Concise Report

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Oxidative Dehydrogenative [3+3] Annulation of Benzylhydrazines with Aziridines Leading to Tetrahydrotriazines

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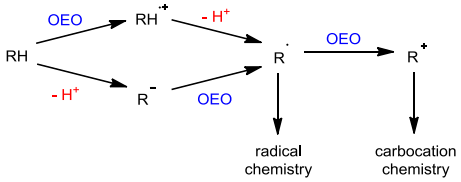
Summary of main observation and conclusion Oxidative dehydrogenative [3+3] annulation of benzylhydrazines with *N*-sulfonylaziridines is described. A series of complex tetrahydro-1,2,4-triazines were produced under mild reaction conditions.

Background and Originality Content

Single electron transfer (SET) is the simplest and smallest elemental reaction in chemistry. One electron oxidation (OEO) means taking an electron away.[1] Usually, there are two pathways to remove an electron from organic compound to subsequently generate radical intermediate, as shown in Scheme 1. In addition, proton-coupled electron transfer (PCET), in which the transferring electron and proton come from the same bond, is also an important pathway for OEO chemistry.[2] With the rapid development of green chemistry and sustainable chemistry, the concepts of "atom economy" become prevalence. In this context, OEO involved oxidative dehydrogenative C—H bond functionalization has become a valuable synthetic approach in the last decade.[3] Oxidative dehydrogenative cyclization has become one of the hot research topics in the last decade.[4]

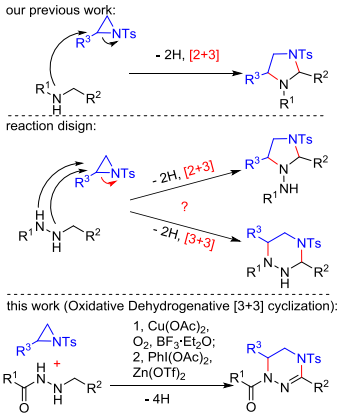
Scheme 1 One electron oxidation (OEO) chemistry



1,2,4-Triazines and their derivatives display a broad spectrum of biological activities, such as antitumor, antiviral, antibacterial, anti-inflammatory, *etc*.[5] These compounds possess a wide range of applications in medicinal chemistry and agricultural chemistry. The triazine units are also valuable synthetic building blocks for the preparation of complex heterocyclic systems.[6] In addition, these triazine skeletons are widely used as ligands for transition-metal complexes.[7] Thus, the development of new and atom-economic synthetic approaches to triazine derivatives is highly desirable.

Very recently, our group achieved an oxidative dehydrogenative [2+3]-cyclization of secondary amines with *N*-sulfonylaziridines to deliver substituted imidazolidines.[8] We questioned if the substrates secondary amines were replaced with secondary hydrazines, as shown in Scheme 2, the method has the potential to produce triazine derivatives through [3+3] manner or *N*-amino imidazolidine derivatives through [2+3] manner. Based on our

Scheme 2 Oxidative dehydrogenative cyclization of aziridines with amines or hydrazines



experience in oxidative dehydrogenative cyclization,[9] we think benzylhydrazines could be chosen instead of the corresponding secondary amines because benzyl position of benzylhydrazine derivatives may be easily oxidized to generate carbocations for further transformation. And Carbobenzyloxy (Cbz) could be selected as protecting group because: (1) It will improve the tolerance of hydrazine motif under oxidation conditions; (2) It will differentiate two hydrazine N atoms' nucleophilic ability; (3) It is easy to be removed.

With these considerations in mind, we describe herein a facile and practical approach to highly functionalized tetrahydro-1,2,4-triazine derivatives based on the dehydrogenation, subsequential nucleophilic ring opening and finally intramolecular oxidative amination reaction of benzylhydrazines with *N*-sulfonylaziridines.

Results and Discussion

Our investigation began with optimization of the reaction of benzyl 2-benzylhydrazinecarboxylate **1a** with 2-phenyl-1-tosylaziridine **2a** (Scheme 3a). Under the similar reaction conditions of the ref 8, a product **B** was isolated. After overall screening, we found that the optimized reaction conditions for the coupling of two substrates include 10 mol% of copper acetate as the dehydrogenation catalyst under aerobic conditions, 20 mol% of boron trifluoride diethyl etherate as the nucleophilic ring opening cata-

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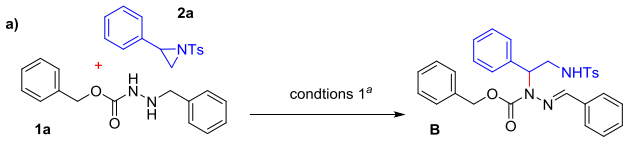
lyst, and dichloromethane as solvent under room temperature. The coupling product (**B**) was obtained in 69% yield (Scheme 3a, entry 4). A variety of redox-active metal salts were tested (Scheme 3a, entries 1—5), and $Cu(OAc)_2$ provided the highest yield. When the loading of $Cu(OAc)_2$ was reduced (5 mol%) or increased (15 mol%), compound **B** was obtained in lower yields (Scheme 3a, entries 6—7). Importantly, O_2 was found superior than classic chemical oxidants such as quinone (DDQ) and peroxide (TBHP), which constitutes a practical advantage in terms of economics and sustainability. Various Lewis acids and Bronsted acids, such as different BF_3 ethers, $Y(OTf)_3$, $Sc(OTf)_3$, HCl and PTSA, were investigated as additives. No higher yield than that of $BF_3{\cdot}Et_2O$ was observed (Scheme 3a, entries 11—16). A lower yield was observed when the amount of $BF_3{\cdot}Et_2O$ was decreased or increased (Scheme 3a, entries 17—18).

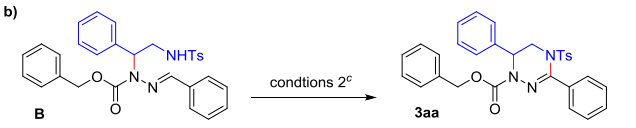
Likewise, the performance of the process at higher temperatures did not improve the reaction (Scheme 3a, entry 22). Then compound **B** was used to optimize the reaction conditions of ring-closure oxidative amination (Scheme 3b). Again, after careful screening, we found that the desired product tetrahydro-1,2,4-triazine **3aa** was obtained in 89% yield with a combination of 2 equiv. of iodobenzene diacetate as the oxidant, 20 mol% of zinc triflate as the additive, and dichloroethane as solvent at 60 °C.

With a set of optimized reaction conditions in hand (Scheme 3a, entry 4; Scheme 3b, entry 1), we explored the scope of the oxidative dehydrogenative [3+3] annulation reaction by investigating the reaction between different benzylhydrazines **1** and 2-phenyl-1-tosylaziridine **2a** (Scheme 4). Various benzylhydrazines with valuable functional groups on the aromatic ring, either electron-donating or -withdrawing groups, could react smoothly with **2a** to afford the corresponding products (**3aa**—**3ka**) in good yields. The substituents at the *ortho*-, *meta*-, and *para*-positions of the phenyl ring were all tolerated in the cyclization reaction, providing corresponding products (**3da**—**3fa**) in good yields. The excellent functional group tolerance enables potential application of the reaction in synthesis of complex tetrahydrotriazines by functionalization of bioactive compounds or pharmaceuticals. Compound **3ja** derived from menthol and compound **3ka** derived from diacetonefructose were successfully achieved in 54% and 46% yields, respectively. This example indicates that this protocol represents a practical application in synthetic medicinal chemistry. We next focused our attention to the scope of the aziridines (Scheme 4). Pleasingly, a variety of *N*-sulfonylaziridines reacted smoothly with

Scheme 3 Screening of reaction conditions[a,b,c]



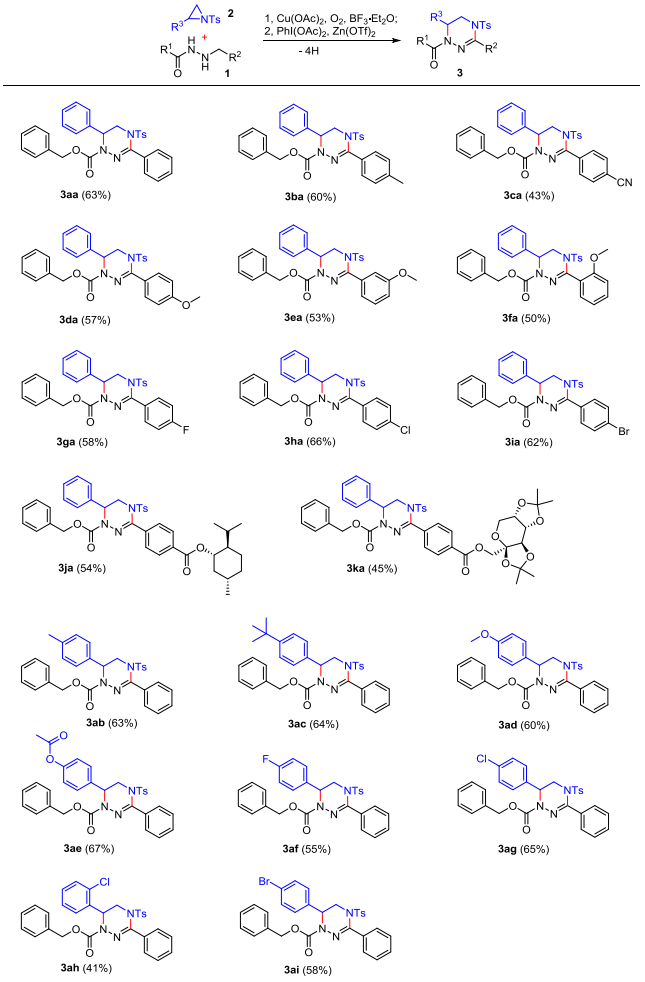
Entry	Catalyst	Oxidant 1	Additive 1	Solvent 1	Temp.	**B** (yield/%)[b]
1	$CuCl_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	34
2	CuCl (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	21
3	$CuBr_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	31
4	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	69
5	$FeCl_3$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	30
6	$Cu(OAc)_2$ (5 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	48
7	$Cu(OAc)_2$ (15 mol%)	O_2	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	68
8	$Cu(OAc)_2$ (10 mol%)	DDQ	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	31
9	$Cu(OAc)_2$ (10 mol%)	TBHP	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	30
10	$Cu(OAc)_2$ (10 mol%)	air	$BF_3{\cdot}OEt_2$ (20 mol%)	CH_2Cl_2	rt	59
11	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}THF$ (20 mol%)	CH_2Cl_2	rt	66
12	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OMe_2$ (20 mol%)	CH_2Cl_2	rt	68
13	$Cu(OAc)_2$ (10 mol%)	O_2	$Y(OTf)_3$ (20 mol%)	CH_2Cl_2	rt	25
14	$Cu(OAc)_2$ (10 mol%)	O_2	$Sc(OTf)_3$ (20 mol%)	CH_2Cl_2	rt	31
15	$Cu(OAc)_2$ (10 mol%)	O_2	HCl (20 mol%)	CH_2Cl_2	rt	—
16	$Cu(OAc)_2$ (10 mol%)	O_2	PTSA (20 mol%)	CH_2Cl_2	rt	—
17	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (10 mol%)	CH_2Cl_2	rt	55
18	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$ (30 mol%)	CH_2Cl_2	rt	65
19	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$	$(CH_2Cl)_2$	rt	65
20	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$	CH_3Cl	rt	53
21	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$	toluene	rt	32
22	$Cu(OAc)_2$ (10 mol%)	O_2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	30 °C	68



Entry	Oxidant 2	Additive 2	Solvent 2	Temp.	**3aa** (yield/%)[b]
1	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (10 mol%)	$(CH_2Cl)_2$	60 °C	89
2	$PhI(OAc)_2$ (2 equiv.)	$Y(OTf)_3$ (10 mol%)	$(CH_2Cl)_2$	60 °C	73
3	$PhI(OAc)_2$ (2 equiv.)	$Sc(OTf)_3$ (10 mol%)	$(CH_2Cl)_2$	60 °C	78
4	$PhI(OAc)_2$ (2 equiv.)	$Cu(OTf)_2$ (10 mol%)	$(CH_2Cl)_2$	60 °C	76
5	$PhI(OAc)_2$ (2 equiv.)	$Cu(OAc)_2$ (10 mol%)	$(CH_2Cl)_2$	60 °C	—
6	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (5 mol%)	$(CH_2Cl)_2$	60 °C	80
7	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (15 mol%)	$(CH_2Cl)_2$	60 °C	84
8	$PhI(OAc)_2$ (1.5 equiv.)	$Zn(OTf)_2$ (10 mol%)	$(CH_2Cl)_2$	60 °C	73
9	$PhI(OAc)_2$ (2.5 equiv.)	$Zn(OTf)_2$ (10 mol%)	$(CH_2Cl)_2$	60 °C	86
10	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (10 mol%)	CH_3Cl	60 °C	66
11	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (10 mol%)	toluene	60 °C	—
12	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (10 mol%)	DCE	50 °C	62
13	$PhI(OAc)_2$ (2 equiv.)	$Zn(OTf)_2$ (10 mol%)	DCE	70 °C	87

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), catalyst, oxidant 1, additive 1, solvent 1 (3 mL), 3 h; [b] Yield of the isolated product; [c] oxidant 2, additive 2, solvent 2 (1 mL), 60 °C, 2 h.

Scheme 4 Oxidative dehydrogenative [3+3] cyclization reaction of benzylhydrazines with aziridines

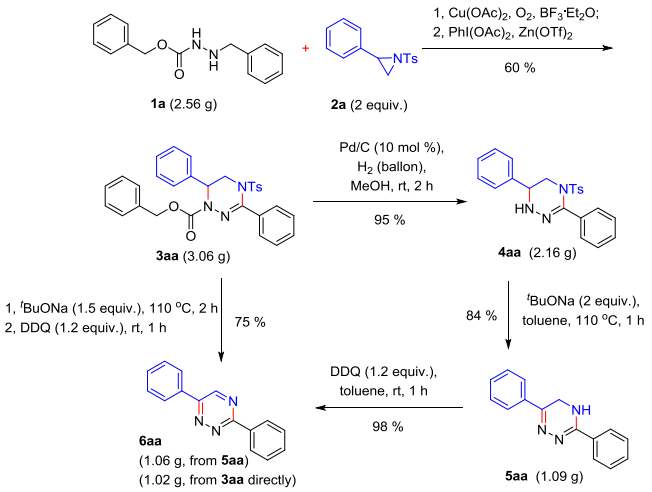


[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), $Cu(OAc)_2$ (10 mol%), $BF_3{\cdot}Et_2O$ (20 mol%), O_2 (balloon), DCE (3 mL), rt, 3—10 h; $PhI(OAc)_2$ (2 equiv.), $Zn(OTf)_2$ (10 mol%), DCE (1 mL), 60 °C, 4—8 h. [b] Yield of the isolated product.

benzylhydrazine **1a**. Aziridines bearing various functional groups on the phenyl ring were tolerated well, delivering the desired products in good yields (**3aa—3ai**). Depressingly, no corresponding cyclization product was obtained when *N*-Benzoyl analog of **2a** was used. Furthermore, a series of substituted tetrahydrotriazines with halo or ester groups at the phenyl ring reacted smoothly to produce the corresponding products (**3ae—3ai**), which provided useful handles for further transformations.

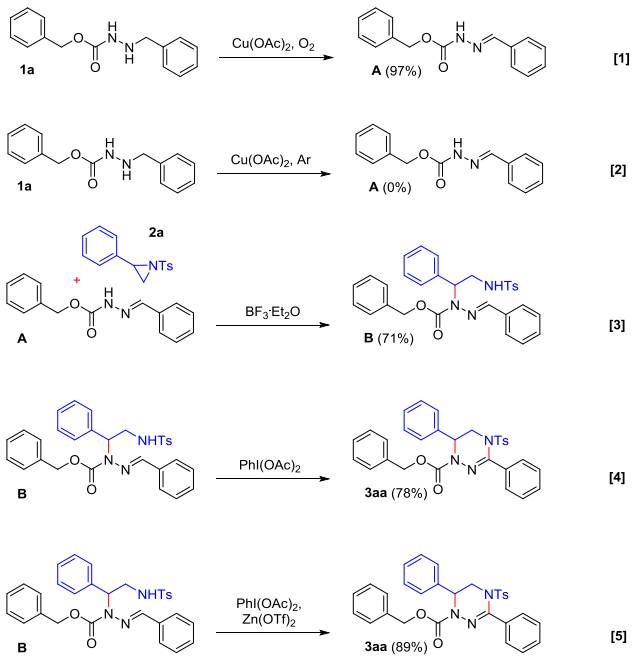
The reaction was amenable to scale-up to gram quantity in a similar yield leading to the formation of **3aa** in 60% yield, as shown in Scheme 5. In order to better illustrate our obtained tetrahydro-1,2,4-triazine products, further deprotection of the units was conducted. The versatile **3aa** could be treated with Pd/C/H_2 to remove the cbz protecting group and give the compound **4aa** in 95% yield. In addition, compound **4aa** could be treated with ^{t}BuONa to remove the Ts protecting group and give the protecting-free tetrahydro-1,2,4-triazine **5aa** in 84% yield. The dehydrogenation also occurred in this step to generate a big conjugate system because the reaction was not carried out under inert gas. Furthermore, compound **5aa** could be easily and efficiently aromatized to the corresponding 3,6-diphenyl-1,2,4-triazine **6aa** by oxidation with DDQ at room temperature in an hour. Moreover, deprotection of Cbz and Ts and the following aromatization could be also accomplished in one-pot manner to give 3,6-diphenyl-1,2,4-triazine **6aa** directly in 75% yield. The structure of **6aa** was confirmed using single crystal X-ray diffraction.[10]

Scheme 5 Scale-up experiment and further transformation of tetrahydro-1,2,4-triazine **3aa**



To gain insight into the mechanism, control experiments were conducted. Firstly, the reaction of benzyl 2-benzylhydrazinecarboxylate **1a** in the absence of 2-phenyl-1-tosylaziridine **2a** under the Cu(OAc)$_2$ catalyzed aerobic conditions was investigated. Hydrazone **A** was isolated in an excellent yield (Scheme 6, rxn. 1). At the same time, no reaction occurred under argon atmosphere (Scheme 6, rxn. 2). These results indicate that the hydrazone **A** is involved as an intermediate and copper salt acts as the redox catalyst with O_2 as terminal oxidant. Secondly, the reaction of **A** and **2a** in the presence of $BF_3{\cdot}Et_2O$ (Scheme 6, rxn. 3) was investigated. The nucleophilic ring opening product **B** was obtained in a high yield. This result indicates that $BF_3{\cdot}Et_2O$ is crucial for this step and acts as Lewis acid catalyst. Thirdly, the ring closure reaction of **B** was investigated. When PhI(OAc)$_2$ was used, the desired product **3aa** was detected, albeit in a relatively lower yield and longer reaction time (Scheme 6, rxn. 4). When catalytic amount of Zn(OTf)$_2$ was added, the desired product **3aa** was obtained in a higher yield (Scheme 6, rxn. 5). These results indicate that hypervalent iodine reagent PhI(OAc)$_2$ is the oxidant for this oxidative

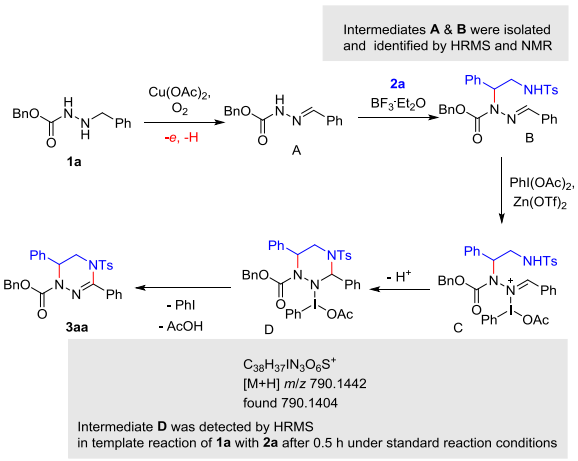
Scheme 6 Control experiments



amination reaction and Zn(OTf)$_2$ improved the oxidation potential of PhI(OAc)$_2$ through ligand exchange.

The plausible mechanism for this oxidative dehydrogenative [3+3] cyclization protocol is outlined in Scheme 7. With the aid of Cu(OAc)$_2$ as redox catalyst and O_2 as terminal oxidant, hydrazine **1a** is oxidized and generates hydrazone **A**. Ring opening of aziridine **2a** then occurs to form C—N coupling product **B** with intermediate **A** as nucleophile and $BF_3{\cdot}Et_2O$ as Lewis acid catalyst, which sequentially undergoes intramolecular oxidative amination by the PhI(OAc)$_2$/Zn(OTf)$_2$ system to afford the desired product **3aa**.

Scheme 7 Proposed mechanism



Conclusions

In conclusion, we demonstrate the first oxidative dehydrogenative formal [3+3]-cyclization of benzylhydrazines with aziridines under mild reaction conditions, providing an efficient and general method for the synthesis of highly functionalized tetrahydro-1,2,4-triazines, a core structure in many bioactive compounds. The protocol is atom-economic and exhibits a broad substrate scope and wide functional group compatibility. Scalability was

demonstrated by a gram scale reaction without diminished yield. Further studies on developing more type of oxidative dehydrogenative cyclization reactions to the synthesis of cyclic compounds are currently underway.

Experimental

To a 10 mL reaction tube with a magnetic stirring bar were added CH_2Cl_2 (3 mL), benzylhydrazines (**1**, 0.5 mmol) and $Cu(OAc)_2$ (0.05 mmol) successively. The resulting reaction mixture was performed at room temperature under oxygen atmosphere (balloon) for 1 h. 3 Å molecular sieve was added for another 1 h. Aziridines (**2**, 1 mmol) and $BF_3{\cdot}Et_2O$ (0.1 mmol) were then added. The solution was stirred at room temperature and completed within 3—10 h as monitored by TLC. The compounds **B** were isolated by column chromatographic separation (hexane/DCM/EA = 5 : 3 : 0.2 to 5 : 3 : 0.6). Then to a 10 mL reaction tube with a magnetic stirring bar were added above isolated compounds **B**, $(CH_2Cl)_2$ (1 mL), $PhI(OAc)_2$ (2 equiv.) and $Zn(OTf)_2$ (10 mol%) successively. The resulting reaction mixture was performed at 60 °C for 2—8 h as monitored by TLC. After the reaction was completed, the reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography to afford desired products **3** (EA/hexane = 1 : 6 to 1 : 2).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.201900214.

Acknowledgement

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References

[1] (a) Wurster, C.; Sendtner, R. Zur Kenntniss des Dimethylparaphenylendiamins. *Chem*. *Ber*. **1879**, *12*, 1803–1807; (b) Weitz, E.; Schwechten, H. W. Über den Ammonium-Charakter *der* Triarylamine. (VII. Mitteilung über freie Ammonium-Radikale.). *Chem*. *Ber*. **1926**, *59*, 2307; (c) Bauld, N. L.; Bellville, D. J.; Harirchian, B.; Lorenz, K. T.; Pabon Jr, R. A.; Reynolds, D. W.; Wirth, D. D.; Chiou, H. S.; Marsh, B. K. Cation Radical Pericyclic Reactions. *Acc*. *Chem*. *Res*. **1987**, *20*, 371–378; (d) Bauld, N. L. Cation Radical Cycloadditions and Related Sigmatropic Reactions. *Tetrahedron* **1989**, *45*, 5307–5363; (e) Popielarz, R.; Arnold, D. R. Radical Ions in Photochemistry. Carbon-Carbon Bond Cleavage of Radical Cations in Solution: Theory and Application. *J*. *Am*. *Chem*. *Soc*. **1990**, *112*, 3068–3082; (f) Schmittle, M.; Burghart, A. Understanding Reactivity Patterns of Radical Cations. *Angew*. *Chem*. *Int*. *Ed*. **1997**, *36*, 2550–2589; (g) Zhang, C.; Tang, C.; Jiao, N. Recent Advances in Copper-Catalyzed Dehydrogenative Functionalization *via* a Single Electron Transfer (SET) Process. *Chem*. *Soc*. *Rev*. **2012**, *41*, 3464–3484; (h) Gini, A.; Brandhofer, T.; Mancheño, O. G. Recent Progress in Mild Csp^3–H Bond Dehydrogenative or (mono-) Oxidative Functionalization. *Org*. *Biomol*. *Chem*. **2017**, *15*, 1294–1312; (i) 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.

[2] Huynh, M. H. V.; Meyer, T. J. Proton-Coupled Electron Transfer. *Chem*. *Rev*. **2007**, *107*, 5004–5064.

[3] (a) Girard, S. A.; Knauber, T.; Li, C.-J. The Cross-Dehydrogenative Coupling of C sp^3-H Bonds: A Versatile Strategy for C-C Bond Formations. *Angew*. *Chem*. *Int*. *Ed*. **2014**, *53*, 74–100; (b) Murahashi, S.-I.; Zhang, D. Ruthenium Catalyzed Biomimetic Oxidation in Organic Synthesis Inspired by Cytochrome P-450. *Chem*. *Soc*. *Rev*. **2008**, *37*, 1490–1501; (c) Lakshman, M. K.; Vurama, P. K. Cross-Dehydrogenative Coupling and Oxidative-Amination Reactions of Ethers and Alcohols with Aromatics and Heteroaromatics. *Chem*. *Sci*. **2017**, *8*, 5845–5888; (d) Guo, S.-r.; Kumar, P. S.; Yang, M. Recent Advances of Oxidative Radical Cross-Coupling Reactions: Direct α-C(sp^3)-H Bond Functionalization of Ethers and Alcohols. *Adv*. *Synth*. *Catal*. **2017**, *359*, 2–25; (e) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C–H Activation/Radical Cross-Coupling. *Chem*. *Rev*. **2017**, *117*, 9016–9085; (f) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C–H Functionalizations. *Chem*. *Rev*. **2015**, *115*, 12138–12204; (g) Narayan, R.; Matcha, K.; Antonchick, A. P. Metal-Free Oxidative C-C Bond Formation through C-H Bond Functionalization. *Chem*. *Eur*. *J*. **2015**, *21*, 14678–14693; (h) 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; (i) Qin, Y.; Zhu, L.; Luo, S. Organocatalysis in Inert C–H Bond Functionalization. *Chem*. *Rev*. **2017**, *117*, 9433–9520; (j) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S.-g. Transition Metal-Catalyzed Site- and Regio-Divergent C-H Bond Bunctionalization. *Chem*. *Soc*. *Rev*. **2017**, *46*, 4299–4328.

[4] (a) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. Electroremovable Traceless Hydrazides for Cobalt-Catalyzed Electro-Oxidative C–H/N–H Activation with Internal Alkynes. *J*. *Am*. *Chem*. *Soc*. **2018**, *140*, 7913–7921; (b) Li, J.; Huang, W.; Chen, J.; He, L.; Cheng, X.; Li, G. Electrochemical Aziridination by Alkene Activation Using a Sulfamate as the Nitrogen Source. *Angew*. *Chem*. *Int*. *Ed*. **2018**, *57*, 5695–5698; (c) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed Coupling of Benzoic Acid C-H Bonds with Alkynes, Styrenes, and 1,3-Dienes. *Angew*. *Chem*. *Int*. *Ed*. **2018**, *57*, 1688–1691; (d) Hou, Z.-W.; Mao, Z.-Y.; Melcamu, Y. Y.; Lu, X.; Xu, H.-C. Electrochemical Synthesis of Imidazo-Fused *N*-Heteroaromatic Compounds through a C-N Bond-Forming Radical Cascade. *Angew*. *Chem*. *Int*. *Ed*. **2018**, *57*, 1636–1639; (e) Pan, J.; Li, X.; Qiu, X.; Luo, X.; Jiao, N. Copper-Catalyzed Oxygenation Approach to Oxazoles from Amines, Alkynes, and Molecular Oxygen. *Org*. *Lett*. **2018**, *20*, 2762–2765; (f) Li, H.; Huang, S.; Wang, Y.; Huo, C. Oxidative Dehydrogenative [2 + 3]-Cyclization of Glycine Esters with Aziridines Leading to Imidazolidines. *Org*. *Lett*. **2018**, *20*, 92–95; (g) Yi, H.; Niu, L.; Song, C.; Li, Y.; Dou, B.; Singh, A. K.; Lei, A. Photocatalytic Dehydrogenative Cross-Coupling of Alkenes with Alcohols or Azoles without External Oxidant. *Angew*. *Chem*. *Int*. *Ed*. **2017**, *56*, 1120–1124; (h) Liu, K.; Tang, S.; Huang, P.; Lei, A. External Oxidant-free Electrooxidative [3+2] Annulation between Phenol and Indole Derivatives. *Nat*. *Commun*. **2017**, *8*, 775; (i) Xie, Z.; Jia, J.; Liu, X.; Liu, L. Copper(II) Triflate-Catalyzed Aerobic Oxidative C-H Functionalization of Glycine Derivatives with Olefins and Organoboranes. *Adv*. *Synth*. *Catal*. **2016**, *358*, 919–925; (j) Xie, Z.; Liu, X.; Liu, L. Copper-Catalyzed Aerobic Enantioselective Cross-Dehydrogenative Coupling of *N*-Aryl Glycine Esters with Terminal Alkynes. *Org*. *Lett*. **2016**, *18*, 2982–2985; (k) Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J.-X.; Wu, L.-Z.; Lei, A. External Oxidant-Free Oxidative Cross-Coupling: A Photoredox Cobalt-Catalyzed Aromatic C–H Thiolation for Constructing C–S Bonds. *J*. *Am*. *Chem*. *Soc*. **2015**, *137*, 9273–9280; (l) Manna, S.; Antonchick, A. P. Copper-Catalyzed (2+1) Annulation of Acetophenones with Maleimides: Direct Synthesis of Cyclopropanes. *Angew*. *Chem*. *Int*. *Ed*. **2015**, *54*, 14845–14848; (m) Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. Auto-Oxidative Coupling of Glycine Derivatives. *Angew*. *Chem*. *Int*. *Ed*. **2014**, *53*, 13544–14547.

[5] (a) Khoshneviszadeh, M.; Ghahremani, M. H.; Foroumadi, A.; Miri, R.; Firuzi, O.; Madadkar-Sobhani, A.; Edraki, N.; Parsa, M.; Shafiee, A. Design, Synthesis and Biological Evaluation of Novel Anti-Cytokine 1,2,4-Triazine Derivatives. *Bioorg*. *Med*. *Chem*. **2013**, *21*, 6708–6717; (b) Karczmarzyk, Z.; Wysocki, W.; Urbańczyk-Lipkowska, Z.; Kalicki, P.; Bielawska, A.; Bielawski, K.; Ławecka, J. Synthetic Approaches for Sulfur Derivatives Containing 1,2,4-Triazine Moiety: Their Activity for *in vitro* Screening towards Two Human Cancer Cell Lines. *J*. *Chem*. *Pharm*. *Bull*. **2015**, *63*, 531–537; (c) Sztanke, K.; Pasternak, K.; Rajtar,

B.; Sztanke, M.; Majek, M.; Polz-Dacewicz, M. Identification of Antibacterial and Antiviral Activities of Novel Fused 1,2,4-Triazine Esters. *Bioorg*. *Med*. *Chem*. **2007**, *15*, 5480–5486; (d) Culakova, H.; Dzugasova, V.; Gbelska, Y.; Subik, J. Antibacterial Activity of CTBT (7-Chlorotetrazolo [5,1-c] Benzo [1,2,4] Triazine) Generating Reactive Oxygen Species. *Microbiol*. *Res*. **2013**, *168*, 147–152; (e) Rusinov, V. L.; Egorov, I. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Serova, O. A. Synthesis and Antiviral Activity of 1,2,4-Triazine Derivatives. *Pharm*. *Chem*. *J*. **2012**, *45*, 655–659.

[6] (a) Boger, D. L. Diels-Alder Reactions of Heterocyclic Aza Dienes. Scope and Applications. *Chem*. *Rev*. **1986**, *86*, 781–793; (b) Raw, S. A.; Taylor, R. J. K. Cascade Reactions of Substituted 1,2,4-Triazines: Rapid Access to Nitrogen-Containing Polycycles. *J*. *Am*. *Chem*. *Soc*. **2004**, *126*, 12260–12261; (c) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. Synthesis of the Louisianin Alkaloid Family *via* a 1,2,4-Triazine Inverse-Electron-Demand Diels–Alder Approach. *J*. *Org*. *Chem*. **2009**, *74*, 8343–8354; (d) Shi, B.; Lewis, W.; Campbell, I. B.; Moody, C. J. A Concise Route to Pyridines from Hydrazides by Metal Carbene N–H Insertion, 1,2,4-Triazine Formation, and Diels–Alder Reaction. *Org*. *Lett*. **2009**, *11*, 3686-3688; (e) Lorion, M.; Guillaumet, G.; Brière, J.-F.; Suzenet, F. Sequential Michael Addition and Enamine-Promoted Inverse Electron Demanding Diels–Alder Reaction upon 3-Vinyl-1,2,4-triazine Platforms. *Org*. *Lett*. **2015**, *17*, 3154–3157; (f) Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D. C.; Ley, S. V. One-Pot Acid-Catalyzed Ring-Opening/Cyclization/Oxidation of Aziridines with N-Tosylhydrazones: Access to 1,2,4-Triazines. *Org*. *Lett*. **2017**, *19*, 1084–1087; (g) Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. Copper-Catalyzed Tandem Nucleophilic Ring-Opening/Intramolecular Oxidative Amidation of *N*-Tosylaziridines and Hydrazones under Aerobic Conditions. *Org*. *Lett*. **2009**, *11*, 5678–5681.

[7] (a) Lewis, F. W.; Harwood, L. M.; Hudson, M. J.; Geist, A.; Kozhevnikov, V. N.; Distler, P.; John, J. Hydrophilic Sulfonated bis-1,2,4-Triazine Ligands are highly Effective Reagents for Separating Actinides(III) from Lanthanides(III) via Selective Formation of Aqueous Actinide Complexes. *Chem*. *Sci*. **2015**, *6*, 4812–4821; (b) Coogan, N. T.; Chimes, M. A.; Raftery, J.; Mocilac, P.; Denecke, M. A. Regioselective Synthesis of V-Shaped Bistriazinyl-phenanthrolines. *J*. *Org*. *Chem*. **2015**, *80*, 8684–8693; (c) Guillet, G. L.; Hyatt, I. F. D.; Hillesheim, P. C.; Abboud, K. A.; Scott, M. J. 1,2,4-Triazine-Picolinamide Functionalized, Nonadentate Chelates for the Segregation of Lanthanides(III) and Actinides(III) in Biphasic Systems. *New J*. *Chem*. **2013**, *37*, 119–131; (d) Wolińska, E. Chiral Oxazoline Ligands Containing a 1,2,4-Triazine Ring and Their Application in the Cu-catalyzed Asymmetric Henry Reaction. *Tetrahedron* **2013**, *69*, 7269–7278.

[8] Li, H.; Huang, S.; Wang, Y.; Huo, C. Oxidative Dehydrogenative [2+3]-Cyclization of Glycine Esters with Aziridines Leading to Imidazolidines. *Org*. *Lett*. **2018**, *20*, 92–95.

[9] (a) Huo, C.; Yuan, Y.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. Auto-Oxidative Coupling of Glycine Derivatives. *Angew*. *Chem*. *Int*. *Ed*. **2014**, *53*, 13544–13547; (b) 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*, 5028–5031; (c) Huo, C.; Yuan, Y.; Chen, F.; Wang, Y. A Catalytic Approach to Quinoline Fused Lactones and Lactams from Glycine Derivatives. *Adv*. *Synth*. *Catal*. **2015**, *357*, 3648–3654; (d) Huo, C.; Xie, H.; Chen, F.; Tang, J.; Wang, Y. Double-Oxidative Dehydrogenative (DOD) Cyclization of Glycine Derivatives with Dioxane under Metal-Free Aerobic Conditions. *Adv*. *Synth*. *Catal*. **2016**, *358*, 724–730; (e) Huo, C.; Tang, J.; Xie, H.; Wang, Y.; Dong, J. CBr4 Mediated Oxidative C–N Bond Formation: Applied in the Synthesis of Imidazo[1,2-α] pyridines and Imidazo [1,2-α] pyrimidines. *Org*. *Lett*. **2016**, *18*, 1016–1019; (f) Huo, C.; Yuan, Y.; Chen, F.; Tang, J.; Wang, Y. Copper-Catalyzed Aerobic Oxidative Dehydrogenative Formal [2+3] Cyclization of Glycine Esters with α-Angelicalactone: Approach to Construct Polysubstituted Pyrrolidones. *Org*. *Lett*. **2015**, *17*, 4208–4211; (g) Jiang, W.; Wang, Y.; Niu, P.; Quan, Z.; Su, Y.; Huo, C. Double-Oxidative Dehydrogenative (DOD) [4+2]-Cyclization/Oxidative Aromatization Tandem Reaction of Glycine Derivatives with Ethylbenzenes. *Org*. *Lett*. **2018**, *20*, 4649–4653.

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