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I_2-mediated aerobic oxidative annulation of amidines with tertiary amines via C-H amination/C-N cleavage for the synthesis of 2,4-disubstitued 1,3,5-triazines

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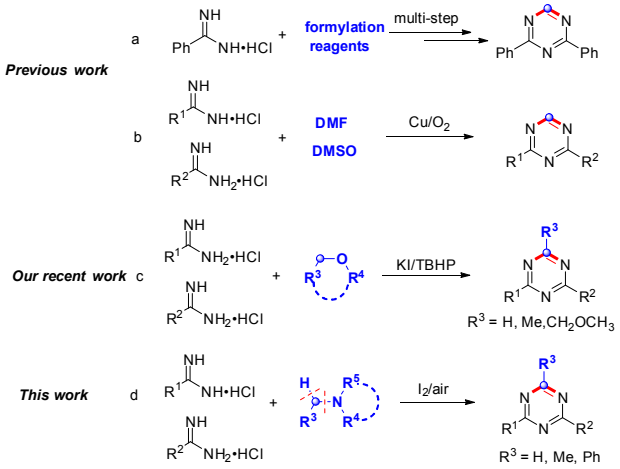
An iodine-mediated formal oxidative cycloaddition of amidines with tertiary amines was first demonstrated under air. Both symmetrical and unsymmetrical 2,4-disubstitued 1,3,5-triazines were obtained in up to 85% yields. It is noted that tertiary amine was employed as one carbon synthon of 1,3,5-triazines and two C-N bonds were formed in one pot. Control experiments revealed the reaction underwent a radical pathway promoted by I^+. The method is transition-metal-free, peroxide-free, and operationally simple to implement with a wide scope of substrates.

2,4-Disubstitued 1,3,5-triazines represent an important and valuable class of nitrogen-containing heterocycles in organic chemistry. Due to good biological activities, they have been already widely applied in medicinal chemistry.[1] Moreover, they were used as a nitrogen ligand in fields of organometallic materials and metal catalysis.[2] Over the past decades, 2,4-disubstitued 1,3,5-triazines were prepared via the direct formylation and condensation of amidines with various formylation reagents (Scheme 1a).[3] However, only symmetrical 2,4-disubstitued 1,3,5-triazines were obtained with narrow substrate scope and low yields under harsh conditions, which limited their further applications. Recently, copper-catalyzed oxidative cyclization of amidines with various carbon synthons has been developed for the synthesis of 2,4-disubstituted 1,3,5-triazines (Scheme 1b).[4] In these reactions, the *N*-methyl of *N,N*-dimethylformamide (DMF) or *S*-methyl group of dimethyl sulfoxide (DMSO) was employed as the carbon source of 1,3,5-triazine ring. Although the reaction yield was good and unsymmetrical products were first obtained, copper catalyst was still required for this transformation. More recently, our group has developed an iodide-catalyzed formal oxidative [3+2+1] cycloaddition of amidines with alkyl ethers, affording symmetrical and



Scheme 1 Strategies for the synthesis of 2,4-disubstituted 1,3,5-triazines

unsymmetrical 2,4-disubstitued 1,3,5-triazines in good yields (Scheme 1c).[5] In this reaction, alkyl ether was used as a novel carbon source. Although transition metal was avoided, the use of ether and *tert*-butyl hydroperoxide limited its industrial expansion production due to potential explosion hazard. Therefore, the development of a simple and environmentally friendly protocol for 2,4-disubstitued 1,3,5-triazines remains highly desirable.

On the other hand, tertiary amines have been developed as a useful carbon source via C-H activation/C–N bond cleavage in recent years. Many valuable compounds could be constructed from various types of nucleophiles and tertiary amines.[6] Recently, we[7] and others[5b,8] have realized the construction of various nitrogen-containing heterocycles via the reaction of nitrogen nucleophile with tertiary amines via C-H amination/C–N bond cleavage. Inspired by these significant findings and our research on metal-free synthesis of heterocycles[5,7,9], herein we report an iodine-mediated formal oxidative [3+2+1] cycloaddition for the synthesis of 2,4-disubstitued 1,3,5-triazines from amidines and tertiary amines under air (Scheme 1d). A series of symmetrical and

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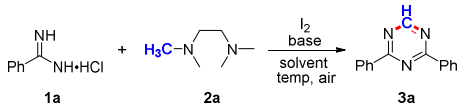
unsymmetrical 2,4-disubstitued 1,3,5-triazines were obtained in up to 85% yields with good functional group compatibility. The extra carbon atom of 1,3,5-triazine ring originated from tertiary amines via oxidative C(sp^3)–H amination and C(sp^3)–N cleavage. The reaction is involved in a domino C-H amination of tertiary amine with amidine, C-N cleavage, nucleophilic addition, condensation and aromatization process.

Table 1 Optimization of reaction conditions[a]

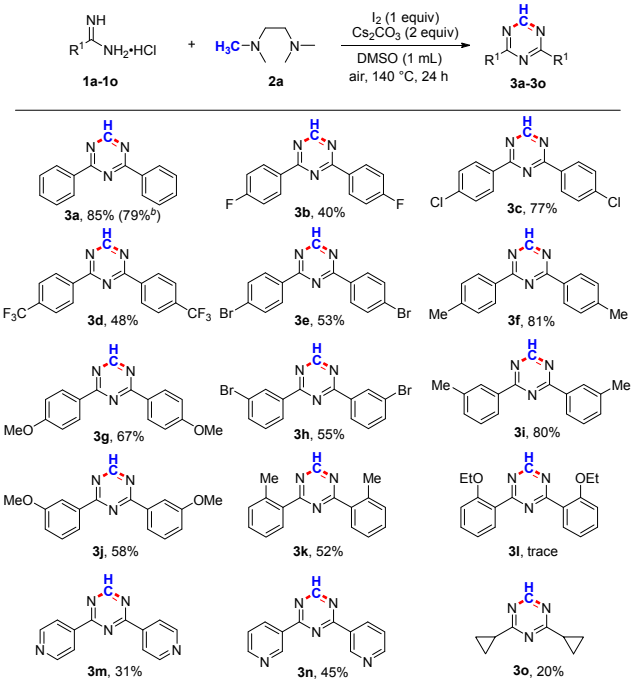


1a 2a 3a

Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1[c,d]	K_2CO_3	DMSO	120	30
2[c,e]	K_2CO_3	DMSO	120	24
3[c]	K_2CO_3	DMSO	120	40
4	K_2CO_3	DMSO	120	47
5	Na_2CO_3	DMSO	120	32
6	Cs_2CO_3	DMSO	120	59
7	*t*BuONa	DMSO	120	22
8	*t*BuOK	DMSO	120	trace
9	KOH	DMSO	120	trace
10	NaOH	DMSO	120	trace
11	K_3PO_4	DMSO	120	50
12	KOAc	DMSO	120	42
13		DMSO	120	n.d.
14	Cs_2CO_3	DMSO	120	25[f], 30[g],44[h], 49[i]
15	Cs_2CO_3	DMF	120	39
16	Cs_2CO_3	NMP	120	35
17	Cs_2CO_3	H_2O	120	trace
18	Cs_2CO_3	DMSO	130	79
19	**Cs_2CO_3**	**DMSO**	**140**	**85**
20[j]	Cs_2CO_3	DMSO	140	n.d.

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1 equiv), I_2 (1 equiv), base (2 equiv), solvent (1 mL), air, 24 h. [b] Isolated yield. [c] 12 h. [d] 20 mol % of I_2 and 2 equiv of TBHP. [e] 20 mol % of I_2. [f] 1 equiv of Cs_2CO_3. [g] 1.5 equiv of Cs_2CO_3. [h] 2.5 equiv of Cs_2CO_3. [i] 3 equiv of Cs_2CO_3. [j] no **2a** used.

Initially, we began our study with the reaction of 1 equiv of benzamidine hydrochloride (**1a**), 1 equiv of *N,N,N',N'*-tetramethylethylenediamine (TMEDA, **2a**), 20 mol % of iodine as the catalyst, 2 equiv of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) as the oxidant, and 2 equiv of K_2CO_3 as th base. When the reaction mixture was heated in DMSO at 120 °C for 12 h, 2,4-diphenyl-1,3,5-triazine (**3a**) was obtained in 30% yield (Table 1, entry 1). In the absence of TBHP, **3a** was also obtained in 24% yield, which indicated that peroxidant was not essential to this reaction (Table 1, entry 2). The yield of this reaction was obviously improved by increasing amount of iodine to 1 equiv (Table 1, entry 3). Prolonging reaction time also resulted in an increase of yield from 40% to 47% (Table 1, entry 4). Among the examination of various bases, such as Na_2CO_3, Cs_2CO_3, *t*BuONa, *t*BuOK, NaOH, KOH, K_3PO_4, and KOAc, Cs_2CO_3, afforded **3a** in a highest 59% yield (Table 1, entries 5-12). No **3a** was detected without any base (Table 1, entry 13). Increasing or decreasing the amount of Cs_2CO_3 was inefficient to the reaction yield (Table 1, entries 14). The variation of reaction solvents, such DMF, NMP and even H_2O, didn't improve the reaction yield (Table 1, entries 15-17). The effect of temperature on the reaction was also investigated. Notably, the desired product **3a** was obtained in good 79% yield at 130 °C (Table 1, entry 18). When the reaction temperature was further increased from 130 °C to 140 °C, 85% yield of **3a** was obtained. **3a** was not detected in the absence of **2a**, which proved that only **2a** provided one carbon synthon in this reaction (Table 1, entry 20). Therefore, the optimal conditions were established as described in entry 19.



Scheme 2 Homocoupling oxidative annulation of amidines[a]

[a] Reaction conditions: **1** (0.4 mmol), **2a** (1 equiv), I_2 (1 equiv), Cs_2CO_3 (2 equiv), DMSO (1 mL), air, 140 °C, 24 h; Isolated yield. [b] 10 mmol scale.

Under the optimal reaction conditions, the generality of this synthetic protocol for various amidines **1** was investigated (Scheme 2). Firstly, aryl amidines (**1a-1k**) bearing electron-donating or electron-deficient groups on the phenyl ring could be employed in this reaction, giving the desired and symmetrical 2,4-diaryl-1,3,5-triazines (**3a-3k**) in moderate to good yields. Notably, aryl amidines bearing electron-donating groups (Me and OMe) gave higher yields than that bearing electron-deficient ones (F, Br, and CF_3). Moreover, *ortho*-substituted aryl amidines (**1k** and **1l**) gave a lower yield compared to *para*-subsititued ones (**1f** and **1g**) due to steric hindrance. In addition, heterocyclic amidines were also tolerated in this reaction. **1n** gave the desired product 2,4-di(pyridin-3-yl)-1,3,5-triazine in higher yield than **1m** because of electronic effect. It is noteworthy that C-X bond on the phenyl ring and C–H bond of 1,3,5-triazine ring in products **3** provide the potential for further derivatizations.

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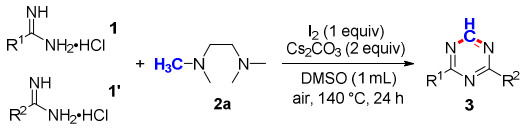
Table 2 Cross-coupling oxidative annulation of amidines[a]

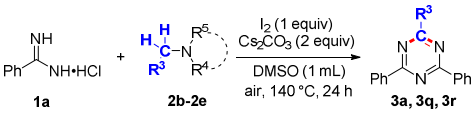


Entry	R^1 (**1**)	R^2 (**1'**)	Product (Yield, %)[b]	
			Unsymmetric	Symmetric
1	4-OMe-Ph (**1g**)	Ph (**1a**)	**3ga** (23)	**3a** (33)
2	4-OMe-Ph (**1g**)	4-Cl-Ph (**1c**)	**3gc** (16)	**3c** (35)
3	4-OMe-Ph (**1g**)	4-Me-Ph (**1f**)	**3gf** (22)	**3f** (25)
4	3-OMe-Ph (**1j**)	Ph (**1a**)	**3ja** (16)	**3a** (28)
5	4-NO_2-Ph (**1p**)	Ph (**1a**)	**3pa** (27)	**3a** (27)
6	cyclopropyl (**1o**)	Ph (**1a**)	**3oa** (14)	**3a** (15)

[a] Reaction conditions: **1** (0.2 mmol), **1'** (0.8 mmol), **2a** (1 equiv), I_2 (1 equiv), Cs_2CO_3 (2 equiv), DMSO (1 mL), air, 140 °C, 24 h. [b] Isolated yield.

Subsequently, the cross-coupling reactions by employing two different aryl amidines were performed (Table 2). Expectedly, the desired unsymmetrical 2,4-disubstituted-1,3,5-triazines were obtained with two homocoupling products generated at the same time. Initially, the reaction of 4-methoxybenzamidine (**1g**) and benzamidine (**1a**) in equimolar ratio could afford two homocoupling products (**3g** and **3a**) and a cross-coupling product **3ga**. To improve the yield of **3ga**, the molar ratio of **1g** to **1a** was changed into 1:4. To our delight, **3ga** and **3a** were obtained in 23% and 33% yield, respectively. Meanwhile, the other homocoupling product **3g** was not detected (Table 2, entry 1). Similarly, when **1a** was replaced with **1c** or **1d**, the unsymmetrical products **3gc** or **3gf** could be obtained in 16% and 22% yields, respectively (Table 2, entries 2 and 3). In addition, the reaction of **1j**, **1p** and **1o** with **1a** also gave the unsymmetrical products **3ja**, **3pa** and **3oa** in 14-27% yields (Table 2, entries 4-6).

Table 3 Substrate scope of amines [a]



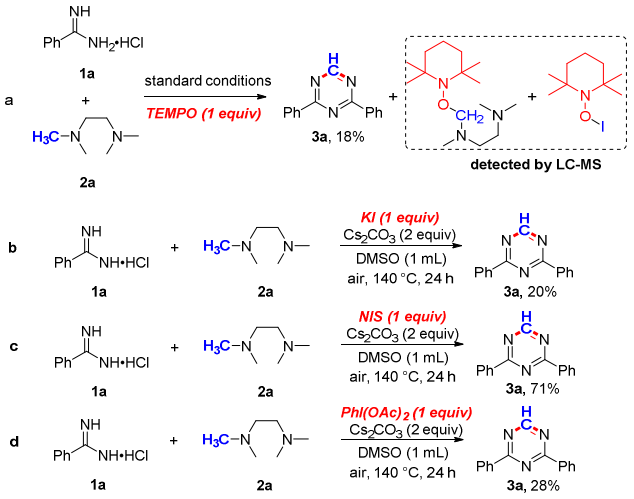
Entry	Amine		Product	Yield (%)[b]
1		**2b**	**3a**	43
2		**2c**	**3a**	40
3		**2d**	**3a**	43
4		**2e**	R^3 = Me, **3p**	15
5		**2f**	**3a** R^3 = Ph, **3q**	28 40

[a] Reaction conditions: **1a** (0.4 mmol), **2** (1 equiv), I_2 (1 equiv), Cs_2CO_3 (2 equiv), DMSO (1 mL), air, 140 °C, 24 h. [b] Isolated yield.

Then the substrate scope of amines **2** was also examined under the optimal reaction conditions (Table 3). When various amines bearing *N*-methyl group, such as *N,N'*-dimethylethylenediamine (**2b**), *N*-methylpiperidine (**2c**), and *N*-methylmorpholine (**2d**) were employed, the corresponding product **3a** were obtained in 40-43% yields (Table 3, entries 1-3). In spite of low yield, the reaction of **1a** with triethylamine (**2e**) could give the desired product 2-methyl-4,6-diphenyl-1,3,5-triazine (Table 3, entry 4). In addition, *N,N*-dimethylbenzylamine, which have two types of $C(sp^3)$-H bonds adjacent to the nitrogen atom, afforded **3a** and 2,4,6-triphenyl-1,3,5-triazine (**3q**) in 28% and 40% yields, respectively. Notably, the reaction with secondary C-H bond gave the corresponding product in higher yield than primary C-H bond. This is probably because secondary C-H bond has lower bond dissociation energy (BDE) than primary C-H bond (Table 3, entry 5).

To gain an insight into the mechanism, several control experiments were carried out (Scheme 3). First, only 18% yield of **3a** was obtained in the presence of one equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical inhibitor. This obvious inhibiting effect indicated that this reaction might undergo a radical pathway (Scheme 3a). Fortunately, trace amount of *N,N,N'*-trimethyl-*N'*-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)ethane-1,2-diamine and 2,2,6,6-tetramethylpiperidin-1-yl hypoiodite as radical trapping products were detected by LC-MS. This implied that a carbon radical and an iodine radical were generated in situ, respectively. In addition, iodine effect was also investigated by using various iodine reagents, such as KI, NIS, and $PhI(OAc)_2$. Among three reactions, NIS gave **3a** in a highest 71% yield. This result indicated that I^+ might be an active catalyst and I_2/I^+ redox process played an important role in the reaction.

On the basis of the results above and previous reports[9,10], a plausible mechanism was proposed (Scheme 4). Initially, TMEDA gave a carbon radical **A** via an oxidative C-H cleavage



Scheme 3 Control experiments for mechanistic studies

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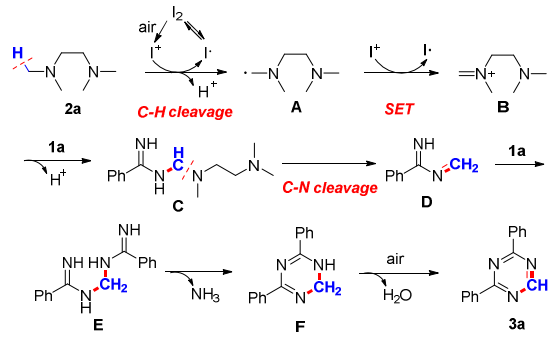

Scheme 4 A plausible mechanism

promoted by I^+, which was generated in situ from molecular iodine under air.[11] Then the radical **A** was further changed into an imine cation **B** via a single-electron-transfer (SET) process in the presence of I^+. Subsequently, the nucleophilic addition of **1a** to **B** provided an intermediate **C**. A sequential C-N cleavage of **C** could generated an imine **D** and a nucleophilic addition of **1a** to **D** provided an intermediate **E**. Then **E** could be transformed to **F** by removing ammonia. Finally, an oxidative aromatization of **F** could produce **3a** under air.

In summary, we have developed an iodine-mediated oxidative annulation of amidines and tertiary amines, affording a variety of symmetrical and unsymmetrical 2,4-disubstitued 1,3,5-triazines. Tertiary amine was employed as one carbon synthon via C–H/C–N cleavage. Compared to previous reports, this novel protocol is distinguished by (1) transition-metal-free, (2) operational simplicity, (3) peroxide-free, (4) good functional groups tolerance. The synthesis of other nitrogen-containing heterocycles using tertiary amines as the carbon source is ongoing in our laboratory.

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Notes and references

1 (*a*) R. Kaminsky and R. Brun, *Antimicrob. Agents Chemother.*, 1998, **42**, 2858; (*b*) C. J. Bacchi, M. Vargas, D. Rattendi, B. Goldberg and W. Zhou, *Antimicrob. Agents Chemother.*, 1998, **42**, 2718; (*c*) Y. Iino, T. Karakida, N. Sugamata, T. Andoh, H. Takei, M. Takahashi, S. Yaguchi, T. Matsuno, M. Takehara, M. Sakato, S. Kawashima and Y. Morishita, *Anticancer Res.*, 1998, **18**, 171; (*d*) T. Irikura, Y. Abe, K. Okamura, K. Higo, A. Maeda, F. Morinaga, G. Shirai and S. Hatae, *J. Med. Chem.*, 1970, **13**, 1081; (*e*) A. Suda, K. Kawasaki, S. Komiyama, Y. Isshiki, D.- O. Yoon, S. J. Kim, Y.-J. Na, K. Hasegawa, T. A. Fukami and S. Sato, *Bioorg. Med. Chem.*, 2014, **22**, 892; (*f*) B. Klenke, M. Stewart, M. P. Barrett, R. Brun and I. H. Gilbert, *J. Med. Chem.*, 2001, **44**, 3440; (*g*) A. R. Katritzky, D. C. Oniciu, I. Ghiviriga and R. A. Barcock, *J. Chem. Soc. Perkin Trans. 2*, 1995, **0**, 785; (*h*) B. R. Baker and B.-T. Ho, *J. Heterocycl. Chem.*, 1965, **2**, 340.

2 (*a*) S. Naik, M. Kumaravel, J. T. Mague and M. S. Balakrishna, *Inorg. Chem.,* 2014, **53**, 1370; (*b*) C.-Y. Xiao, Y.-M. Li, H.-J. Lun, C.-Y. Cui and Y.-Q. Xu, *J. Solid State Chem.*, 2013, **208**, 127; (*c*) M. Hernandez-Juarez, M. Vaquero, E. Alvarez, V. Salazar and A. Suarez, *Dalton Trans.*, 2013, **42**, 351; (*d*) P. K. Santra and P. Sagar, *J. Mol. Catal. A: Chem.*, 2003, **197**, 37.

3 (*a*) H. Gold, *Angew. Chem.*, 1960, **72**, 72956; (*b*) H. Bredereck, F. Effenberger and A. Hofmann, *Chem. Ber.*, 1963, **96**, 3265; *(c)* K. R. Huffman and F. C. Schaefer, *J. Org. Chem.*, 1963, **28**, 1812; (*d*) P. Wessig and J. Schwarz, *Monatsh. Chem.*, 1995, **126**, 99; (*e*) T. P. Popovich and B. S. Drach, *Zh. Org. Khim.*, 1987, **23**, 2443; (*f*) A. Diaz-Ortiz, A. De La Hoz, A. Moreno, A. Sanchez-Migallon and G. Valiente, *Green Chem.*, 2002, **4**, 339; (*g*) S. Biswas and S. Batra, *Eur. J. Org. Chem.*, 2012, **18**, 3492.

4 (*a*) X. Xu, M. Zhang, H. Jiang, J. Zheng and Y. Li, *Org. Lett.*, 2014, **16**, 3540; (*b*) H. Huang, W. Guo, W. Wu, C.-J. Li and H. Jiang, *Org. Lett.*, 2015, **17**, 2894; (*c*) Q. You, F. Wang, C. Wu, T. Shi, D. Min, H. Chen and W. Zhang, *Org. Biomol. Chem.*, 2015, **13**, 6723.

5 Y. Yan, Z. Li, H. Li, C. Cui, M. Shi and Y. Liu, *Org. Lett.*, 2017, **19**, 6228.

6 (*a*) H. Li, Z. He, X. Guo, W. J. Li, X. H. Zhao and Z. Li, *Org. Lett.*, 2009, **11**, 4176; (*b*) K. Ramachandiran, D. Muralidharan and P. T. Perumal, *Tetrahedron Lett.*, 2011, **52**, 3579; (*c*) Y. Liu, B. Yao, C. Deng, R. Tang, X. Zhang and J. Li, *Org. Lett.*, 2011, **13**, 2184; (*d*) L. Zhang, C. Peng, D. Zhao, Y. Wang, H. Fu, Q. Shen and J. Li, *Chem. Commun.*, 2012, **48**, 5928; (*e*) J. Chen, B. Liu, D. Liu, S. Liu and J. Cheng, *Adv. Synth. Catal.*, 2012, **354**, 2438; (*f*) L. Li, H. Li, L. Xing, L. Wen, P. Wang and B. Wang, *Org. Biomol. Chem.*, 2012, **10**, 9519; (g) X. Li, X. Gu, Y. Li and P. Li, *ACS Catal.*, 2014, **4**, 1897; (*h*) B. Liu, J. Wang, B. Zhang, Y. Sun, L. Wang, J. Chen and J. Cheng, *Chem. Commun.*, 2014, **50**, 2315.

7 Y. Yan, Y. Xu, B. Niu, H. Xie and Y. Liu, *J. Org. Chem.*, 2015, **80**, 5581.

8 (*a*) Y. Lv, Y. Li, T. Xiong, W. Pu, H. Zhang, K. Sun, Q. Liu and Q. Zhang, *Chem. Commun.*, 2013, **49**, 6439; (*b*) X. Chen, T. Chen, Y. Zhou, D. Han, L. Han and S. Yin, *Org. Biomol. Chem.*, 2014, **12**. 3802.

9 (*a*) Y. Yan, B. Niu, K. Xu, J. Yu, H. Zhi and Y. Liu, *Adv. Synth. Catal.*, 2016, **358**, 212; (*b*) Y. Yan, H. Li, B. Niu, C. Zhu, T. Chen and Y. Liu, *Tetrahedron Lett.*, 2016, **57**, 4170; (*c*) Y. Yan, Y. Zhang, Z. Zha and Z. Wang, *Org. Lett.*, 2013, **15**, 2274; (*d*) Y. Yan, Y. Zhang, C. Feng, Z. Zha and Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8077; (*e*) Y. Yan and Z. Wang, *Chem. Commun.*, 2011, **47**, 9513.

10 For oxidative C-H functionalization of tertiary amine, see: (*a*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*b*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*c*) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev.*, 2011, **111**, 1293; (*d*) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464; (*e*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74.

11 For recent examples of iodine catalysis, see: (*a*) Y. Takeda, R. Kajihara, N. Kobayashi, K. Noguchi and A. Saito, *Org. Lett.*, 2017, **19**, 6744; (*b*) H. Wang, W. Xu, L. Xin, W. Liu, Z. Wang and K. Xu, *J. Org. Chem.*, 2016, **81**, 3681; (*c*) T. Aggarwal, S. Kumar and A. K. Verma, *Org. Biomol. Chem.*, 2016, **14**, 7639.

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Table of Conetents Entry

I_2-mediated aerobic oxidative annulation of amidines with tertiary amines via C-H amination/C-N cleavage for the synthesis of 2,4-disubstitued 1,3,5-triazines

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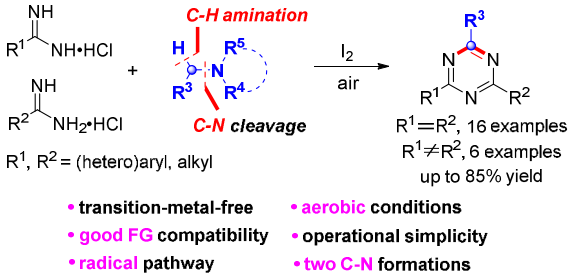

An iodine-mediated aerobic oxidative cycloaddition of amidines with tertiary amines was first demonstrated, affording symmetrical and unsymmetrical 2,4-disubstitued 1,3,5-triazines.