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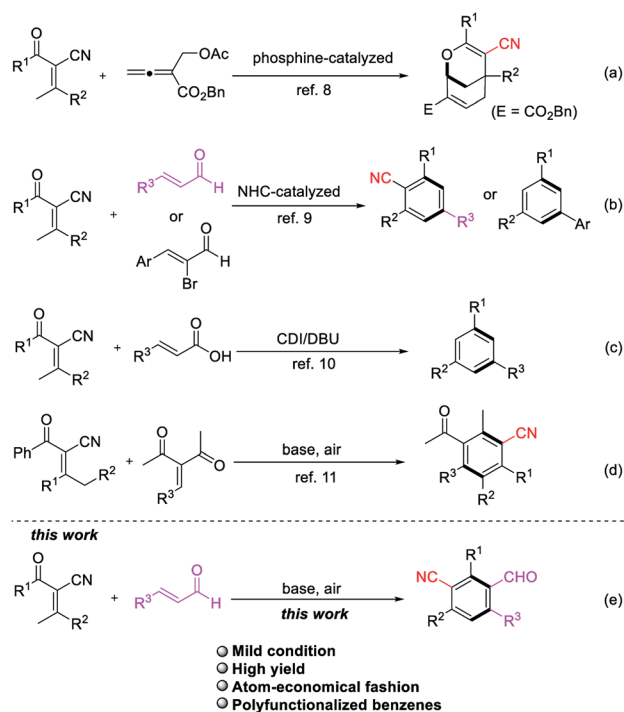
Direct access to multi-functionalized benzenes via [4 + 2] annulation of α -cyano- β -methyleneones and α,β -unsaturated aldehydes†

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 An efficient [4 + 2] benzannulation of α -cyano- β -methyleneones and α,β -unsaturated aldehydes was achieved under metal-free reaction conditions selectively delivering a wide range of polyfunctional benzenes in high yields respectively (up to 94% yield).

Multi-substituted benzenes are privileged structural units ubiquitous in pharmaceuticals,¹ natural products² and advanced functional materials.³ Various excellent methodologies have been investigated for the construction of functionalized aromatics including nucleophilic or electrophilic substitution,⁴ transition metal-catalyzed coupling reactions⁵ and directed metalation.⁶ However, the widespread application of these strategies established thus far suffer from the limitations of functional groups introduced on the pre-existing benzene and regioselectivity issues. Among various synthetic methods, tandem benzannulation reactions arguably represent an attractive alternative to classical methods for rapid construction of polysubstituted benzenes in an atom-economical fashion.⁷ This protocol featuring an efficient transformation of acyclic building blocks into structurally valuable benzene skeletons. In this context, α -cyano- β -methyleneones has been employed as substrates to format six-membered ring in tandem cyclization reactions due to the activation of the pronucleophile methyl group. In 2015, Tong and co-workers developed a phosphine-catalyzed addition/cycloaddition domino reactions of β -acetoxy allenolate with 2-acyl-3-methyl-acrylonitriles to give 2-oxabicyclo[3.3.1]nonanes (Scheme 1a).⁸ Soon after that, the construction of benzonitrile derivatives and 1,3,5-trisubstituted benzenes *via* N-heterocyclic carbene catalysis has been reported by the groups of Wang and Ye independently (Scheme 1b).⁹ Then the synthesis of 1,3,5-trisubstituted benzenes by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated annulation of α -cyano- β -methyleneones and α,β -unsaturated carboxylic acids was also developed by Ye and

co-workers (Scheme 1c).¹⁰ Shi *et al.* reported a base-promoted tandem cyclization reaction of α -cyano- β -methyleneones and α,β -unsaturated enones, which have electron-withdrawing group (EWG), accessing to a wide range of benzonitriles in a different C–C bond formation process (Scheme 1d).¹¹ As part of our ongoing interest in harnessing enones for developing new methodologies for the construction of functionalized benzenes, we have recently demonstrated NHC-catalyzed convenient benzonitrile assembly in the presence of oxidant.^{9a} While the same reaction of enals and α -cyano- β -methyleneones

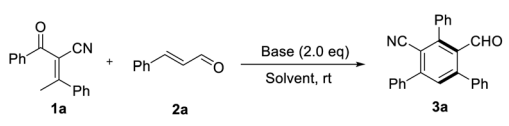

 Scheme 1 α -Cyano- β -methyleneones in cycloaddition domino reactions.

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Table 1 Optimization of the reaction conditions^a


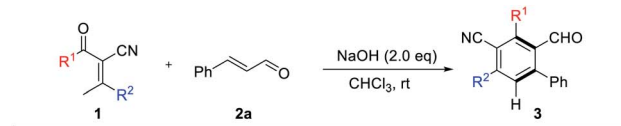
| Entry | Base | Solvent | Time (h) | Yield ^b (%) |
|-----------------|---------------------------------|-------------------|----------|------------------------|
| 1 | CS ₂ CO ₃ | Toluene | 24 | 70 |
| 2 | Na ₂ CO ₃ | Toluene | 24 | 42 |
| 3 | K ₂ CO ₃ | Toluene | 24 | 38 |
| 4 | NaOH | Toluene | 12 | 78 |
| 5 | NaOAc | Toluene | 24 | 52 |
| 6 | KOH | Toluene | 12 | 74 |
| 7 | K ₃ PO ₄ | Toluene | 24 | 58 |
| 8 | DBU | Toluene | 24 | 33 |
| 9 | Et ₃ N | Toluene | 48 | 46 |
| 10 | NaOH | DCM | 12 | 88 |
| 11 | NaOH | CHCl ₃ | 12 | 94 |
| 12 | NaOH | DCE | 12 | 84 |
| 13 | NaOH | H ₂ O | 48 | 0 |
| 14 ^c | NaOH | CHCl ₃ | 12 | 85 |
| 15 ^d | NaOH | CHCl ₃ | 12 | 84 |
| 16 ^e | NaOH | CHCl ₃ | 12 | 80 |

^a Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), base (0.2 mmol, 2.0 equiv.), and solvent (1 mL) for 12 h. ^b Isolated yields. ^c **1a** : **2a** = 1 : 1.2. ^d NaOH used 1.2 equiv. ^e 50 °C.

was conducted in the basic condition without NHC, a novel polyfunctionalized benzene product was obtained (Scheme 1e). The result inspired us to extend the synthetic potential of benzannulation strategy to access diverse benzonitriles, particularly from simpler, abundantly available starting materials.

At the outset, model reaction of 2-benzoyl-3-phenylbut-2-enitrile **1a** and cinnamaldehyde **2a** was used to evaluate reaction parameters. Key results of condition optimization are summarized in Table 1. Several inorganic or organic bases were screened and NaOH turned out to be the most efficient for this transformation to give a novel product **3a**. (33–78% yields, entries 1–9, Table 1). The structure of **3a** was confirmed by X-ray crystallography as an unprecedented functionalized benzene.¹² The configuration of products were assigned unambiguously by X-ray analysis of the product **3a**. A quick solvent screening demonstrated that chloroform is the best choice to produce the benzannulation product **3a** in a desirable yield (entries 10–13, Table 1. For additional details, see the ESI†). Reducing the loading of the cinnamaldehyde or NaOH to 1.2 equivalence led to dramatical loss of the yield (entries 14 & 15, Table 1). And raising the reaction temperature to 50 °C resulted in lower yield (80% yield, entries 16, Table 1).

Finally, the standard reaction conditions for the base-promoted synthesis of the multi-functionalized benzene derivatives identified as follows: 1.5 equivalence of NaOH and CHCl₃ as the solvent under an atmosphere of air for 12 hours at room temperature.

Table 2 Scope of enones^a


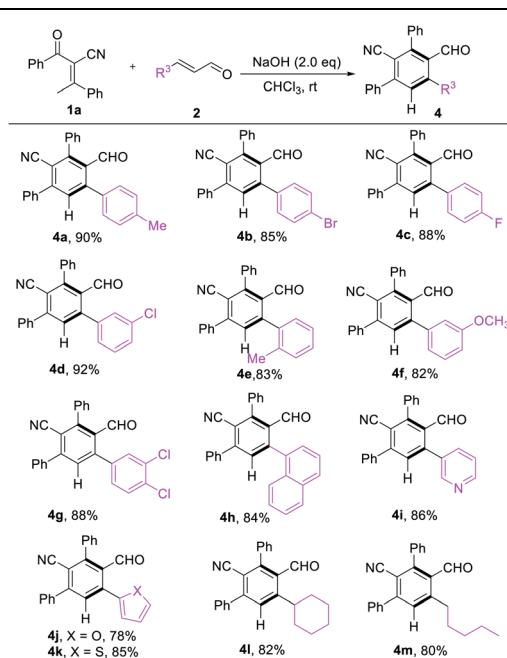
| | | | | |
|------------------------|---|---|---|-------------------------|
| 3b , X = F, 90% | 3c , X = Cl, 93% | 3d , X = I, 85% | 3e , 92% | 3f , 86% |
| 3g , 88% | 3h , R = 2-CH ₃ , 83% | 3i , R = 3-CH ₃ , 85% | 3j , R = 4-CH ₃ , 88% | 3k , 85% |
| 3l , 84% | 3m , X = F, 84% | 3n , X = Cl, 90% | 3o , X = I, 87% | 3p , X = CN, 86% |
| 3q , X = S, 86% | 3r , X = O, 71% | 3s , 82% | 3t , 83% | 3u , n = 0, 78% |
| | | | | 3v , n = 1, 80% |

^a Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), NaOH (0.2 mmol, 2.0 equiv.), and CHCl₃ (1 mL) for 12 h.

With the optimized reaction conditions in hand, we explored the scope of the reaction. A series of enones were examined, variation of the electronic nature of the aromatic ring (R¹, including the substituted phenyl or thienyl) has little influence on the reaction efficiency (**3b–f**, 86–93% yields, Table 2). We subsequently examined the effect of R² with different substitution patterns and electronic nature, β-arylenones with electron-rich and electron-deficient substituents were worked well to afford the functional benzonitriles in high yields (**3g–r**, 80–90% yields, Table 2). Enones with alkyl group on R² position can also be used to afford their corresponding products (**3s–v**, 78–83% yields, Table 2) in good chemical yields.

We next turned our attention to examine the scope of enals. Different substituents on the phenyl ring of cinnamaldehydes were tolerated even disregarding the position and properties, giving **4a–g** in satisfying yields (82–92% yields, Table 3). With respect to heterocycles such as pyridine, furan, thiophene and naphthalenes were also compatible with the reaction conditions (**4h–k**, 82–88% yields, Table 3). Replacement of the β-phenyl substituent with an alkyl unit **4l** & **4m** had limited effect on reaction conversion, the corresponding products were obtained in good yields (82% & 80% yield, Table 3).



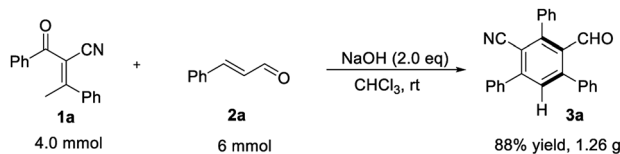
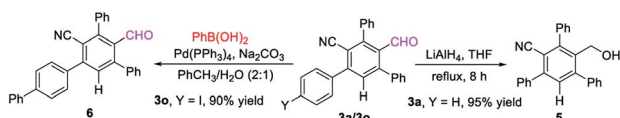
Table 3 Scope of enals^a

^a Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), NaOH (0.2 mmol, 2.0 equiv.), and CHCl₃ (1 mL) for 12 h.

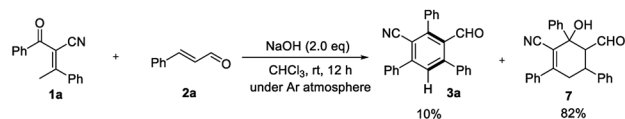
To highlight the practicality of this mild and efficient method, the reaction of 2-benzoyl-3-phenylbut-2-enitrile **1a** at 4.0 mmol scale proceed well under the standard conditions to generate the desired product in 88% yield (Scheme 2).

The formyl group could be easily reduced by using LiAlH₄ in THF at reflux, leading to the formation of the benzyl alcohol product **5** in 95% yield while keeping the CN group intact. Suzuki coupling of **3o** with phenylboronic acid furnished derivative **6** in 90% yield¹³ (Scheme 3).

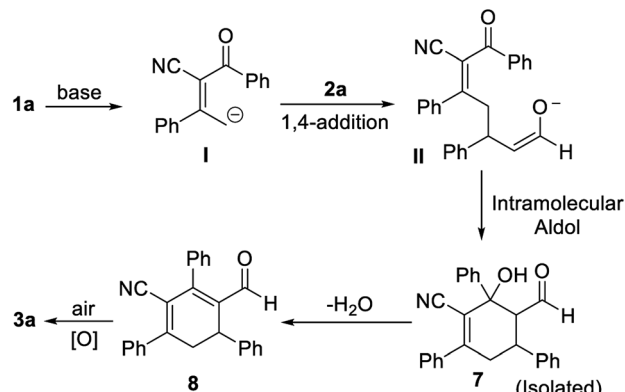
To gain insight into the role of air in this reaction, a control experiment was designed and investigated (Scheme 4). When the reaction of **1a** and **2a** was carried out under an argon atmosphere, the desired product **3a** was obtained in 10% yield

Scheme 2 Gram-Scale Synthesis of **3a**.

Scheme 3 Synthetic transformation.



Scheme 4 Control experiment.



Scheme 5 The proposed mechanism.

and product **7** could be isolated in 82% yield. The results indicate that oxygen is necessary for the oxidation process and played a key role in this reaction.

A postulated reaction course is illustrated in Scheme 5. Briefly, α -deprotonation of enone **1a** in the presence of bases, subsequent 1,4-addition of deprotonated enone **I** to enal **2a** generates intermediate **II**, which undergoes an intramolecular aldol reaction to yield the adduct **7**.¹⁴ Lastly, dehydration of **7** followed by spontaneous oxidative aromatization affords the polysubstituted benzonitrile **3a**.

Conclusions

In summary, we have developed the example of catalyst-free [4 + 2] cycloaddition reaction of α -cyano- β -methyleneones and α,β -unsaturated aldehydes. This protocol provides straightforward access to the corresponding highly functionalized benzenes in good to excellent yields under ambient conditions. Such studies are actively underway in our laboratory, and more results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 14 The adduct **7** was isolated from the reaction of **1a** and **2a** under standard conditions for 0.5 h and the structure was determined by NMR, HRMS, for details, see the ESI.†

