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Synthesis of 2-arylbenzofuran-3-carbaldehydes *via* an organocatalytic [3+2] annulation/oxidative aromatization reaction

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A novel organocatalytic [3+2] annulation/oxidative aromatization reaction of enals with 2-halophenols or β-naphthols is reported. This process enables chemo- and regioselective access to 2-arylbenzofuran-3-carbaldehydes without the use of transition metals or strong oxidants. Preliminary mechanistic studies reveal that an unprecedented orgaocatalytic direct α-arylation pathway is involved.

Benzofurans, particularly 2,3-disubstituted benzofurans, are privileged scaffolds found in a wide range of natural products[1] and pharmaceuticals.[2] In contrast to classical two-step synthetic routes, employing internal alkynes or alkenes as substrates offers an ideal approach to construct such skeletons, whereby the introduction of two pre-installed functional groups onto benzofuran cores is achieved in a single step. In this context, prominent strategies include: (i) base-mediated nucleophilic addition followed by the intramolecular Heck coupling of 2-halophenols with activated alkynes,[3] (ii) transition-metal-catalyzed oxidative annulation of phenols with symmetrical alkynes,[4] and (iii) Pd-catalyzed decarboxylative cyclization of phenols and alkenylcarboxylic acids.[5] However, these methods generally yield poor site-selectivity and still require the use of transition-metal catalysts or strong oxidants. Therefore, the development of a selective and transition-metal-free method for the synthesis of 2,3-disubstituted benzofurans is highly desirable.

Over the past two decades, organocatalytic annulations of arenes with α,β-unsaturated aldehydes have become powerful tools for the construction of diverse heterocycles.[6] However, the use of aryl halides as substrates to undergo organocatalyitc annulations with α,β-unsaturated aldehydes, in which the C–C bond form at the challenging *ipso*-positions (C–X), is still very limited. Recent advances in organocatalytic direct C–H arylation (cross-coupling) reactions have provided elegant approaches to achieve C–C bond formation.[7] In 2007, Wang *et al.* disclosed the first organocatalytic α-arylation of enals with *para*-halophenols via a Michael-type Friedel–Crafts reaction/cyclopropanation/ring-opening cascade.[8] We recently questioned whether this strategy could be extended to sterically hindered 2-halophenols, thereby giving the corresponding α-arylation intermediates that might undergo the chemoselective (C=C versus C=O) intramolecular cyclization and aromatization to afford 2,3-disubstituted benzofurans (Scheme 1b).

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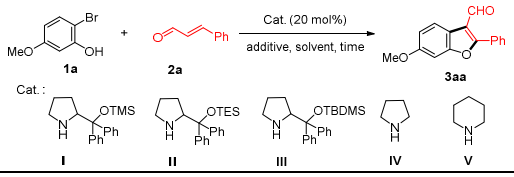
the difficulty of forming sterically more crowded halogen-substituted quaternary carbon centers. Six-membered lactol derivatives were often preferentially generated as the undesired side-products by an *ortho*-selective (C−H) Friedel−Crafts alkylation and hemiacetalization sequence.[9] Second, intramolecular C−O cyclization/aromatization reactions are generally performed under harsh oxidative conditions (e.g., DDQ,[10] *m*-CPBA,[11] TBHP[12]), which may promote the overoxidation of aldehyde moieties to carboxylic acids. We addressed these issues, and herein disclose the first chemo- and regioselective synthesis of 2,3-disubstituted benzofurans *via* an organocatalytic [3+2] annulation/oxidative aromatization reaction. Key to the success of this chemistry is a novel α-arylation of enals with sterically encumbered 2-halophenols, which is, to the best of our knowledge, the first example of this kind. The transition-metal-free reaction proceeds under mild conditions and uses atmospheric oxygen as an oxidant. Moreover, this step-economical cascade gives products bearing a formyl group at the C3 position, allowing for further elaboration to various natural products[1a,1c,1d] and pharmaceuticals[2] (Scheme 1c), whereas it was typically introduced by the Vilsmeier-Haack reaction using large excesses of environmentally unfriendly $POCl_3$ and DMF.[13]

Table 1 Optimization of reaction conditions[a]

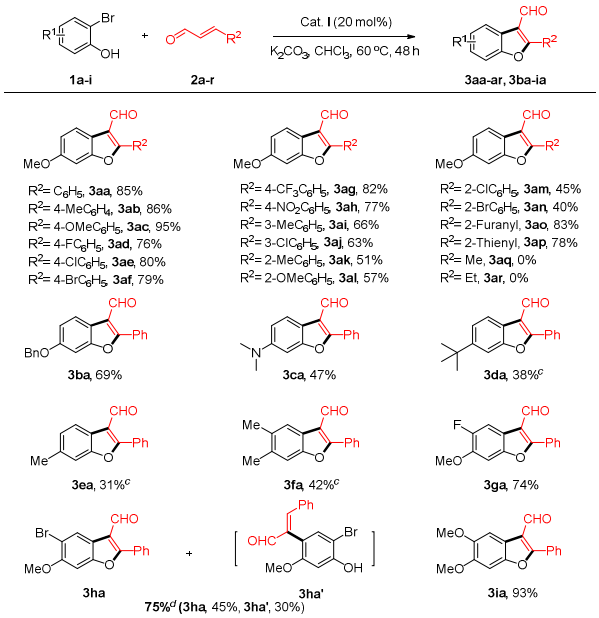


Entry	Catalyst	Solvent	Additive	Time (days)	Yield[b] (%)
1	**I**	$CHCl_3$	Na_2CO_3	5	20
2	**I**	$CHCl_3$	K_2CO_3	5	35
3	**I**	$CHCl_3$	Cs_2CO_3	5	n.r.
4	**I**	$CHCl_3$	NaOAc	5	30
5	**I**	$CHCl_3$	DABCO	5	25
6	**I**	CH_3CN	K_2CO_3	5	16
7	**I**	THF	K_2CO_3	5	trace
8	**II**	$CHCl_3$	K_2CO_3	5	29
9	**III**	$CHCl_3$	K_2CO_3	5	25
10	**IV**	$CHCl_3$	K_2CO_3	5	<10
11	**V**	$CHCl_3$	K_2CO_3	5	trace
12[c]	**I**	$CHCl_3$	K_2CO_3	2	51
13[d]	**I**	$CHCl_3$	K_2CO_3	2	85[e]
14[f]	**I**	$CHCl_3$	K_2CO_3	2	<10
15[g]	**I**	$CHCl_3$	K_2CO_3	2	23
16[h]	**I**	$CHCl_3$	K_2CO_3	2	17
17[d,i]	**I**	$CHCl_3$	K_2CO_3	2	38

[a]Reaction conditions: a mixture of **1a** (2.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), additive (5.0 equiv.) and catalyst (20 mol%) in solvent (2.0 mL) was stirred at 60 °C. [b]Determined by ^{1}H NMR analysis using dibromomethane as an internal standard. [c]4 equiv. of **1a**. [d]6 equiv. of **1a**. [e]isolated yield. [f]Slow addition of **2a** over 7 h. [g]Slow addition of **2a** over 14 h. [h]Slow addition of **2a** over 21 h. [i]2-iodo-5-methoxypheol was used instead of **1a**. DABCO = 1,4-diazabicyclo[2.2.2]octane.

We first studied the reaction of 2-bromophenol (0.2 mmol) with *trans*-cinnamaldehyde (0.1 mmol) using diphenylprolinol trimethylsilyl ether (Cat. **I**, 20 mol%) as the catalyst, Na_2CO_3 (0.5 mmol) as the additive and $CHCl_3$ (2.0 mL) as the solvent at 60 °C for 7 days. However, neither the desired molecule nor the competitive reaction byproduct (often formed in the presence of acid co-catalysts[9,14]) was observed under these conditions. Considering 2-bromophenol was not nucleophilic enough to initiate the *ipso*-selective (C−Br) Michael-type Friedel-Crafts reaction, electron-rich 2-bromo-5-methyoxyphenol was chosen as a Michael donor. Gratifyingly, the demanding energy barrier was overcome by the increased electron density to afford the desired product **3aa**, albeit in only 20% yield (Table 1, entry 1). Screening of additives revealed K_2CO_3 to be optimal (entry 2). Although variation of solvents and catalysts did not enhance the efficiency (entries 6-11, for more details see ESI†), further investigations revealed that increasing the amount of **1a** could improve the reaction yields (entries 12 and 13). Inspired by these results, slow addition of **2a** was employed. However, it didn't lead to desirable results (entries 14-16). Other potential leaving groups were also evaluated while giving lower yields (entry 17, for more details see ESI†).

Table 2 [3+2] Annulations of enals with 2-bromophenols[a,b]



[a]Reactions conditions: a mixture of **1** (6.0 equiv.), **2** (0.1 mmol, 1.0 equiv.), K_2CO_3 (5.0 equiv.) and catalyst **I** (20 mol%) in $CHCl_3$ (2.0 mL) was stirred at 60 °C. [b]Isolated yields. [c]Performed for 7 days. [d]Performed on a 0.2 mmol scale.

With the optimized conditions in hand, the scope of enals was further explored. Enals bearing substituents with different electronic properties at the *para* or *meta*-position of the phenyl ring were converted to the corresponding products in moderate to excellent yields (Table 2, **3aa-3aj**), while introducing functional groups at the *ortho*-position of the phenyl ring led to lower yields probably due to the steric

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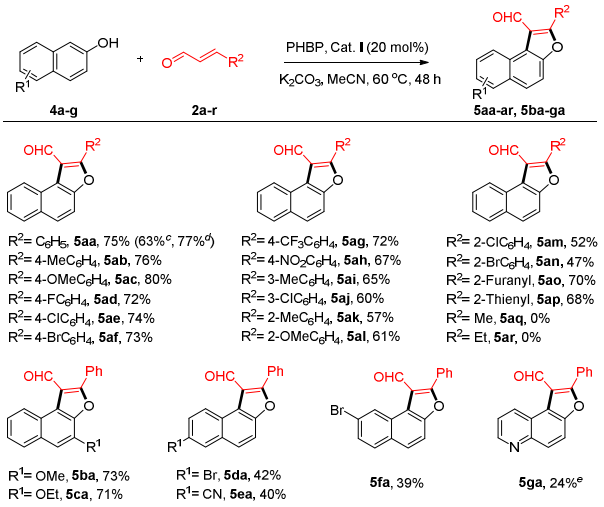
hindrance (**3ak-3an**). Heteroaryl enals were also amenable to this reaction and the target products were isolated in 83% and 78% yields, respectively (**3ao** and **3ap**). However, aliphatic enals didn't react to give the desired products.

A series of 2-bromophenols were also tested. Substrates with strong electron-donating groups (e.g., methoxyl, benzyloxy) were well-tolerated to produce the 3-formylbenzofurans in good yields (**3ia** and **3ba**). On the other hand, moderate electron-donating groups, such as methyl and *tert*-butyl, were also viable substrates (**3ea**, **3fa** and **3da**). Gratifyingly, incorporation of an amino group on the phenol moiety did not interfere with the reaction and afforded **3ca** in 47% yield, while it proved ineffectual in the previously reported oxidative annulation method.[4c] When 2,4-dibrominated substituent **1h** was employed in this reaction, target product **3ha** was provided in 45% yield along with a *para*-cross-coupling product **3ha'** in 30% yield. Unfortunately, *meta*-chloro and *para*-methoxyl substituted phenol derivatives failed to give the target products (see ESI†), suggesting that electron-donating groups at C5 position of phenols were essential to increase the electron density for the electrophilic aromatic substitution step.

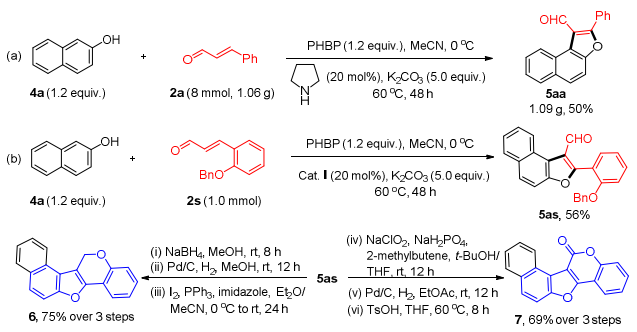
Table 3 [3+2] Annulations of enals with β-naphthols[a,b]



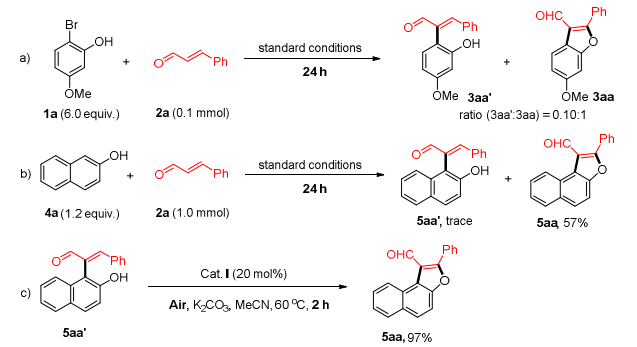
[a]Reaction conditions: 0 °C, to a solution of **4** (1.2 equiv.) was added PHBP (1.2 equiv.), followed by addition of **2** (1.0 mmol, 1.0 equiv.), Cat. **I** (20 mol%) and K_2CO_3 (5.0 equiv.), then the reaction was stirred at 60 °C for 48 h. [b]isolated yields. [c]Using pyrrolidine (20 mol%) as the catalyst. [d]cis-cinnamaldehyde was used. [e]Performed on a 2 mmol scale.

Note that our previous study demonstrated the selective bromination of β-naphthol in the presence of pyridine hydrobromide perbromide (PHBP),[8b] we thus began to develop a one-pot strategy for the preparation of 2,3-disubstituted naphthofurans using simple β-naphthols as substrates. We found that *in situ* generated 1-bromo-2-naphthols showed higher reactivity than 2-bromophenols, as only a slight excess of β-naphthols (1.2 equiv.) was required for this transformation (Table 3). Various enals were transformed to the desired products in moderate to good yields (**5aa-5ap**). To our delight, *cis*-cinnamaldehyde could also be applied to generate **5aa** without a compromising yield, indicating the *E*/*Z* stereoisomeric of enals did not affect the reaction efficiency. Naphthols bearing alkoxyl group were applicable to the reaction and gave the intended products **5ba-5ca** in 71-73% yields. In contrast, substrates with electron-deficient substituents on the naphthyl ring afforded the products **5da-5ga** in relatively lower yield. The structure of **5ac** was unambiguously confirmed by X-ray crystallography (see ESI†).

To highlight the practicability of this method, a gram-scale reaction of **4a** with **2a** was performed. As illustrated in Scheme 2a, the reaction was easily scalable and **5aa** was isolated in 50% yield even with pyrrolidine as the catalyst. Moreover, benzofurans bearing a formyl group at the C3 position could serve as versatile building blocks for isoflavonoid-derived natural products syntheses,[15] as exemplified by the concise synthesis of pterocarpene derivative **6** and coumestan derivative **7** in moderate yields (Scheme 2b).



Scheme 2 Gram-scale reaction and further transformations



Scheme 3 Control experiments

To gain mechanistic insight into this reaction, several control experiments were conducted. We succeeded in isolating the putative intermediates **3aa'** and **5aa'** (Scheme 3).[16] As expected, isolated intermediate **5aa'** could be converted to **5aa** in a quantitative yield under the standard conditions. These evidences strongly support the proposed pathway in Scheme 1b, and also represent the first example of organocatalytic α-arylation of enals using sterically congested 2-bromophenols as coupling partners. Thus, a plausible mechanism is depicted in Scheme 4. The Michael-type

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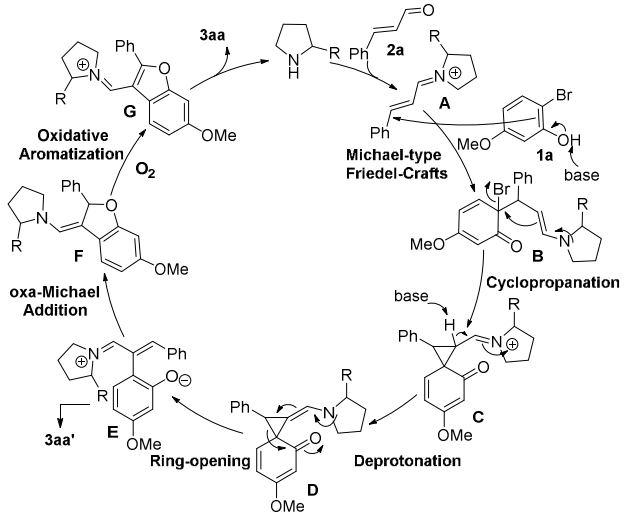
Friedel–Crafts reaction of **1a** with iminium ion **A** selectively occurs at the C2 position (C–Br) to generate the Michael adduct **B**, which then undergoes an intramolecular cyclopropanation[17] to give **C**. Deprotonation of **C** with subsequent ring-opening reaction affords the zwitterionic species **E**.[8a,17c] The α-arylation intermediate **3aa'** can be obtained through hydrolysis of **E**. Alternatively, **E** participates in intramolecular oxa-Michael addition followed by air oxidation of enamine[18] to produce **G**. Finally, product **3aa** is formed after hydrolysis and regenerates the amine catalyst for the next catalytic cycle.



Scheme 4 Proposed mechanism

In summary, we have reported a transition-metal-free method for the synthesis of 2-arylbenzofuran-3-carbaldehydes based on an organocatalytic [3+2] annulation/oxidative aromatization reaction of enals with 2-halophenols or β-naphthols. The reaction proceeds under mild conditions and uses air as the terminal oxidant. Mechanistic investigations provide evidence for a novel organocatalytic direct α-arylation event. Further mechanistic studies as well as other applications of this method are in progress.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) Z. Yang, P. M. Hon, K. Y. Chui, Z. L. Xu, H. M. Chang, C. M. Lee, Y. X. Cui, H. N. C. Wong, C. D. Poon and B. M. Fung, *Tetrahedron Lett.*, 1991, **32**, 2061; (b) Y. Fukuyama, M. Nakahara, H. Minami and M. Kodama, *Chem. Pharm. Bull.*, 1996, **44**, 1418; (c) W. Wang, Y. Y. Zhao, H. Liang, Q. Jia and H. B. Chen, *J. Nat. Prod.*, 2006, **69**, 876; (d) A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.*, 2013, **113**, 1614; (e) V. A. Tuskaev, *Pharm. Chem. J.*, 2013, **47**, 1.

2 R. J. Nevagi, S. N. Dighe and S. N. Dighe, *Eur. J. Med. Chem.*, 2015, **97**, 561.

3 (a) R. C. Larock, E. K. Yum, M. J. Doty and K. K. C. Sham, *J. Org. Chem.*, 1995, **60**, 3270; (b) T. Konno, J. Chae, T. Ishihara and H. Yamanaka, *Tetrahedron*, 2004, **60**, 11695; (c) H. Yuan, K.-J. Bi, B. Li, R.-C. Yue, J. Ye, Y.-H. Shen, L. Shan, H.-Z. Jin, Q.-Y. Sun and W.-D. Zhang, *Org. Lett.*, 2013, **15**, 4742.

4 (a) M. R. Kuram, M. Bhanuchandra and A. K. Sahoo, *Angew. Chem. Int. Ed.*, 2013, **52**, 4607; (b) W. Zeng, W. Wu, H. Jiang, L. Huang, Y. Sun, Z. Chen and X. Li, *Chem. Commun.*, 2013, **49**, 6611; (c) R. Zhu, J. Wei and Z. Shi, *Chem. Sci.*, 2013, **4**, 3706.

5 (a) S. Agasti, S. Maity, K. J. Szabo and D. Maiti, *Adv. Synth. Catal.*, 2015, **357**, 2331; (b) S. Agasti, A. Dey and D. Maiti, *Chem. Commun.*, 2017, **53**, 6544.

6 (a) Ł. Albrecht, L. K. Ransborg, V. Lauridsen, M. Overgaard, T. Zweifel and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 12496; (b) Ł. Albrecht, L. K. Ransborg, A. Albrecht, L. Lykke and K. A. Jørgensen, *Chem. Eur. J.*, 2011, **17**, 13240; (c) C. Wang, X. Yang, G. Raabe and D. Enders, *Adv. Synth. Catal.*, 2012, **354**, 2629; (d) Ł. Albrecht, L. K. Ransborg and K. A. Jørgensen, *Catalysis Science & Technology*, 2012, **2**, 1089; (e) J. Izquierdo, A. Orue and K. A. Scheidt, *J. Am. Chem. Soc.*, 2013, **135**, 10634; (f) P. H. Poulsen, K. S. Feu, B. M. Paz, F. Jensen and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2015, **54**, 8203; (g) G.-T. Li, Q. Gu and S.-L. You, *Chem. Sci.*, 2015, **6**, 4273; (h) G.-T. Li, Z.-K. Li, Q. Gu and S.-L. You, *Org. Lett.*, 2017, **19**, 1318.

7 (a) S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673; (b) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nature Chem.*, 2010, **2**, 1044; (c) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737; (d) C.-L. Sun, Y.-F. Gu, B. Wang and Z.-J. Shi, *Chem. Eur. J.*, 2011, **17**, 10844; (e) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, **114**, 9219.

8 (a) X. Song, A. Song, F. Zhang, H.-X. Li and W. Wang, *Nat. Commun.*, 2011, **2**, 524; (b) Y. Hu, Y. Ma, R. Sun, X. Yu, H. Xie and W. Wang, *Chem. Asian J.*, 2015, **10**, 1859.

9 L. Hong, L. Wang, W. Sun, K. Wong and R. Wang, *J. Org. Chem.*, 2009, **74**, 6881.

10 G. Cardillo, R. Cricchio and L. Merlini, *Tetrahedron*, 1971, **27**, 1875.

11 S. N. Aslam, P. C. Stevenson, S. J. Phythian, N. C. Veitch and D. R. Hall, *Tetrahedron*, 2006, **62**, 4214.

12 A. Lattanzi, A. Senatore, A. Massa and A. Scettri, *J. Org. Chem.*, 2003, **68**, 3691.

13 G. Jones and S. P. Stanforth, *Org. React.*, 1997, **49**, 1.

14 O. Dirat, A. J. Bibb, C. M. Burns, G. D. Checksfield, B. R. Dillon, S. E. Field, S. J. Fussell, S. P. Green, C. Mason, J. Mathew, S. Mathew, I. B. Moses, P. I. Nikiforov, A. J. Pettman and F. Susanne, *Org. Process Res. Dev.*, 2011, **15**, 1010.

15 (a) A. Fürstner, E. K. Heilmann and P. W. Davies, *Angew. Chem.*, 2007, **119**, 4844; (b) A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.*, 2012, **113**, 1614.

16 For details see ESI†.

17 (a) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley and M. J. Gaunt, *Angew. Chem. Int. Ed.*, 2004, **43**, 4641; (b) R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziedzic and A. Córdova, *Adv. Synth. Catal.*, 2007, **349**, 1028; (c) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 10886.

18 (a) S.-L. Zhang, H.-X. Xie, J. Zhu, H. Li, X.-S. Zhang, J. Li and W. Wang, *Nat. Commun.*, 2011, **2**, 211; (b) Y. Hayashi, T. Itoh and H. Ishikawa, *Angew. Chem. Int. Ed.*, 2011, **50**, 3920; (c) X. Zeng, Q. Ni, G. Raabe and D. Enders, *Angew. Chem. Int. Ed.*, 2013, **52**, 2977.

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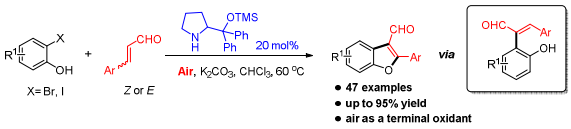

A novel organocatalytic [3+2] annulation/oxidative aromatization reaction of enals with 2-halophenols is developed for the synthesis of 2-arylbenzofuran-3-carbaldehydes.