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 biomedicals 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 biomedicals, 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) and two synthetic bioactive molecules 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 step, 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. 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 \([2+2]\) or \([4+2]\) reactions such as acetylene trimerizations developed by Reppe et al. 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 yields (Fig. 1d). A plausible pathway of our NHC-catalyzed \([3+3]\) cycloaddition reaction involving formal \(\alpha,\beta\)-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, and former enal \(\gamma\)-carbon deprotonation leads to vinyl enolate intermediate. Notably, similar vinyl enolate intermediate could also be accessed from ketenes by Ye or esters in our laboratory. Nucleophilic Michael-type addition of the \(\gamma\)-carbon of to enone affords intermediate bearing a NHC-bound \(\alpha,\beta\)-unsaturated ester.
moiety. Subsequent γ-CH deprotonation of IV lead to dienolate intermediate V that undergoes 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.

**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 and Cs₂CO₃ 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NHC precatalyst (mol%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>A (30)</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>B (30)</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>C (30)</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>D (30)</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>E (30)</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>F (30)</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>G (30)</td>
<td>Trace</td>
</tr>
<tr>
<td>9</td>
<td>C (5)</td>
<td>76</td>
</tr>
</tbody>
</table>

NHC, N-heterocyclic carbene.

The reaction was carried out in 1.0 ml solvent under N₂. Yields of 3a were isolated yields after SiO₂ chromatography purification. See Supplementary Table 1 for results under other conditions.
Although the combination of tetrahydrofuran and Cs$_2$CO$_3$ was optimal, other common organic solvents (such as CH$_2$Cl$_2$, toluene, CH$_3$CN and DMF) and organic/inorganic bases (such as Et$_3$N, DBU, tBuOK and K$_2$CO$_3$) 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 (Ar = 4-OCH$_3$-C$_6$H$_4$) as model nucleophile, the scope of enones was also examined. As shown in Fig. 3 (products 3k–z1), in nearly all...
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 (R²) of the enone substrates. α-Substituent (R¹) 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 (R⁴) 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 benzoate 3n required seven steps with less than 10% overall yields²⁵; previous synthesis of benzoate 3o was difficult to prepare previously. For example, (methylation⁵²–⁵⁴ of aryl molecules still remains challenging to indene 7. Arockiam, P. B., Bruneau, C. & Dixneuf, P. H. Ruthenium (II)-catalyzed 

**Methods**

**Materials.** For ¹H, ¹³C and ¹⁹F NMR spectra of compounds in this manuscript, see Supplementary Figs 1–3. For details of the synthetic procedures, see Supplementary Methods.

**Synthesis of 3.** Under N₂ atmosphere, a solution of enal (0.1 mmol), enone (0.1 mmol), oxidant 4 (82 mg, 0.2 mmol), Cs₂CO₃ (48.7 mmg, 0.15 mmol) and imidazolid 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 project, and drafted the manuscript with the assistance from all co-authors. All authors contributed to discussions.

Additional information

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