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Direct bromocarboxylation of arynes using allyl bromides and carbon dioxide†

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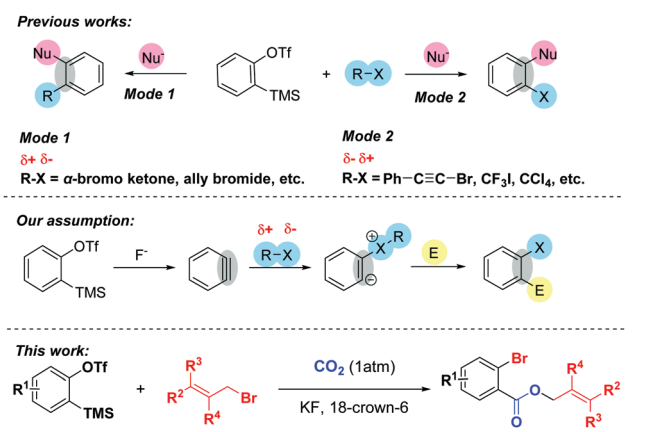
An unprecedented three-component coupling involving arynes, allyl bromides, and CO_2 is described, providing efficient and facile access to structurally diverse *ortho*-brominated aryl esters. Unlike the conventional role played in organic synthesis as electrophiles, organic bromides served as nucleophiles in this reaction, affording a new approach to multicomponent reactions (MCRs) involving aryne intermediates. Additionally, Hammett analysis suggests that two reaction mechanisms exist, depending on the electronic nature of the cinnamyl bromides used.

Arynes have become versatile synthetic tools in organic synthesis, especially for the construction of diverse 1,2-functionalized aromatic rings.[1] Due to their highly electrophilic strained triple bond, arynes can undergo different types of reactions such as cycloaddition reaction, multicomponent coupling, and insertion reaction to realize the double functionalization. Among them, the combination of organic halides and arynes with various nucleophiles provides an alternative way to preserve halogen atoms or organic parts in the final products. Typically, organic halides such as α-bromo ketones[2] can undergo nucleophilic attack by *in situ* zwitterions or nucleophiles to afford the corresponding alkylated products (Scheme 1, Mode 1). On the other hand, the incorporation of halogen atoms into arynes, which greatly influences the pharmacological activities of bioactive molecules[3] and is utilized for diverse functional group transformations,[4] can be accomplished by using alkynyl or polyfluoroaryl bromides,[5a,g] perfluoroalkyl[5b,c] or alkynyl iodides,[5d,e] and carbon tetrachloride[5f,g] (Scheme 1, Mode 2).

Despite these elegant studies described, as far as we know, there has been no precedent utilizing organic halides as nucleophiles to trigger MCRs involving aryne intermediates. Inspired by Yoshida's brilliant work[6] that arynes could be inserted into the C–X σ-bonds of acid halides and the fact that arynes could even be initiated with different solvents such as THF,[5a,7] DMF[8] and DMSO,[9] we envisaged that the benzyne intermediate generated *in situ* might undergo nucleophilic attack by the halogen atoms of organic halides, and the corresponding zwitterions might capture another electrophilic reagent to furnish the functionalized halobenzenes.[10] Additionally, given that CO_2 is an inexpensive, safe and renewable C1 building block, the transformation of CO_2 into high value-added products shows great potential in organic synthesis and has attracted numerous organic chemists' attention.[11] However, very limited success involving both CO_2 and arynes has been achieved so far.[12]

Recently, we[12g] reported a 3P-4CR of arynes to afford diverse *o*-chlorobenzoates using KCl as a Cl source. Surprisingly, we found that the reaction could give a moderate yield of allyl 2-bromobenzoate **3aa** when the solvent DCE (1,2-dichloroethane) was replaced with allyl bromide even without KBr. Therefore, as part of our continuous interest in the utilization of CO_2,[13] herein, we report an unprecedented three-component coupling reaction of arynes, allyl bromides and CO_2. Compared with our previous studies, the reaction proceeded well without any additional



Scheme 1 Background and our approach.

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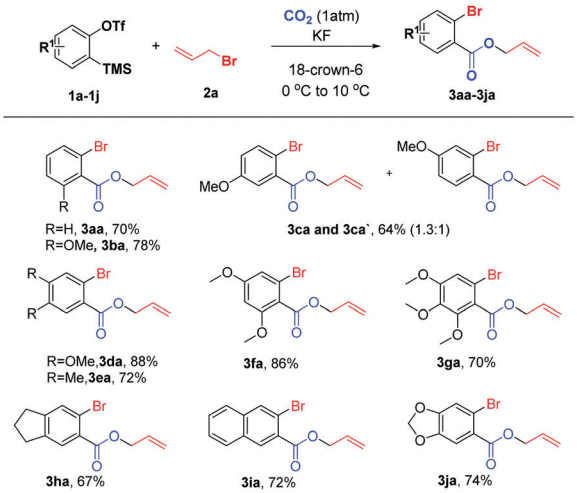
† Electronic supplementary information (ESI) available: Experimental details and characterization of all compounds, and copies of ^{1}H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/c9cc05495b



Scheme 2 Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mL), CO_2 (1 atm), KF (4 equiv.), 18-crown-6 (4 equiv.), 0 to 10 °C for 12 h.

inorganic salts and the incorporation of both Br and CO_2 into the arynes made further facile functionalizations possible.

We initially investigated the reaction of aryne precursor **1a**[14] with allyl bromide **2a** under 1 atm CO_2 at 46 °C for 12 h, and observed that the three-component coupling product **3aa** was obtained in 52% yield. After screening of temperatures, we were delighted to discover that the reaction yield could be optimized to 79%.[15] The reaction system could be compatible with various benzyne precursors (Scheme 2), especially for those containing the methoxy group, affording allyl *o*-bromobenzoate derivatives in good to excellent yields. As expected, the reaction of 4-methoxybenzyne (generated from **1c**) provided the corresponding product in 64% yield with poor regioselectivity (1.3 : 1). Moreover, both multisubstituted symmetrical and unsymmetrical silyl aryl triflates (**1d–1g**) reacted smoothly with complete regioselectivity[16] under the reaction conditions. Furthermore, indanyl and 1,3-benzodioxole derivatives (**1h** and **1j**) as well as 2,3-naphthalyne (**1i**) could also work well, furnishing the expected products in 67–74% yields. However, the reaction of the 4,5-difluoroaryne precursor with allyl bromide **2a** resulted in a much lower yield.

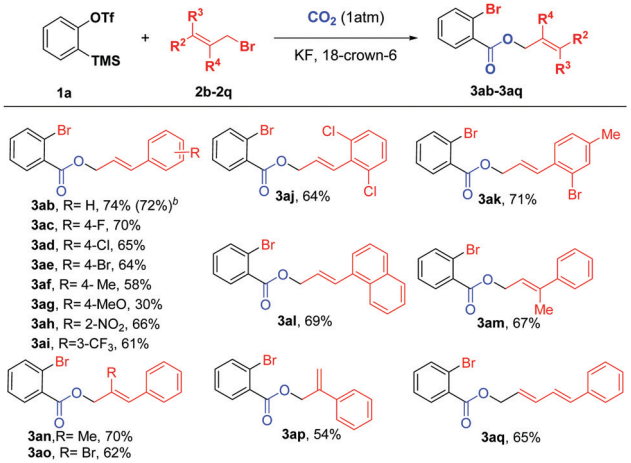
Encouraged by these preliminary results, we then directed our attention to the optimization of non-terminal allyl bromide **2b** (Table 1). Among the different solvents examined, CF_3-Ph was found to be the best solvent, whereas the other solvents afforded inferior results (entries 1–4). The reaction yield could be further improved to 56% by performing the reaction at −10 °C and gradually warming the reaction mixture to 10 °C (entry 5). Remarkably, when we proportionally decreased the dosages of both the aryne precursor and F source, the yield of **3ab** increased to 66% (entries 5–7). To our delight, a similar result was achieved even when the amounts of KF and 18-crown-6 were reduced to 2.4 equivalents (entry 8). Finally, diluting the reaction mixture and altering the charging way of **2b** gave the best result, with **3ab** obtained in 76% yield (entry 10). The control experiments indicated that both 18-crown-6 and CO_2 were essential for transformation (entries 11 and 12).

Table 1 Optimization of reaction conditions[a]

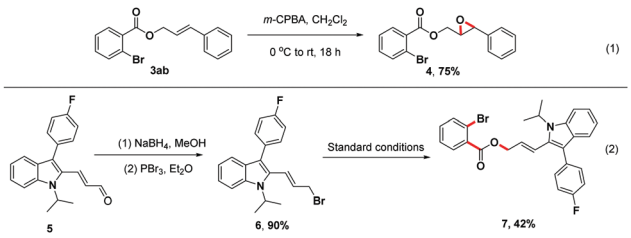
Entry	**1a** : **2b**	F^- source (equiv.)	Solvent (mL)	T [°C]	Yield[b] [%]
1	1.5 : 1	4	THF	0	21
2	1.5 : 1	4	MeCN	0	n.d.
3	1.5 : 1	4	DCE	0	12
4	1.5 : 1	4	CF_3-Ph	0	41
5[c]	1.5 : 1	4	CF_3-Ph	−10 to 10	56
6[c]	1.2 : 1	3.2	CF_3-Ph	−10 to 10	66
7[c]	1 : 1	2.6	CF_3-Ph	−10 to 10	64
8[c]	1.2 : 1	2.4	CF_3-Ph	−10 to 10	66
9[d]	1.2 : 1	2.4	CF_3-Ph	−10 to 10	69
10[d,e]	**1.2 : 1**	**2.4**	**CF_3-Ph**	**−10 to 10**	**76**
11[d,e,f]	1.2 : 1	2.4	CF_3-Ph	−10 to 10	—
12[d,e,g]	1.2 : 1	2.4	CF_3-Ph	−10 to 10	—

[a] Reaction conditions: **2b** (0.2 mmol), KF (4 equiv.) and 18-crown-6 (4 equiv.) in solvent (0.1 mL), CO_2 (1 atm), 12 h. [b] Determined by ^{1}H NMR analysis using CH_3NO_2 as an internal standard. [c] CF_3-Ph (0.5 mL). [d] CF_3-Ph (1.0 mL). [e] **2b** was added in the N_2 glove box [f] Without 18-crown-6. [g] Under a N_2 atmosphere.

Next, we examined various cinnamyl bromides[17] under the optimized reaction conditions, and the results are shown in Scheme 3. To our delight, a broad range of cinnamyl bromides (**3ab–3ai**) reacted smoothly to afford the corresponding carboxylated products in moderate to good yields, allowing F, Cl, Br, NO_2, and CF_3 substituents on the aryl ring to be tolerated. Intriguingly, cinnamyl bromides with electron-neutral groups provided higher yields than those with electron-withdrawing or electron-donating groups, and the substrates with electron-donating groups (**3af** and **3ag**) led to dramatic decreases in the yields of the products. In addition, both disubstituted and 1-naphthyl-substituted cinnamyl bromides (**3aj–3al**) were suitable reaction partners, leading to the desired products in 64–71% yields. Furthermore, the substrate scope was further expanded to the allyl groups at different positions with various substituents



Scheme 3 [a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), CO_2 (1 atm), KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), CF_3–Ph (1 mL), −10 to 10 °C for 12 h. [b]Reaction conditions: **1a** (1.2 mmol), **2** (1 mmol), CO_2 (balloon), KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), CF_3-Ph (5 mL), −10 to 10 °C for 12 h.

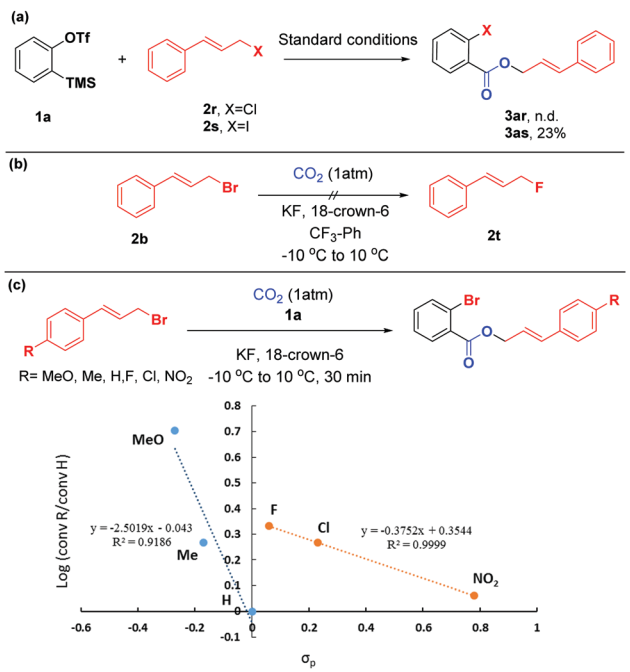


Scheme 4 Synthetic applications.

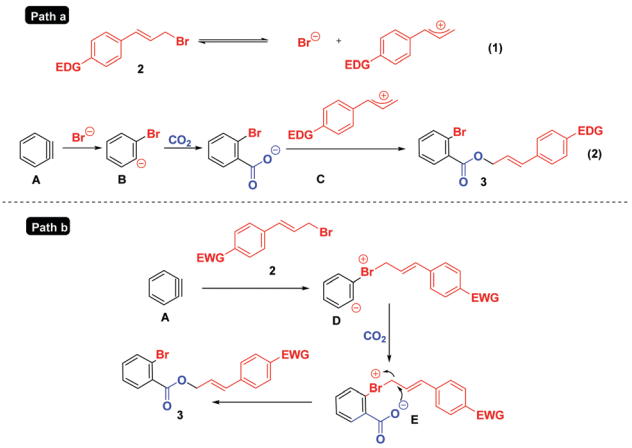
(**3am**–**3ap**), all of which were compatible with our reaction system. Moreover, when 1-bromo-5-phenyl-2,4-pentadiene (**2q**) was employed, **3aq** could also be obtained in 65% yield, thus demonstrating the versatility of this new protocol.

To further illustrate the utility of this unique three-component reaction, treatment of product **3ab** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 provided the desired epoxide derivative **4** in 75% isolated yield[18a] (Scheme 4, (1)). Moreover, the indole derivative **5**, a synthetic precursor for the construction of Fluvastatin,[18b,c] underwent reduction and bromination efficiently to afford brominated compound **6**, which could be transformed to the structurally complex product **7** in 42% isolated yield using this one-step strategy (Scheme 4, (2)).

To shed light on the mechanism of this difunctionalization reaction of arynes, a series of control experiments were performed (Scheme 5). Compared with cinnamyl bromide **2b**, the reaction of cinnamyl chloride **2r** with aryne precursor **1a** failed to give the target product **3ar**, while cinnamyl iodine **2s** could only afford the corresponding product **3as** in 23% yield (based on ^{1}H NMR), with iodobenzene and *ortho*-diiodobenzene as the main side products (detected by GC-MS). These observations indicated that cinnamyl bromide possessed a more appropriate nucleophilicity



Scheme 5 Mechanistic experiments.



Scheme 6 Plausible mechanisms.

toward arynes. Additionally, given that the organic bromide might undergo nucleophilic fluorination by KF,[19] we conducted the reaction without aryne precursor **1a**. To our surprise, the formation of **2t** was not detected by ^{19}F NMR spectroscopy (Scheme 5(b)). We further evaluated the electronic effects of this reaction by Hammett analysis.[20] The two lines with different negative ρ values indicated that a considerable build-up of positive charge in the transition state, however, with a change in the mechanism or rate-determining step, depending on the character of the substituents on the cinnamyl bromides. For substituents with $\sigma_p < 0$, the value $\rho = -2.5$ was consistent with an S_N1-like mechanism.[21] But in the case of electron deficient substrates, the sensitivity constant ρ was only -0.4, which might proceed in a different way (Scheme 5(c)).

Based on the above results and previous studies,[6,12] two tentative mechanisms are proposed in Scheme 6. For substrates containing electron-rich/-neutral groups (Path a), the ionization[22] of **2** generates a cinnamyl cation and Br^-; the latter reacts with aryne intermediate **A**, CO_2 and the cinnamyl cation successively to deliver the final products **3**. However, in the case of electron deficient substrates (Path b), which do not easily undergo the ionization process due to the instability of the cinnamyl cation, the reaction may proceed as follows: the nucleophilic attack of cinnamyl bromide **2** on the benzyne intermediate **A** affords the 1,3-zwitterion **D**, which is then intercepted by CO_2 to form the 1,5-zwitterion **E**. Finally, a subsequent intramolecular nucleophilic attack of intermediate **E** yields cinnamyl 2-bromobenzoates **3**.

In summary, we have developed an efficient three-component reaction of CO_2 with arynes and allyl bromides to construct various allyl *o*-bromobenzoate scaffolds. The reaction demonstrates the first example using cinnamyl bromide as a nucleophile in MCRs of arynes and helps deepen our understanding of the high electrophilicity of the aryne intermediate. Further studies focusing on the transformation of CO_2 are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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