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Synthesis of Carbonylated Heteroaromatic Compounds via Visible-Light-Driven Intramolecular Decarboxylative Cyclization of *o*-Alkynylated Carboxylic Acids

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An efficient strategy for the easy access to carbonylated heteroaromatic compounds has been developed via a visible-light-promoted intramolecular decarboxylative cyclization reaction of *o*-alkynylated carboxylic acids. This method is characterized by its benign conditions and the tolerance of a wide range of functionalities.

Heteroaromatic compounds, including 3-acylindoles, 3-acylbenzofurans and 3-acylbenzothiophenes, have been widely employed as pervasive structural motifs in numerous natural products and biologically active pharmaceutical molecules[1-4]. For example, pravadoline, which has been synthesized by Sterling Drug (Sterling Research Group, Rensselaer, NY), exhibits significant analgesic activity in humans[2]. Daphnodorin A and B show a broad range of biological activities such as antitumor properties, antiviral activities, and anti-inflammatory properties[3]. Raloxifene has been found as an oral selective estrogen receptor modulator (SERM) to prevent the osteoporosis in postmenopausal women[4]. Therefore considerable efforts have been made towards the development of efficient protocols for the synthesis of carbonylated heteroaromatic compounds[5-8]. Among them the typical methods include Friedel-Crafts reaction[5], Vilsmeier-Haack reaction[6], and transition-metal-catalyzed C3-H activation reaction[7], which almost rely on preformed indoles, benzofurans or benzothiophenes to achieve carbonylated products. However, most of traditional strategies suffer from limited functional group tolerability and harsh conditions. Compared with the prosperous achievements, photoredox catalysis may provide an efficient method for the assembly of 3-acylindoles, 3-acylbenzofurans and 3-acylbenzothiophenes under milder conditions.

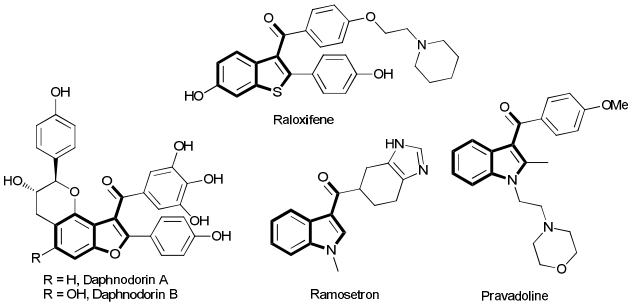

Figure 1. Examples of bioactive carbonylated heteroaromatic compounds.

Carboxylic acids are readily available and inexpensive basic chemicals, and their radical decarboxylative functionalization has recently received considerable attention as a powerful synthetic method that allows to rapidly construct C-C and/or C-X bonds[9]. In recent years, visible-light-promoted radical decarboxylative functionalization of carboxylic acids and their derivatives has arguably gained considerable momentum[10]. With this regard, the applications on the visible-light-driven decarboxylation process for the construction of C-C and/or C-X bonds have been reported[11]. In contrast to the previous achievements in intermolecular C–C bond and/or C-X bonds formation via decarboxylative functionalization, research on visible-light-induced intramolecular decarboxylative cyclization to construct C-C bond and C-O bond remains scarce. Herein, we reported a novel visible-light-driven intramolecular decarboxylative cyclization of *o*-alkynylated carboxylic acids in the presence of air, base and photocatalyst for the formation of 3-acylindoles, 3-acylbenzofurans and 3-acylbenzothiophenes, in which alkyl radical generated from decarboxylation could undergo intramolecular radical addition to the C-C triple bond, followed by a C-O bond formation, to synthesize the corresponding carbonylated compounds.

Optimization of the reaction conditions was investigated by irradiating a mixture of carboxylic acid, base, and photocatalyst under air atmosphere using blue LEDs as the light source (Table 1). On the basis of reported successes of radical decarboxylative reactions[10-11], our initial investigation was carried out using *o*-alkynylated *α*-amino acid **1a** as the substrate, K_2HPO_4 as base and [Ir{dF(CF$_3$ppy)}$_2$(dtbbpy)]PF$_6$ as

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†Electronic Supplementary Information (ESI) available: Experimental procedures and spectral data for all compounds. See DOI: 10.1039/x0xx00000x

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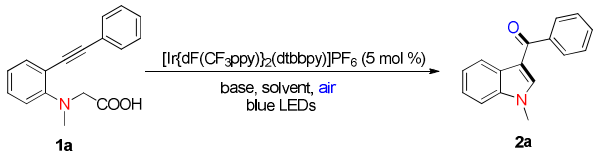
Table 1. Optimization of the Reaction Conditions[a]



1a 2a

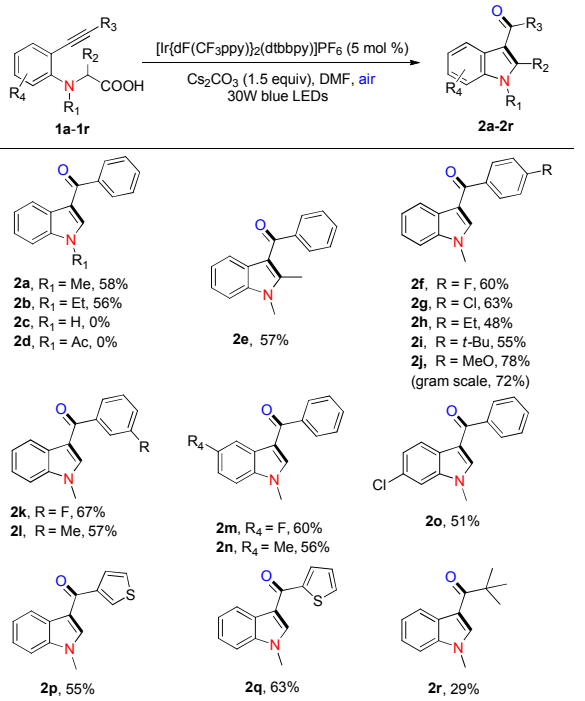
entry	base	solvent	yield (%)[b]
1	K_2HPO_4	DMF	44
2	2,6-Lutidine	DMF	48
3	**Cs_2CO_3**	**DMF**	**58**
4	DBU	DMF	32
5	no	DMF	31
6	Cs_2CO_3	DMSO	54
7	Cs_2CO_3	MeCN	46
8	Cs_2CO_3	1,2-DCE	36
9[c]	Cs_2CO_3	DMF	54
10[d]	Cs_2CO_3	DMF	0
11[e]	Cs_2CO_3	DMF	0
12[f]	Cs_2CO_3	DMF	34

[a]Reaction conditions: **1a** (0.1 mmol), [Ir{dF(CF$_3$ppy)}$_2$(dtbbpy)]PF$_6$ (0.005 mmol), base (0.15 mmol), solvent (anhydrous, 4 ml), air, 30 W blue LEDs, room temperature (rt), 24 h. [b]Isolated yield. [c]Under O_2 atmosphere. [d]Under N_2 atmosphere. [e]In the dark. [f]No photocatalyst.

photocatalyst in DMF. Gratifyingly, the desired 3-acylindole **2a** was obtained in 44% isolated yield (entry 1), and further screening on diverse bases showed that Cr_2CO_3 could provide an obviously improvement in reaction efficiency (entries 2-5). Subsequently, examination on the solvent revealed that DMF was still the optimal reaction medium for this transformation (entries 6-8). Interestingly, it was found that the yield of the product was decreased when using pure oxygen instead of air, and the reaction was completely suppressed under N_2 atmosphere (entries 9-10). A control experiment confirmed that visible light was essential for the desired transformation to occur (entry 11). Notably, when the photocatalyst was absent in the reaction mixture, the desired product **2a** could also be obtained with a decreased yield of 34% (entry 12), which might be owing to the fact that the *o*-alkynylated *α*-amino acid **1a** could be directly oxidized by oxygen of air under irradiation with light to form the corresponding radical intermediate.

With the optimized reaction conditions in hand, we then explored the scope of *α*-amino acid derivatives. As shown in Table 2, a wide range of structurally diverse *o*-alkynylated *α*-amino acids were readily converted to the corresponding 3-acylindoles. It is important to note that the reaction efficiency is closely relevant to the substitution effect on the nitrogen atom, wherein substrates with electron-donating groups, e.g. methyl and ethyl, readily delivered products (**2a**-**2b**). However, for less-substituted or acetyl-substituted carboxylic acid, the corresponding products were not observed (**2c**-**2d**). Substrate **1e** bearing a methyl group in the *α*-position of the carboxyl group performed well under the optimized conditions to furnish a 2, 3-disubstituted indole product. To our delight, a variety of *α*-amino acid derivatives with either electron-withdrawing or electron-donating substituents on the aromatic ring at the terminal alkyne were all competent partners in this reaction (**2f**-**2l**), especially substrate **1j** with a strong electron-donating group was successfully converted to **2j** in 78% yield. Note that the yield of product **2j** remained positive when the reaction was carried out even at gram scale. Different substituents, including F, Cl and Me on the aromatic ring of the aniline moiety all smoothly led to the desired 3-acylindoles (**2m**-**2o**). Moreover, we were pleased to find that the acids with a heteroaromatic ring were competent substrates for this transformation (**2p**-**2q**). Finally, when carboxylic acid **1r** with a bulky *tert*-butyl group at the terminal alkyne was employed, the desired 3-acylindoles **2r** could be isolated in 29% yield.

Table 2. Scope of *α*-Amino Acid Derivatives[a, b]



[a]Reaction conditions: **1** (0.1 mmol), [Ir{dF(CF$_3$ppy)}$_2$(dtbbpy)]PF$_6$ (0.005 mmol), Cr_2CO_3 (0.15 mmol), DMF (anhydrous, 4 ml), air, 30 W blue LEDs, rt, 24 h. [b]Isolated yield.

The generality of this method was next explored for the synthesis of various 3-acylbenzofurans. As described in Table 3, a series of *o*-alkynylated phenoxyacetic acids could undergo efficient decarboxylative cyclization/carbonylation to afford the desired 3-acylbenzofurans successfully. Importantly, this transformation appears to be restricted to the substituent at the *α*-position of the carboxyl group. When phenoxyacetic acid **3b** incorporated with *α*-phenyl group was employed as a substrate, the reaction worked more smoothly to deliver the desired product (**4a**-**4c**). This result may be rationalized by stability of the respective radical intermediate. Moreover, for *ortho*-substituted carboxylic acid **3d**, it was observed that the reactivity was decreased compared with its *para*- or *meta*- substituted counterpart (**4d**-**4f**). Subsequently, we

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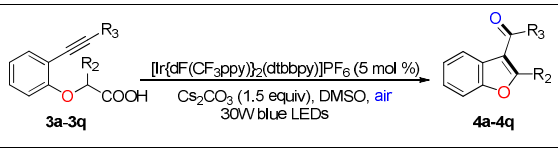
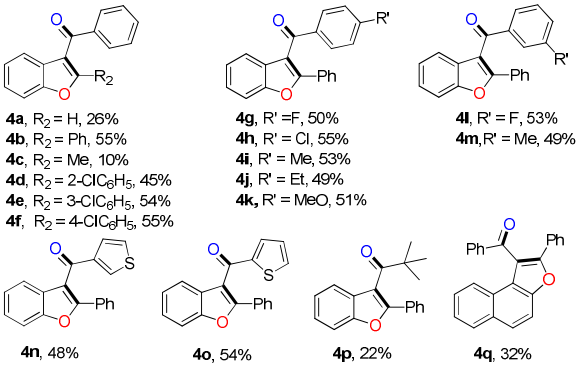
evaluated the substitution effect of the aromatic ring at the terminal alkyne. It was observed that both electron-withdrawing and electron-donating aromatic substituents were well tolerated (**4g**-**4m**). In addition, this protocol could be applied to heteroaryl-substituted phenoxyacetic acids (**4n**-**4o**). A substrate bearing a *tert*-butyl group at the terminal alkyne was also subjected to this reaction, and **4p** was obtained in 22% yield. Interestingly, this process was extended to the acid **3q** with a naphthalene ring.

Table 3. Scope of Phenoxyacetic Acid Derivatives[a, b]



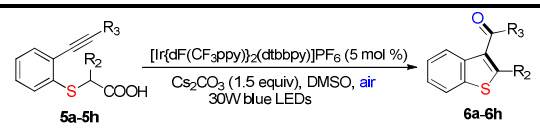


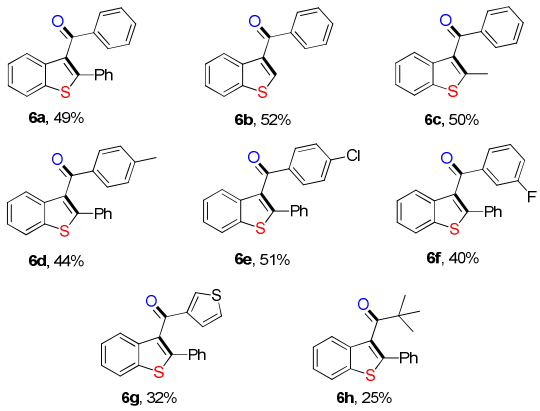
[a]Reaction conditions: **3** (0.1 mmol), [Ir{dF(CF$_3$ppy)}$_2$(dtbbpy)]PF$_6$ (0.005 mmol), Cr_2CO_3 (0.15 mmol), DMSO (anhydrous, 4 ml), air, 30 W blue LEDs, rt, 48 h. [b]Isolated yield.

Finally, to further explore the scope of this protocol, we turn our attention to the decarboxylative cyclization of (phenylthio)acetic acid derivatives (Table 4). As a result of this endeavor, this transformation could also be applied to furnish a variety of differentially substituted 3-acylbenzothiophenes in acceptable yields. Fortunately, various substitutions at the α-position of the carboxyl group were well tolerated with the reaction conditions to obtain the expected products with moderate efficiency (**6a**-**6c**). As expected, the acids with a substituent on the aromatic ring at the terminal alkyne also worked smoothly (**6d**-**6f**). However, in the case of substrates with a 3-thienyl group or a *tert*-butyl group at the terminal alkyne, lower yields of the desired products were formed (**6g** and **6h**, 32% and 25%, respectively).

To gain some information about this transformation, several control experiments were conducted. As illustrated in Scheme 1, when the acid **3b** or **5a** was employed, the reactions did not proceed in the absence of either photocatalyst or light, which highlighted the essential roles of the light and photocatalyst in this transformation (eq 1). Under the optimized conditions, **2a** was not observed in the presence of TEMPO, which revealed that the reaction might occur through a radical process (eq 2). Meanwhile, to further elucidate the origin of the oxygen atom of the ketonic carbonyl group, ^{18}O-labeling experiments were carried out. As expected, it was observed that an ^{18}O atom was incorporated into

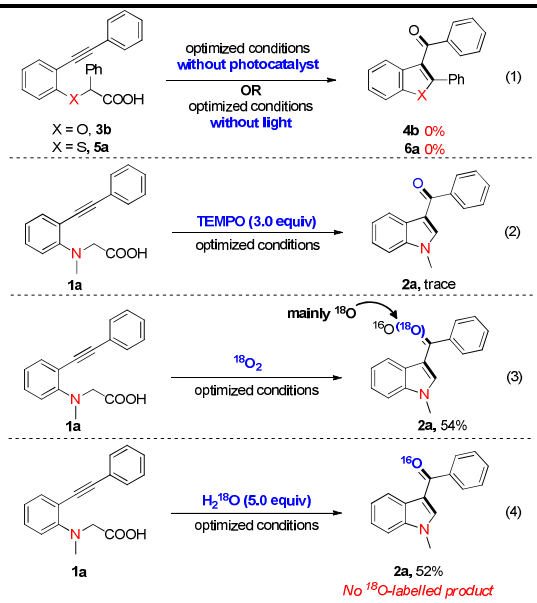
Table 4. Scope of (Phenylthio)acetic Acid Derivatives[a, b]





[a]Reaction conditions: **5** (0.1 mmol), [Ir{dF(CF$_3$ppy)}$_2$(dtbbpy)]PF$_6$ (0.005 mmol), Cr_2CO_3 (0.15 mmol), DMSO (anhydrous, 4 ml), air, 30 W blue LEDs, rt, 48 h. [b]Isolated yield.

Scheme 1. Control Experiments



the ketonic carbonyl group under $^{18}O_2$ atmosphere based upon GC-MS analysis (eq 3). However, in the presence of $H_2{}^{18}O$ (5 equiv) and anhydrous DMF, an ^{18}O-labelled product was not observed (eq 4).

On the basis of the above results, a plausible mechanism was proposed as outlined in Scheme 2[12]. Upon irradiation with visible light, the photocatalyst was excited to *Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$ (**2**) ($E^{Red}_{1/2}$ = +1.21 V vs SCE), which was readily reduced by *o*-alkynylated carboxylic acids (**1a**, $E^{Red}_{1/2}$ = +0.45 V vs SCE; **3b,** $E^{Red}_{1/2}$ = +1.18 V vs SCE; **5a,** $E^{Red}_{1/2}$ = +1.09 V vs SCE; see SI) to form the corresponding carboxyl radical specie. The immediate CO_2-extrusion would provide the radical intermediate (**4**). It is to note

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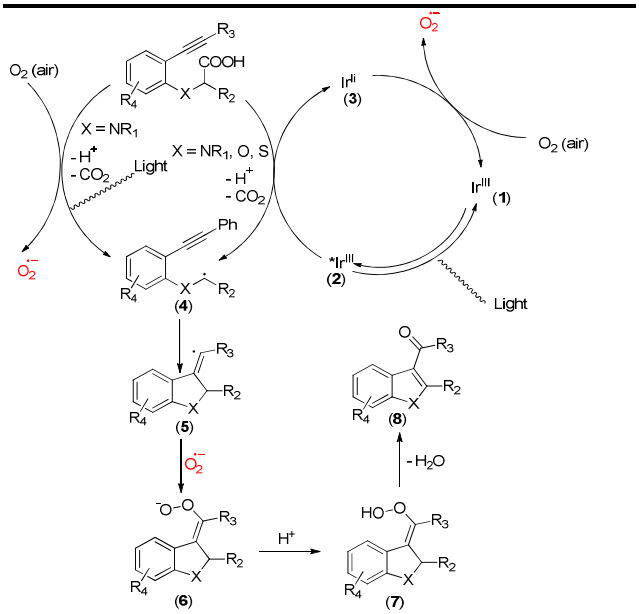
Scheme 2. Plausible Mechanism



that when *o*-alkynylated *α*-amino acids **1** was employed, it could directly undergo oxidative quenching with the assistance of visible light and O_2 to generate the radical intermediate (**4**). Following intramolecular addition with the C-C triple bond, the resulting radical intermediate (**5**) was then captured by $O_2^{\cdot-}$ that was derived from the oxidation of Ir^{II} to Ir^{III} by air to form the peroxide radical intermediate (**6**). After abstraction of a proton[13], intermediate **(6)** was converted into peroxide intermediate (**7**) which finally led to the desired product (**8**) after the elimination of H_2O.

In summary, we have developed a photoredox-assisted intramolecular decarboxylative cyclization reaction and demonstrated its utility over various *o*-alkynylated carboxylic acids, which are easily synthesized and a wide range of such derivatives are available. In contrast to previously reported methods, this protocol enables the formation of a variety of 3-acylindoles, 3-acylbenzofurans and 3-acylbenzothiophenes under genuinely simple and benign conditions. We believe that this strategy will find its wide application in organic synthesis.

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Notes and references

1 (a) Y.-S. Wu, M. S. Coumar, J.-Y. Chang, H.-Y. Sun, F.-M. Kuo, C.-C. Kuo, Y.-J. Chen, C.-Y. Chang, C.-L. Hsiao, J.-P. Liou, *J. Med. Chem.,* 2009, **52**, 4941; (b) M. B. Hadimani, M. T. MacDonough, A. Ghatak, T. E. Strecker, R. Lopez, M. Sriram, B. L. Nguyen, J. J. Hall, R. J. Kessler, A. R. Shirali, L. Liu, C. M. Garner, G. R. Pettit, E. Hamel, D. J. Chaplin, R. P. Mason, M. L. Trawick, K. G. Pinney, *J. Nat. Prod*., 2013, **76**, 1668; (c) T. Vasiljevik, L. N. Franks, B. M. Ford, J. T. Douglas, P. L. Prather, W. E. Fantegrossi, T. E. Prisinzano, *J. Med. Chem.,* 2013, **56**, 4537.

2 (a) D. R. Haubrich, S. J. Ward, E. Baizman, M. R. Bell, J. Bradford, R. Ferrari, M. Miller, M. Perrone, A. K. Pierson, J. K. Saelens, D. Luttinger, *J. Pharmacol. Exp. Ther*., 1990, **255**, 511; (b) P. Sharma, R.-S. Liu, *Org. Lett.,* 2016, **18**, 412; (c) H. H. Seltzman, C. Shiner, E. E. Hirt, A. F. Gilliam, B. F. Thomas, R. Maitra, R. Snyder, S. L. Black, P. R. Patel, Y. Mulpuri, I. Spigelman, *J. Med. Chem*., 2016, **59**, 7525.

3 (a) H. Yuan, K.-J. Bi, B. Li, R.-C. Yue, J. Ye, Y.-H. Shen, L. Shan, H.-Z. Jin, Q.-Y. Sun, W.-D. Zhang, *Org. Lett*., 2013, **15**, 4742; (b) H. Yuan, K. Bi, W. Chang, R. Yue, B. Li, J. Ye, Q. Sun, H. Jin, L. Shan, W. Zhang, *Tetrahedron.*, 2014, **70**, 9084.

4 (a) A. D. Palkowitz, A. L. Glasebrook, K. J. Thrasher, K. L. Hauser, L. L. Short, D. L. Phillips, B. S. Muehl, M. Sato, P. K. Shetler, G. J. Cullinan, T. R. Pell, H. U. Bryant, *J. Med. Chem*., 1997, **40**, 1407; (b) S. T. M. Orr, S. L. Ripp, T. E. Ballard, J. L. Henderson, D. O. Scott, R. S. Obach, H. Sun, A. S. Kalgutkar, *J. Med. Chem*., 2012, **55**, 4896.

5 (a) S. K. Guchhait, M. Kashyap, H. Kamble, *J. Org.Chem.,* 2011, **76**, 4753; (b) L. Wang, Y. Shao, Y. Liu, *Org. Lett*., 2012, **14**, 3978; (c) M. Thévenin, S. Thoret, P. Grellier, J. Dubois, *Bioorg. Med. Chem*., 2013, **21**, 4885; (d) R. H. Vekariya, J. Aubé, *Org. Lett*., 2016, **18**, 3534.

6 (a) W. Anthony, *J. Org. Chem*., 1960, **25**, 2049; (b) J. C. Powers, *J. Org. Chem*., 1965, **30**, 2534.

7 (a) Y. Ma, J. You, F. Song, *Chem. Eur. J.,* 2013, **19**, 1189; (b) M.-N. Zhao, L. Ran, M. Chen, Z.-H. Ren, Y.-Y. Wang, Z.-H. Guan, *ACS Catal*., 2015, **5**, 1210; (c) L. Gu, C. Jin, J. Liu, H. Zhang, M. Yuan, G. Li, *Green Chem*., 2016, **18**, 1201.

8 (a) M. Nakamura, L. Ilies, S. Otsubo, E. Nakamura, *Org. Lett*., 2006, **8**, 2803; (b) C.-H. Lin, C.-C. Chen, M.-J. Wu, *Chem. Eur. J.,* 2013, **19**, 2578; (c) A. Gogoi, S. Guin, S. K. Rout, B. K. Patel, *Org. Lett*., 2013, **15**, 1802; (d) P. Zhang, T. Xiao, S. Xiong, X. Dong, L. Zhou, *Org. Lett*., 2014, **16**, 3264; (e) M. Hu, R.-J. Song, J.-H. Li, *Angew. Chem., Int. Ed*., 2015, **54**, 608; (f) Q. Shi, P. Li, X. Zhu, L. Wang, *Green Chem*., 2016, **18**, 4916.

9 (a) N. Rodriguez, L. J. Goossen, *Chem. Soc. Rev*., 2011, **40**, 5030; (b) A. J. J. Straathof, *Chem. Rev*., 2014, **114**, 1871.

10 (a) Y. Yoshimi, T. Itou, M. Hatanaka, *Chem. Commun*., 2007, 5244; (b) T. Itou, Y. Yoshimi, K. Nishikawa, T. Morita, Y. Okada, N. Ichinose, M. Hatanaka, *Chem. Commun*., 2010, **46**, 6177; (c) K. Nishikawa, T. Ando, K. Maeda, T. Morita, Y. Yoshimi, *Org. Lett*., 2013, **15**, 636; (d) J. Xuan, Z.-G. Zhang, W.-J. Xiao, *Angew. Chem., Int. Ed.,* 2015, **54**, 15632; (e) H. Huang, K. Jia, Y. Chen, *ACS Catal.,* 2016, **6**, 4983.

11 (a) J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem., Int. Ed*., 2014, **53**, 502; (b) L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2014, **136**, 10886; (c) Q.-Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L.-Q. Lu, W.-J. Xiao, *Angew. Chem., Int. Ed.,* 2015, **54**, 11196; (d) H. Tan, H. Li, W. Ji, L. Wang, *Angew. Chem., Int. Ed.,* 2015, **54**, 8374; (e) C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature* 2016, **536**, 322; (f) W. Ji, H. Tan, M. Wang, P. Li, L. Wang, *Chem. Commun*., 2016, **52**, 1462; (g) S. J. McCarver, J. X. Qiao, J. Carpenter, R. M. Borzilleri, M. A. Poss, M. D. Eastgate, M. M. Miller, D. W. C. MacMillan, *Angew. Chem., Int. Ed.,* 2017, **56**,728.

12 (a) U. Wille, *Chem. Rev*., 2013, **113**, 813; (b) M. Rueda-Becerril, O. Mahe, M. Drouin, M. B. Majewski, J. G. West, M. O. Wolf, G. M. Sammis, J.-F. Paquin, *J. Am. Chem. Soc*., 2014, **136**, 2637; (c) S. Ventre, F. R. Petronijevic, D. W. C. MacMillan, *J. Am. Chem. Soc*., 2015, **137**, 5654; (d) Q.-B. Zhang, Y.-L. Ban, D.-G. Zhou, P.-P. Zhou, L.-Z. Wu, Q. Liu, *Org. Lett.,* 2016, **18**, 5256.

13 (a) T. Nobuta, S.-i. Hirashima, N. Tada, T. Miura, A. Itoh, *Org. Lett*., 2011, **13**, 2576; (b) H. Sun, C. Yang, F. Gao, Z. Li, W. Xia, *Org. Lett*., 2013, **15**, 624; (c) K. Wang, L.-G. Meng, Q. Zhang, L. Wang, *Green Chem*., 2016, **18**, 2864.

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Synthesis of Carbonylated Heteroaromatic Compounds via Visible-Light-Driven Intramolecular Decarboxylative Cyclization of o-Alkynylated Carboxylic Acids

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An efficient strategy for the easy access to carbonylated heteroaromatic compounds has been developed via a visible-light-promoted intramolecular decarboxylative cyclization reaction of o-alkynylated carboxylic acids.