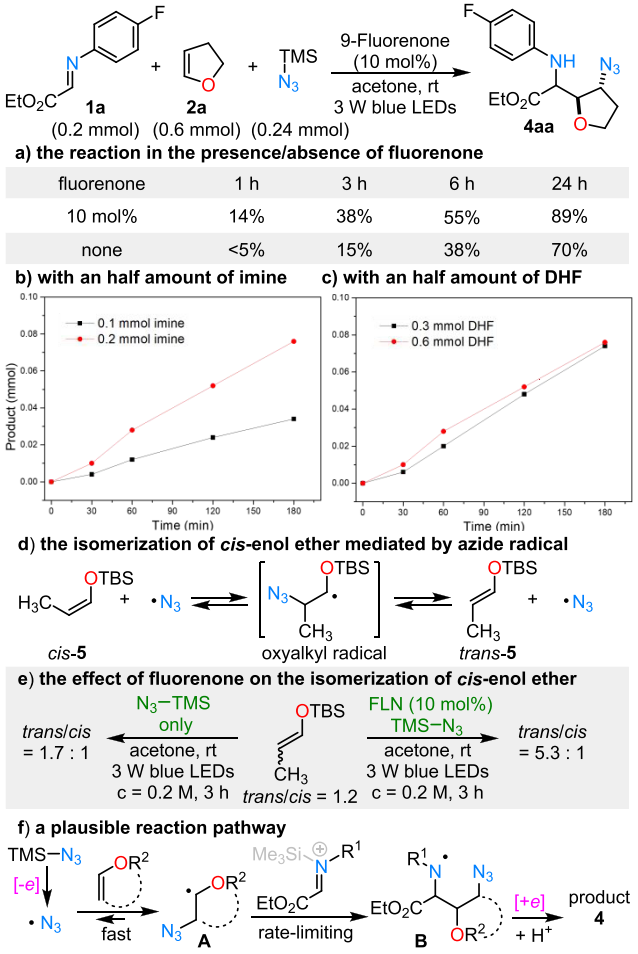


Figure 2. Scope of enol ethers. Unless otherwise stated, the reaction was performed under N_2 with imine **1d** (0.2 mmol), an enol ether (0.6 mmol), and $TMSN_3$ (0.24 mmol) in the presence of fluorenone (0.02 mmol) in acetone under light irradiation (3 W blue LEDs) for 24 h; *dr* was determined through ^1H NMR analysis.

1d to yield **4di** as a pair of diastereomers. This example promises a potential way that integrates an amino acid as an aglycon into a furanose. Furthermore, a propanal-derived silyl enol ether **5** with an acyclic internal double bond showed moderate reactivity in CH_2Cl_2, affording product **6** as a mixture of diastereomers (eq 2).[27]

In order to gain mechanistic insights into this cascade, we performed a series of experiments with **1a** and **2a** to study the reaction kinetic profile (Scheme 2). First, the reactions' progress were compared side by side in the presence/absence of a fluorenone, and the formation of product **4aa** was found to be much faster when fluorenone was used, especially in the initial stage (Scheme 2a). Then, the impact of the concentration of each reagent on the reaction rate was investigated. When the amount of imine was cut by half, the formation of **4aa** slowed down accordingly within the first 3 h (Scheme 2b). In comparison, no distinct rate difference was observed during the early stage when the reaction was performed with a halved amount of dihydrofuran (DHF) (Scheme 2c). These data indicated that imine **1a** was involved in the rate-determining step, while DHF was likely not. Next, the addition of an azide radical to double bonds is reported to be a reversible process, which could cause the isomerization of *cis*-alkenes (Scheme 2d).[28] Therefore, we envisioned probing the efficiency of azide radical generation by monitoring the ratio change of *trans*/*cis*-enol ether **5**. When a mixture of **5** (*trans*/*cis* = 1.2:1) was submitted under the standard reaction conditions, the ratio was increased to 5.3:1 after 3 h. When this experiment was performed in the absence of fluorenone, the ratio was also enhanced after the same amount of time, but to a lesser extent (*trans*/*cis* = 1.7:1, Scheme 2e). This observation verified the fact that product **4aa** was also obtained without a photosensitizer (Table 1, entry 10), and suggested that the azide radical might be gradually generated from $TMSN_3$ under visible light, while this process could be expedited by a proper photosensitizer.

Scheme 2. Preliminary Studies on the Reaction Mechanism

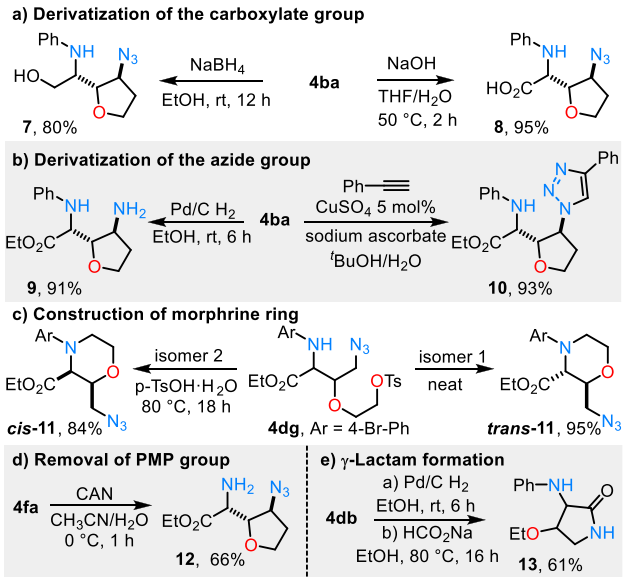


Based on these collected data, we proposed a plausible mechanism for this sequential radical addition (Scheme 2f). First, the azide radical is generated with $TMSN_3$ under visible light with the assistance of fluorenone. Then, the azide radical reversibly adds to an enol ether, rendering an oxyalkyl radical **A** in an equilibrium. Since the concentration of enol ether does not show distinct influence on the reaction rate, the oxyalkyl radical intermediate **A** is probably the thermodynamically favored species in this equilibrium ($[A] \approx [\cdot N_3]$). Consequently, radical **A** adds to an imine, resulting in an *N*-centered radical **B**, which is then reduced and protonated to afford the final product **4**. Notably, as in the TMSOTf promoted Povarov reaction,[26] a Lewis acidic trimethylsilyl cation[29] might also play a role activating the imine toward the oxyalkyl radical. Within the whole process, the addition of **A** to imine is probably the rate-limiting step, so that the overall reaction rate depends on the concentration of imine and intermediate **A**, which, in turn, is influenced by the efficiency of azide radical formation.

Last, the synthetic applications of these azide-containing amino esters obtained with this method were evaluated (Scheme 3). First, the ester group could be readily converted to corresponding alcohol **7** or carboxylic acid **8** via simple reduction or hydrolysis. Then, the azide could be either reduced to amine (**9**) or linked up with an alkyne to give **10** through copper-catalyzed cycloaddition. Next, product **4dg** with a distal tosylate was cyclized to afford morphrine

DOI: 10.1021/acs.orglett.9b03238
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Product Derivatizations and Synthetic Applications



derivatives **11**. Notably, the *trans*-isomer was generated spontaneously, while the formation of *cis*-**11** was much slower and required hasher conditions. Further, the PMP group on compound **4fa** was easily removed with ceric ammonium nitrate (CAN) to give a free amino ester **12**. Moreover, a γ-lactam **13** was obtained through the reduction and lactamization of **4db**.

In summary, we have developed a polarity-reversed, metal-free, and redox-neutral radical addition cascade with a glyoxylate imine, an enol ether, and $TMSN_3$ promoted by visible light. This method implements an efficient approach to γ-azido unnatural amino acids with readily accessible and inexpensive materials. The obtained multifunctional amino esters have showcased versatile applications for the synthesis of amino alcohols, amino acids, and heterocycles. Preliminary mechanistic studies revealed that the azide radical addition to an enol ether is a favorable and quick process to afford an oxyalkyl radical intermediate, while the addition process to an imine presumably limits the overall reaction rate. Further efforts are currently focused on the synthetic applications and the improvement of the stereoselectivity with this method.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03238.

General procedures, experimental details, characterization data of all new compounds as well as NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dlu@hust.edu.cn.

ORCID

Dengfu Lu: 0000-0003-1931-9559

Yuefa Gong: 0000-0001-9944-4055

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Huazhong University of Science & Technology is gratefully acknowledged as well as from the National Natural Science Foundation of China (21801083) and Hubei Provincial Natural Science Foundation of China (0216013067). We also thank Huazhong University of Science & Technology Analytical & Testing Center for characterizing new compounds.

■ REFERENCES

(1) (a) Non-Proteinogenic α-Amino Acids, Natural Origin, Biological Functions. *Asymmetric Synthesis of Non-Proteinogenic Amino Acids*; p 1. (b) Bell, E. A. Nonprotein Amino Acids of Plants: Significance in Medicine, Nutrition, and Agriculture. *J. Agric. Food Chem.* **2003**, *51*, 2854.

(2) Rodgers, K. J. Non-protein amino acids and neurodegeneration: The enemy within. *Exp. Neurol.* **2014**, *253*, 192.

(3) (a) Nunn, P. B.; Bell, E. A.; Watson, A. A.; Nash, R. J. Toxicity of Non-protein Amino Acids to Humans and Domestic Animals. *Nat. Prod. Commun.* **2010**, *5*, 485. (b) Rodgers, K. J.; Samardzic, K.; Main, B. J. Toxic Nonprotein Amino Acids. In *Plant Toxins*; Gopalakrishnakone, P., Carlini, C. R., Ligabue-Braun, R., Eds.; Springer Netherlands: Dordrecht, 2015; p 1.

(4) (a) Walsh, C. T.; O'Brien, R. V.; Khosla, C. Nonproteinogenic Amino Acid Building Blocks for Nonribosomal Peptide and Hybrid Polyketide Scaffolds. *Angew. Chem., Int. Ed.* **2013**, *52*, 7098. (b) Neumann-Staubitz, P.; Neumann, H. The use of unnatural amino acids to study and engineer protein function. *Curr. Opin. Struct. Biol.* **2016**, *38*, 119. (c) Nödling, A. R.; Spear, L. A.; Williams, T. L.; Luk, L. Y. P.; Tsai, Y.-H. Using genetically incorporated unnatural amino acids to control protein functions in mammalian cells. *Essays Biochem.* **2019**, *63*, 237.

(5) Kumar, V.; Mudgal, M. M.; Rani, N.; Jha, A.; Jaggi, M.; Singh, A. T.; Sanna, V. K.; Singh, P.; Sharma, P. K.; Irchhaiya, R.; Burman, A. C. Synthesis of functionalized amino acid derivatives as new pharmacophores for designing anticancer agents. *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 763.

(6) (a) VanBrunt, M. P.; Shanebeck, K.; Caldwell, Z.; Johnson, J.; Thompson, P.; Martin, T.; Dong, H.; Li, G.; Xu, H.; D'Hooge, F.; Masterson, L.; Bariola, P.; Tiberghien, A.; Ezeadi, E.; Williams, D. G.; Hartley, J. A.; Howard, P. W.; Grabstein, K. H.; Bowen, M. A.; Marelli, M. Genetically Encoded Azide Containing Amino Acid in Mammalian Cells Enables Site-Specific Antibody–Drug Conjugates Using Click Cycloaddition Chemistry. *Bioconjugate Chem.* **2015**, *26*, 2249. (b) Tookmanian, E. M.; Fenlon, E. E.; Brewer, S. H. Synthesis and protein incorporation of azido-modified unnatural amino acids. *RSC Adv.* **2015**, *5*, 1274. (c) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. Copper-free click chemistry for dynamic *in vivo* imaging. *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 16793.

(7) (a) Devaraj, N. K. The Future of Bioorthogonal Chemistry. *ACS Cent. Sci.* **2018**, *4*, 952. (b) Li, L.; Zhang, Z. Development and Applications of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) as a Bioorthogonal Reaction. *Molecules* **2016**, *21*, 1393. (c) Kiick, K. L.; Saxon, E.; Tirrell, D. A.; Bertozzi, C. R. Incorporation of azides into recombinant proteins for chemoselective modification by the Staudinger ligation. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 19.

(8) Takagi, S.; Nomoto, K.; Takemoto, T. Physiological aspect of mugineic acid, a possible phytosiderophore of graminaceous plants. *J. Plant Nutr.* **1984**, *7*, 469.

(9) Hirano, S.; Ichikawa, S.; Matsuda, A. Total Synthesis of Caprazol, a Core Structure of the Caprazamycin Antituberculosis Antibiotics. *Angew. Chem., Int. Ed.* **2005**, *44*, 1854.

DOI: 10.1021/acs.orglett.9b03238
Org. Lett. XXXX, XXX, XXX−XXX

(10) For selected examples: (a) Halland, N.; Jørgensen, K. A. Intermolecular addition of alkyl radicals to imines in the absence and in the presence of a Lewis acid. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290. (b) Ji, P.; Zhang, Y.; Wei, Y.; Huang, H.; Hu, W.; Mariano, P. A.; Wang, W. Visible-Light-Mediated, Chemo- and Stereoselective Radical Process for the Synthesis of C-Glycoamino Acids. *Org. Lett.* **2019**, *21*, 3086. (c) Kamimura, D.; Nagatomo, M.; Urabe, D.; Inoue, M. Expanding the scope of Et_3B/O_2-mediated coupling reactions of O,Te-acetal. *Tetrahedron* **2016**, *72*, 7839. (d) Matos, J. L. M.; Vásquez-Céspedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. Branch-Selective Addition of Unactivated Olefins into Imines and Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 16976.

(11) (a) Fernández, M.; Alonso, R. Diastereoselective Intermolecular Addition of the 1,3-Dioxolanyl Radical to N-Acyl Aldohydrazones. Asymmetric Synthesis of α-Amino Acid Derivatives. *Org. Lett.* **2003**, *5*, 2461. (b) Hashizume, S.; Oisaki, K.; Kanai, M. Catalytic Migratory Oxidative Coupling of Nitrones. *Org. Lett.* **2011**, *13*, 4288.

(12) (a) Zeng, H.; Yang, S.; Li, H.; Lu, D.; Gong, Y.; Zhu, J.-T. Site-Specific Functionalization of 1,3-Dioxolane with Imines: A Radical Chain Approach to Masked α-Amino Aldehydes. *J. Org. Chem.* **2018**, *83*, 5256. (b) Yang, S.; Zhu, S.; Lu, D.; Gong, Y. Formylation of Fluoroalkyl Imines through Visible-Light-Enabled H-Atom Transfer Catalysis: Access to Fluorinated α-Amino Aldehydes. *Org. Lett.* **2019**, *21*, 2019.

(13) (a) Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. SnAP reagents for the one-step synthesis of medium-ring saturated N-heterocycles from aldehydes. *Nat. Chem.* **2014**, *6*, 310. (b) Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. SnAP Reagents for the Synthesis of Piperazines and Morpholines. *Org. Lett.* **2014**, *16*, 1236. (c) Luescher, M. U.; Bode, J. W. Catalytic Synthesis of N-Unprotected Piperazines, Morpholines, and Thiomorpholines from Aldehydes and SnAP Reagents. *Angew. Chem., Int. Ed.* **2015**, *54*, 10884.

(14) (a) Jackl, M. K.; Legnani, L.; Morandi, B.; Bode, J. W. Continuous Flow Synthesis of Morpholines and Oxazepanes with Silicon Amine Protocol (SLAP) Reagents and Lewis Acid Facilitated Photoredox Catalysis. *Org. Lett.* **2017**, *19*, 4696. (b) Hsieh, S.-Y.; Bode, J. W. Silicon Amine Reagents for the Photocatalytic Synthesis of Piperazines from Aldehydes and Ketones. *Org. Lett.* **2016**, *18*, 2098.

(15) Wang, Y.-Y.; Bode, J. W. Olefin Amine (OLA) Reagents for the Synthesis of Bridged Bicyclic and Spirocyclic Saturated N-Heterocycles by Catalytic Hydrogen Atom Transfer (HAT) Reactions. *J. Am. Chem. Soc.* **2019**, *141*, 9739.

(16) (a) Huang, D.; Yan, G. Recent Advances in Reactions of Azides. *Adv. Synth. Catal.* **2017**, *359*, 1600. (b) Intrieri, D.; Zardi, P.; Caselli, A.; Gallo, E. Organic azides: "energetic reagents" for the intermolecular amination of C−H bonds. *Chem. Commun.* **2014**, *50*, 11440. (c) Minozzi, M.; Nanni, D.; Spagnolo, P. From Azides to Nitrogen-Centered Radicals: Applications of Azide Radical Chemistry to Organic Synthesis. *Chem. - Eur. J.* **2009**, *15*, 7830. (d) Scriven, E. F. V.; Turnbull, K. Azides: their preparation and synthetic uses. *Chem. Rev.* **1988**, *88*, 297.

(17) Wu, K.; Liang, Y.; Jiao, N. Azidation in the Difunctionalization of Olefins. *Molecules* **2016**, *21*, 352.

(18) (a) Chen, Y.; Tian, T.; Li, Z. Mn-Catalyzed azidation−peroxidation of alkenes. *Org. Chem. Front.* **2019**, *6*, 632. (b) Hossain, A.; Vidyasagar, A.; Eichinger, C.; Lankes, C.; Phan, J.; Rehbein, J.; Reiser, O. Visible-Light-Accelerated Copper(II)-Catalyzed Regio- and Chemoselective Oxo-Azidation of Vinyl Arenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 8288. (c) Sun, X.; Li, X.; Song, S.; Zhu, Y.; Liang, Y.-F.; Jiao, N. Mn-Catalyzed Highly Efficient Aerobic Oxidative Hydroxyazidation of Olefins: A Direct Approach to β-Azido Alcohols. *J. Am. Chem. Soc.* **2015**, *137*, 6059. (d) Yuan, Y.-A.; Lu, D.-F.; Chen, Y.-R.; Xu, H. Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins. *Angew. Chem., Int. Ed.* **2016**, *55*, 534.

(19) (a) Fu, N.; Sauer, G. S.; Saha, A.; Loo, A.; Lin, S. Metal-catalyzed electrochemical diazidation of alkenes. *Science* **2017**, *357*, 575. (b) Siu, J. C.; Sauer, G. S.; Saha, A.; Macey, R. L.; Fu, N.; Chauviré, T.; Lancaster, K. M.; Lin, S. Electrochemical Azidooxygenation of Alkenes Mediated by a TEMPO−N_3 Charge-Transfer Complex. *J. Am. Chem. Soc.* **2018**, *140*, 12511.

(20) (a) Chen, J.; Zhu, S.; Qin, J.; Chu, L. Intermolecular, redox-neutral azidoarylation of alkenes via photoredox catalysis. *Chem. Commun.* **2019**, *55*, 2336. (b) Wang, J.-J.; Yu, W. Anti-Markovnikov Hydroazidation of Alkenes by Visible-Light Photoredox Catalysis. *Chem. - Eur. J.* **2019**, *25*, 3510. (c) Wei, W.; Cui, H.; Yue, H.; Yang, D. Visible-light-enabled oxyazidation of alkenes leading to α-azidoketones in air. *Green Chem.* **2018**, *20*, 3197. (d) Yang, B.; Lu, Z. Visible-Light-Promoted Metal-Free Aerobic Hydroxyazidation of Alkenes. *ACS Catal.* **2017**, *7*, 8362.

(21) Liu, Z.; Liu, Z.-Q. An Intermolecular Azidoheteroarylation of Simple Alkenes via Free-Radical Multicomponent Cascade Reactions. *Org. Lett.* **2017**, *19*, 5649.

(22) Lear, J. M.; Buquoi, J. Q.; Gu, X.; Pan, K.; Mustafa, D. N.; Nagib, D. A. Multi-component heteroarene couplings via polarity-reversed radical cascades. *Chem. Commun.* **2019**, *55*, 8820.

(23) (a) Huo, C.; Chen, F.; Yuan, Y.; Xie, H.; Wang, Y. Iron Catalyzed Dual-Oxidative Dehydrogenative (DOD) Tandem Annulation of Glycine Derivatives with Tetrahydrofurans. *Org. Lett.* **2015**, *17*, 5028. (b) Boglio, C.; Lemière, G.; Hasenknopf, B.; Thorimbert, S.; Lacôte, E.; Malacria, M. Lanthanide Complexes of the Monovacant Dawson Polyoxotungstate $[\alpha 1\text{-}P_2W_{17}O_{61}]^{10-}$ as Selective and Recoverable Lewis Acid Catalysts. *Angew. Chem., Int. Ed.* **2006**, *45*, 3324. (c) He, Y.; Yan, B.; Tao, H.; Zhang, Y.; Li, Y. Metal-free photocatalyzed aerobic oxidative C_{sp3}−H functionalization of glycine derivatives: one-step generation of quinoline-fused lactones. *Org. Biomol. Chem.* **2018**, *16*, 3816. (d) Ghashghaei, O.; Masdeu, C.; Alonso, C.; Palacios, F.; Lavilla, R. Recent advances of the Povarov reaction in medicinal chemistry. *Drug Discovery Today: Technol.* **2018**, *29*, 71.

(24) (a) Yamanaka, M.; Nishida, A.; Nakagawa, M. Imino Ene Reaction Catalyzed by Ytterbium(III) Triflate and TMSCl or TMSOTf. *J. Org. Chem.* **2003**, *68*, 3112. (b) Oliver, L. H.; Puls, L. A.; Tobey, S. L. Brønsted acid promoted imino-ene reactions. *Tetrahedron Lett.* **2008**, *49*, 4636.

(25) Zhu, H.-T.; Arosio, L.; Villa, R.; Nebuloni, M.; Xu, H. Process Safety Assessment of the Iron-Catalyzed Direct Olefin Diazidation for the Expedient Synthesis of Vicinal Primary Diamines. *Org. Process Res. Dev.* **2017**, *21*, 2068.

(26) For experimental details, see Supporting Information.

(27) Note: butanedione (**BD**) was used as the catalyst for the reaction of **5**. Fluorenone is also able to promote this reaction; however, it is similar in polarity and thus inseperable with product **6**.

(28) Li, H.; Shen, S.-J.; Zhu, C.-L.; Xu, H. Direct Intermolecular Anti-Markovnikov Hydroazidation of Unactivated Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 9415.

(29) For examples on trimethylsilyl-cation-activated imines: (a) Kaboudin, B.; Moradi, K. TMSCl-Promoted Addition of Diethyl Phosphite to an Imine for the Synthesis of Bis[1-diethoxyphosphorylalkyl]amines. *Synthesis* **2006**, *2006*, 2339−2342. (b) Downey, C. W.; Ingersoll, J. A.; Glist, H. M.; Dombrowski, C. M.; Barnett, A. T. One-Pot Silyl Ketene Acetal-Formation Mukaiyama−Mannich Additions to Imines Mediated by Trimethylsilyl Trifluoromethanesulfonate. *Eur. J. Org. Chem.* **2015**, *2015*, 7287−7291.

DOI: 10.1021/acs.orglett.9b03238
Org. Lett. XXXX, XXX, XXX−XXX