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Benzene construction via organocatalytic formal [3 + 3] cycloaddition reaction

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The benzene unit, in its substituted forms, is a most common scaffold in natural products, bioactive molecules and polymer materials. Nearly 80% of the 200 best selling small molecule drugs contain at least one benzene moiety. Not surprisingly, the synthesis of substituted benzenes receives constant attentions. At present, the dominant methods use pre-existing benzene framework to install substituents by using conventional functional group manipulations or transition metal-catalyzed carbon-hydrogen bond activations. These otherwise impressive approaches require multiple synthetic steps and are ineffective from both economic and environmental perspectives. Here we report an efficient method for the synthesis of substituted benzene molecules. Instead of relying on pre-existing aromatic rings, here we construct the benzene core through a carbene-catalyzed formal [3 + 3] reaction. Given the simplicity and high efficiency, we expect this strategy to be of wide use especially for large scale preparation of biomedical and functional materials.

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Multi-substituted benzenes are widely present in natural products. In industry, these benzene frameworks are nearly unavoidable in preparing most of today's biomedical, fine chemicals and polymer materials. The functions of the benzene-containing molecules are determined by the identity and substitution patterns of the substituents installed on the benzene unit. Exemplified in Fig. 1a are one natural product (salvadorin)¹ and two synthetic bioactive molecules^{2,3} containing a benzene core bearing four substituents. Most synthetic methods in synthesizing such multi-substituted aromatics start with pre-existing benzene unit by replacing hydrogen with other functional groups. The classic approach relies on stepwise electrophilic substitution (such as Friedel–Crafts reaction) or electrophilic halogenation and successive transition metal-catalyzed couplings. However, regio-selectivity and chemo-selectivity normally require rather tedious functional group (including protecting group) manipulations. For example, the classic synthesis of a 2,4,6-trisubstituted benzoate needs the introduction of a temporary amine group to ensure selectivities in a key bromination reaction step⁴, and the overall synthesis requires over eight steps (Fig. 1b). Another approach for access to substituted benzenes is based on transition metal-catalyzed direct C–H activations^{5–8}. While providing impressive shortcuts for benzene substitutions, this C–H activation method has its own limitations. For example, the presence of directing groups (for coordination with the metal catalyst) is often necessary and the instruction of multiple substituents is difficult (in part due to steric congestion). In a

different direction for substituted benzene synthesis, the benzene core is newly formed. Representative methods include transition metal-catalyzed [2 + 2 + 2] or [4 + 2] reactions such as acetylene trimerizations developed by Reppe *et al.*^{9–11} In this cycloaddition approach, partial or complete intramolecular reaction is usually indispensable to ensure the regio-selectivity.

Here we report a new strategy for highly effective access to multi-substituted benzenes through the construction of the benzene core via a formal [3 + 3] cycloaddition reaction (Fig. 1d). Our approach uses enals readily prepared in three steps and unsaturated ketones as the starting material and N-heterocyclic carbene (NHC) as the organic catalyst^{12–24}. It is a single-step reaction that affords tetra-substituted benzenes (2,4,6-trisubstituted benzoate and its analogues) with high yield. In comparison, previous approaches to this class of molecules typically need seven steps with less than 10% overall yields²⁵ (Fig. 1d). A plausible pathway of our NHC-catalyzed [3 + 3] cycloaddition reaction involving formal α -, and γ -carbon activations of enal is illustrated in Fig. 2. Briefly, addition of the carbene catalyst to the aldehyde moiety of enal followed by deprotonation forms Breslow intermediate I^{26–28}. This process is followed by oxidative transformation^{29–33}, and former enal γ -CH deprotonation³³ leads to vinyl enolate intermediate III. Notably, similar vinyl enolate intermediate could also be accessed from ketenes³⁴ by Ye or esters in our laboratory³⁵. Nucleophilic Michael-type addition of the γ -carbon of III to enone 2 affords intermediate IV bearing a NHC-bound α,β -unsaturated ester

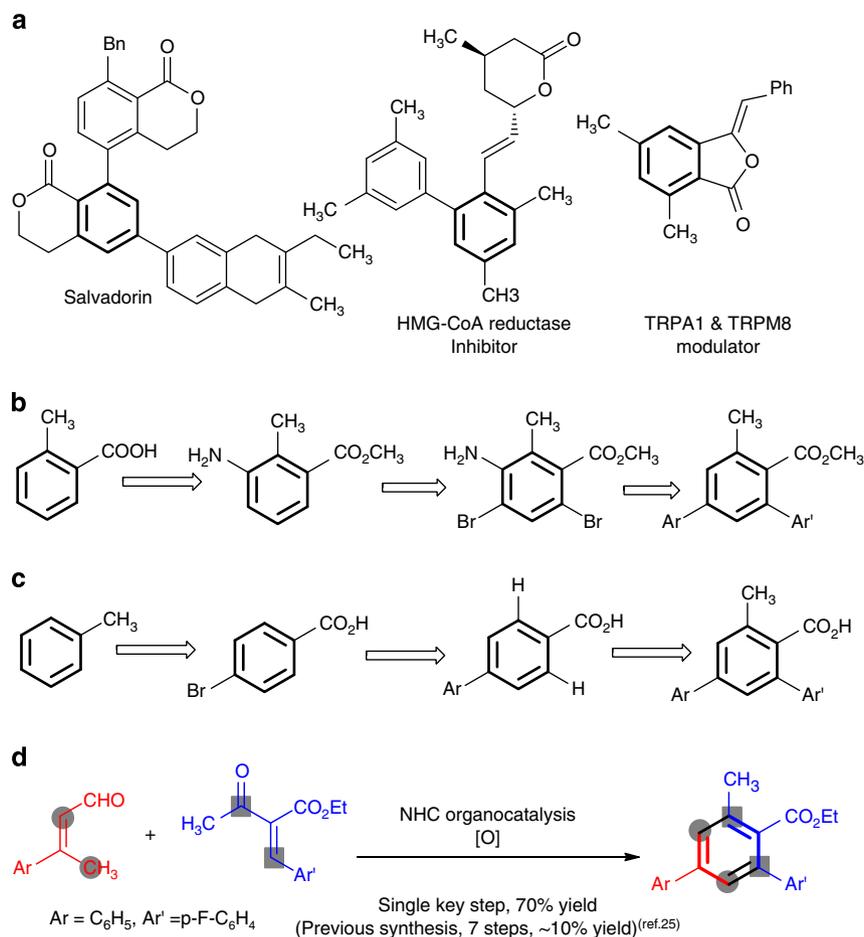


Figure 1 | Multi-substituted benzenes and their synthesis. (a) examples of natural products and bioactive synthetic compounds containing multi-substituted benzene. (b) it took about eight steps for the classical substitution methods to synthesize a 2,4,6-trisubstituted benzoate. (c) transition metal-catalyzed C–H activation methods provides a shortcut (about five steps) for the synthesis. (d) this work: single key step reaction to afford tetra-substituted benzenes via organocatalyzed formal [3 + 3] cycloaddition.

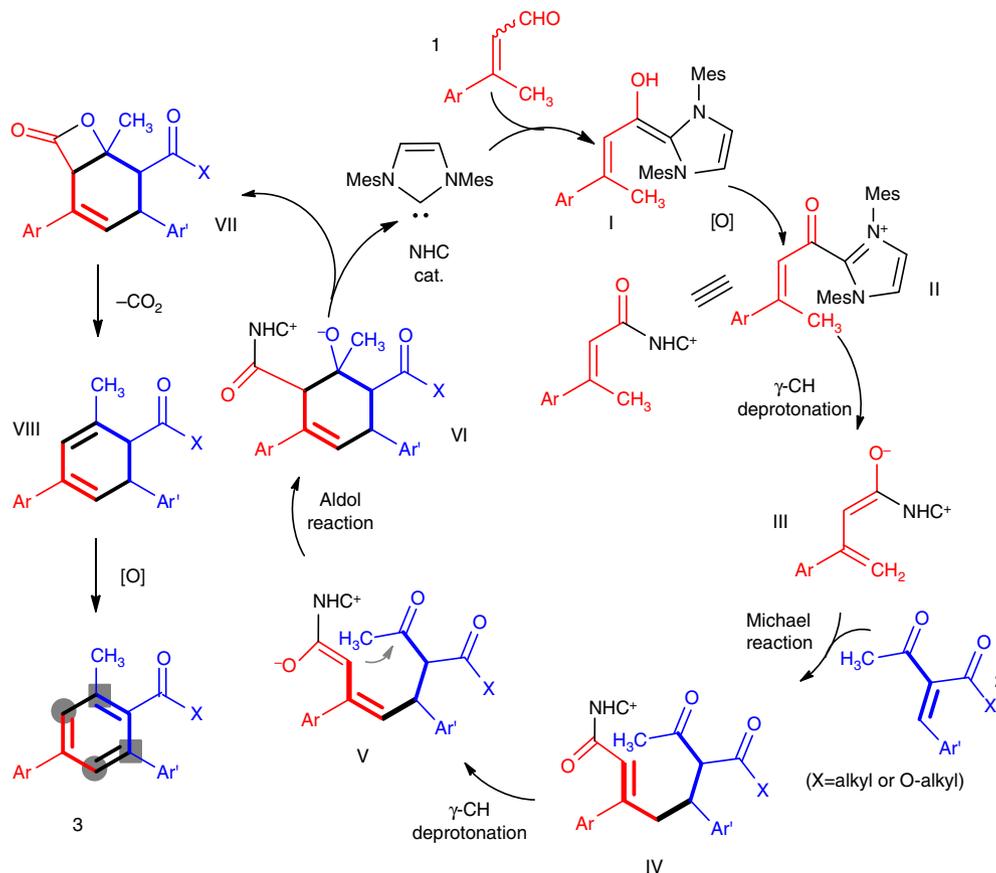


Figure 2 | Postulated pathway. Addition of carbene catalyst to aldehyde followed by oxidative transformation and γ -CH deprotonation leads to intermediate **III**, which undergoes Michael addition to **2** and gives intermediate **IV**. Subsequent γ -CH deprotonation of **IV** lead to **V**, after intramolecular aldol reaction, decarboxylation and oxidation, finally gives a benzene product bearing four substituents in predictable substitution patterns. Mes, 2,4,6-trimethylphenyl. Cat., catalyst.

moiety. Subsequent γ -CH deprotonation of **IV** lead to dienolate intermediate **V** that undergoes an intramolecular aldol to form a cyclic intermediate **VI**. Intramolecular ester formation with the release of NHC catalyst yields a bicyclic adduct **VII** containing a four-membered β -lactone. Spontaneous decarboxylation^{36–39} and oxidation^{40–42} of **VII** effectively affords benzene product bearing four substituents in predictable substitution patterns. Decarboxylation of β -lactone fused with a six-membered ring similar to intermediate **VII** is a highly effective process, as exemplified in Lupton's [4 + 2] reaction via carbene catalysis³⁹.

Results

Reaction optimization. We started by using enal **1a** and enone **2a** as the model substrates, in the presence of 2 equiv. quinone **4** as an oxidant^{29–33} and Cs_2CO_3 as a base. No formation of the proposed benzene **3a** was observed in the absence of an NHC precatalyst (Table 1, entry 1). The *N*-methyl imidazolium NHC **A** (ref. 43) and *N*-phenyl imidazolium **B** could not initiate the reaction (Table 1, entries 2–3). We then found that with *N*-Mes imidazolium **C** (ref. 44) as the NHC precatalyst, the proposed product **3** was formed in 88% isolated yield (Table 1, entry 4). Triazolium-based NHCs behaved similarly as the imidazolium catalysts: triazolium **D** (ref. 45) (with a *N*-phenyl substituent) could not catalyze the reaction; while the use of triazolium **E** (ref. 46) with a *N*-mesityl substituent could lead the formation of **3** in 47% yield (Table 1, entries 5–6). Thiazolium-based NHCs **F** (ref. 47) or **G** (ref. 48) could not initiate the reaction (Table 1, entries 7–8). We then evaluated the effects of solvents and bases.

Table 1 | Condition optimization for NHC-catalyzed [3 + 3] benzene construction.

Entry	NHC precatalyst (mol%)	Yield (%)
1	0	0
2	A (30)	Trace
3	B (30)	Trace
4	C (30)	88
5	D (30)	Trace
6	E (30)	47
7	F (30)	Trace
8	G (30)	Trace
9	C (5)	76

NHC, N-heterocyclic carbene.

The reaction was carried out in 1.0 ml solvent under N_2 . Yields of **3a** were isolated yields after SiO_2 chromatography purification. See Supplementary Table 1 for results under other conditions.

Although the combination of tetrahydrofuran and Cs_2CO_3 was optimal, other common organic solvents (such as CH_2Cl_2 , toluene, CH_3CN and DMF) and organic/inorganic bases (such as Et_3N , DBU, $t\text{BuOK}$ and K_2CO_3) could also be used (see the Supplementary Table 1). Further investigation showed that the catalyst loading of **C** could be decreased to 5 mol% with acceptable 76% yield (Table 1, entry 9).

Scope of enal substrates. With an acceptable reaction condition in hand (Table 1, entry 9), the scope of the reaction was evaluated. To demonstrate broader synthetic utility of this method, we chose enone **2b** bearing an alkene group (amenable for further transformation) as a model enone substrate to study the

generality of the enal substrates (Fig. 3, products **3b–j**). Both electron-donating (products **3c–d**, **3f**) and electron-withdrawing group (products **3e**, **3g**) at the *p*- position (products **3c–e**) or *m*- position (products **3f–g**) of the β -phenyl group were well-tolerated. Replacement of the β -phenyl substituent with a naphthyl (product **3h**) or heteroaryl unit (products **3i–j**) had little effect on the reaction outcome. It is worth to note that *E*- or *Z*-isomer of enal **1** gave essentially the same yields, so a mixture of *E*-/*Z*-enals can be directly used.

Scope of enone substrates. With aldehydes **1a** and **1b** ($\text{Ar} = 4\text{-OCH}_3\text{-C}_6\text{H}_4$) as model nucleophile, the scope of enones was also examined. As shown in Fig. 3 (products **3k–z1**), in nearly all

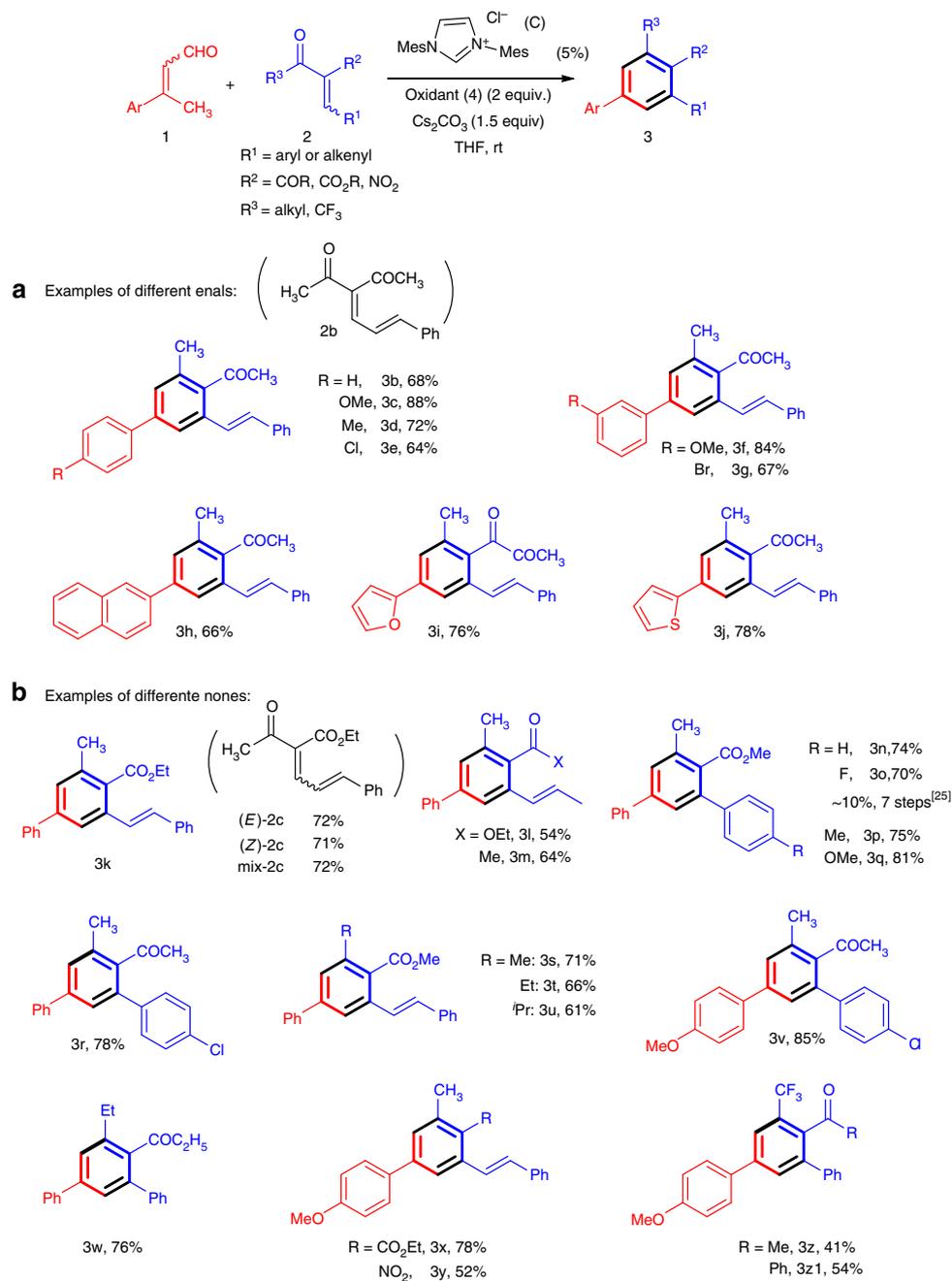


Figure 3 | Substrate scope. (a) Examples of different enals: study of enal substrate generality with ketone **2b** as a model enone substrate. (b) Examples of different enones: study of enones scope with aldehydes **1a** ($\text{Ar} = \text{C}_6\text{H}_5$) and **1b** ($\text{Ar} = 4\text{-OCH}_3\text{-C}_6\text{H}_4$) as model nucleophile. Ph, phenyl; Me, methyl; Et, ethyl.

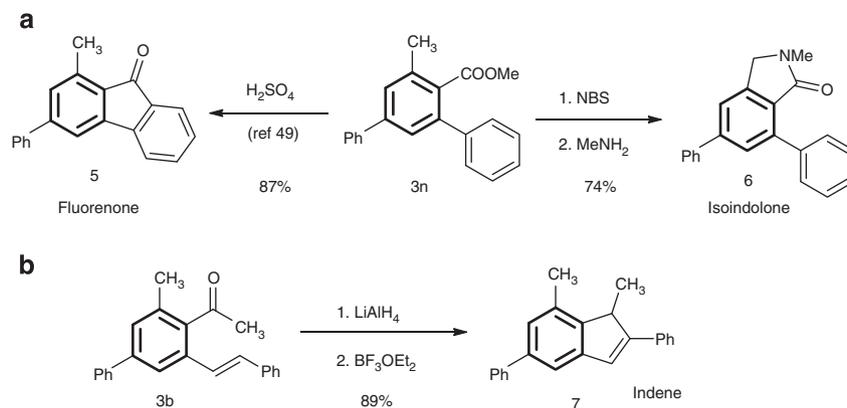


Figure 4 | Synthetic applicability. (a) **3n** can be transformed to fluorenone **5** or isoindolone **6** via straightforward processes. (b) **3b** could be transformed to indene **7** via reduction followed by Lewis acid-mediated cyclization. NBS, *N*-bromosuccinimide.

cases, the reaction proceeded smoothly at room temperature to give polysubstituted benzenes in moderate to good yields. Notably, the *E/Z*-configuration of enone **2** did not affect the reaction outcomes either (for example, see product **3k**), which greatly simplify substrate preparation process. Both electron-rich (products **3p–q**) or electron-deficient (products **3o** and **3r**) aromatic groups, as well as vinyl groups (products **3k–m**) were all tolerated in the β -substituent (R^2) of the enone substrates. α -Substituent (R^3) of the enone substrates can be electron-deficient units such as acyl (**3m**, **3r**, **3v–3w**), ester (**3k–l**, **3n–q**) or nitro (**3y**) groups. Substituent in the carbonyl group of enones **2** (R^4) can be a different alkyl group including methyl (**3k–q**, **3r–s**), ethyl (**3t** and **3w**), isopropyl (**3u**) or trifluoromethyl (**3z–z1**) group.

It is important to note that these polysubstituted benzene molecules were difficult to prepare previously. For example, previous method for the synthesis of benzoate **3o** required seven steps with less than 10% overall yields²⁵; previous synthesis of **3p** and **3q** needed a three-step reaction with 35 and 39% overall yield⁴⁹, respectively. Our method also provides effective access to aromatic molecules with trifluoromethyl (CF_3) substituent. In organic synthesis, regioselective C–H trifluoromethylation^{50,51} or methylation^{52–54} of aryl molecules still remains challenging despite the rapid development in recent years.

Product transformation. We next demonstrated effective transformation of our catalytic reaction products to bicyclic and multicyclic aromatic molecules that are found as a key scaffold in natural products and functional synthetic molecules. For example, the multisubstituted benzene adduct **3b** could be transformed to indene **7** (ref. 55) via reduction followed by Lewis acid-mediated cyclization; 2,4,6-trisubstituted benzoate **3n** can be transformed to fluorenone **5** (refs 56,49) or isoindolone **6** (ref. 57) via straightforward processes (Fig. 4).

Discussion

In summary, we have developed a NHC organocatalytic strategy for the formal [3 + 3] construction of multi-substituted benzenes. Our method directly employs commercially available or easily accessible enals and enones to construct benzene framework with excellent regioselectivities, offering useful insights into the design of concise synthetic strategies for complex molecules. Further studies regarding reaction mechanisms, synthetic applications and axial chirality controls (for the formation of substituted benzene products) are under progress in our laboratory.

Methods

Materials. For ^1H , ^{13}C and ^{19}F NMR spectra of compounds in this manuscript, see Supplementary Figs 1–32. For details of the synthetic procedures, see Supplementary Methods.

Synthesis of 3. Under N_2 atmosphere, a solution of enal (0.1 mmol), enone (0.1 mmol), oxidant **4** (82 mg, 0.2 mmol), Cs_2CO_3 (48.7 mmol, 0.15 mmol) and imidazolium **C** (1.7 mg, 0.005 mmol) in 1.0 ml tetrahydrofuran was stirred at room temperature for 8 h. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography to afford the corresponding product **3**.

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Author contributions

T.Z. conducted most of the experiments; P.Z. and C.M. prepared substrates for the reaction scope evaluation; S.Y., B.-A.S. and Y.R.C. conceptualized and directed the project, and drafted the manuscript with the assistance from all co-authors. All authors contributed to discussions.

Additional information

Supplementary Information accompanies this paper at <http://www.nature.com/naturecommunications>

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