4-Trifluoromethyl-\(p\)-quinols as dielectrophiles: three-component, double nucleophilic addition/aromatization reactions

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In recent years, numerous methods have emerged for the synthesis of trifluoromethylated arenes based on the late-stage introduction of a trifluoromethyl group onto an aryl ring. In sharp comparison, the synthesis of trifluoromethylated arenes based on the pre-introduction of a trifluoromethyl group onto an "aromatic to be" carbon has rarely been addressed. It has been found that 4-trifluoromethyl-\(p\)-quinol silyl ethers, the readily available and relatively stable compounds, can act as dielectrophiles to be applied to multi-component reactions for the synthesis of various trifluoromethylated arenes. Catalyzed by In(OTf)\(_3\), 4-trifluoromethyl-\(p\)-quinol silyl ethers react with C-, N-, and S-nucleophiles, respectively, in a regiospecific 1,2-addition manner to generate the corresponding highly reactive electrophilic intermediates. Further reaction of the in-situ generated electrophiles with a C-nucleophile followed by spontaneous aromatization enables the construction of functionalized trifluoromethyl arenes. This three-component, double nucleophilic addition/aromatization reaction based on the pre-introduction of a trifluoromethyl group onto an "aromatic to be" carbon provides a divergent strategy for the synthesis of trifluoromethylated arenes under mild reaction conditions in a single operation.

In the last decade, the introduction of fluorine-containing groups\(^{1–23}\) into organic molecules has become a major research focus. Trifluoromethyl containing motifs in an aromatic system are common pharmacophores (Fig. 1)\(^{1,2,24–30}\) and there is a great current interest in the discovery of trifluoromethylation methods upon electrophilic and radical trifluoromethylations of arenes and heteroarenes as a consequence of advances in catalysis\(^{3–9}\), and new trifluoromethylating reagents and methods\(^{6–13}\). Such growth based on the late-stage introduction of a trifluoromethyl group onto an aryl ring is in stark contrast to the synthetic applications of trifluoromethyltrimethylsilane (TMSCF\(_3\), also known as Ruppert–Prakash reagent)\(^{14,15}\), as notably less toxic, relatively cheaper, and widely accepted nucleophilc trifluoromethylating reagent, in the synthesis of trifluoromethylated arenes based on the pre-introduction of a trifluoromethyl group onto a "aromatic to be" substrate\(^{1–19}\).

Due to the high electronegativity of fluorine, the nucleophilic CF\(_3\) species are considered as hard nucleophiles, which usually undergo 1,2-addition reactions with \(\alpha,\beta\)-unsaturated carbonyl compounds\(^{16–20,31,32}\), including divinyl ketones\(^{20}\) and \(p\)-quinones\(^{31–33}\). In 1989, Stahly and Bell described the monotrifluoromethylation of \(p\)-quinones with Et\(_3\)SiCF\(_3\) and the further transformation to otherwise hardly accessible (trifluoromethyl)phenols by treatment of the adducts, 4-(trifluoromethyl)-\(p\)-quinol silyl ethers, (or the corresponding alcohols, 4-(trifluoromethyl)-\(p\)-quinols) by dissolving metal reduction (Fig. 2a)\(^{31}\). Stahly’s method provides the first example for the synthesis of trifluoromethylated arenes based on nucleophilic trifluoromethylation of non-aromatic precursors. Although Stahly’s method is limited to a few of simple trifluoromethylated alkyl phenols (3 examples) and uses two equivalents of zinc as the reductant, this method opened a route for the synthesis of trifluoromethylated arenes from simple precursors via the bond formation between the CF\(_3\) group and the “aromatic to be” carbon\(^{11,12,31–35}\).

In our recent research on the synthesis of trifluoromethylated arenes using the readily available 4-(trifluoromethyl)-\(p\)-quinones as non-aromatic precursors, a new reaction, the 1,3-carbothiolation/aromatization of 4-(trifluoromethyl)-\(p\)-quinols, has been developed\(^{32}\). This reaction enables two different nucleophiles, a thiol and a carboxyl nucleophile generated in situ from ketene dithioacetals\(^{36,37}\), to be introduced on "aromatic to be"...
carbons\textsuperscript{31–35} in the \textit{ortho} and \textit{para} positions of the \textit{CF}_3 group of 4-(\textit{trifluoromethyl})-\textit{p}-quinol s via a novel \textit{meta}-double functionalization fashion (Fig. 2b)\textsuperscript{32}. Encouraged by the advantage of the 1,3-carbothiolation/aromatization reaction, such as readily available substrates\textsuperscript{31–33,38,39}, operational simplicity, and double functionalization on the “aromatic to be” carbons in a single operation\textsuperscript{32–35}, we pursued the three-component, double nucleophilic addition/aromatization reaction of 4-(\textit{trifluoromethyl})-\textit{p}-quinol silyl ethers as dielectrophiles with two nucleophiles, named \textit{Nu1} and \textit{Nu2} (Fig. 2c). In the double nucleophilic addition/aromatization reactions, \textit{Nu1} can be a S-, N-, or C-nucleophile that attacks, in a regiospecific 1,2-addition manner, at the carbonyl carbon of a 4-(\textit{trifluoromethyl})-\textit{p}-quinol silyl ether to form a highly reactive electrophilic intermediate as the crucial step. As a result, the subsequent nucleophilic addition of \textit{Nu2} to the \textit{in-situ} generated electrophilic intermediate followed by spontaneous aromatization can lead to a functionalized trifluoromethyl arene. Herein we present these three-component, double nucleophilic addition/aromatization reactions using 4-(\textit{trifluoromethyl})-\textit{p}-quinol silyl ethers as the versatile dielectrophilic “aromatic to be” precursors. These approaches allow a variety of functional groups, including an alkylthio, an amino, an aryl group or various carbonyl methyl groups to be introduced onto the “aromatic ring” in a single operation under mild reaction conditions (Fig. 2c).

Results and Discussion

Three-component, double nucleophilic 1,3-carbothiolation/aromatization reactions using active methylenes as C-nucleophiles. 4-(\textit{Trifluoromethyl})-\textit{p}-quinol silyl ethers \textit{1} can be prepared in high yields with the readily available \textit{p}-quinones\textsuperscript{38,39} as electrophiles and TMS\textsubscript{CF}_3 as the nucleophile\textsuperscript{16–19,31,32}. In the present research, the three-component reactions of 4-(\textit{trifluoromethyl})-\textit{p}-quinol silyl ether \textit{1a} as double electrophile\textsuperscript{32}, 1-dodecanethiol as S-nucleophile (\textit{Nu1})\textsuperscript{25–27,40} and acetone \textit{2a} as C-nucleophile (\textit{Nu2}) were first examined (Fig. 3). As a result, the desired product, a trifluoromethyl arene \textit{3aa}, was obtained in moderate yield (Fig. 3, entry 1) under identical reaction conditions as the previous work, catalyzed by indium(III) trifluoromethanesulfonate (In(OTf)_3) in the solvent, 1,2-dichloroethane (DCE) in the presence of trimethylsilyl chloride (TMSCl) as additive at 70 °C\textsuperscript{32}. Under similar reaction conditions as above but in the absence of TMSCl, \textit{3aa} was obtained in lower yield along with arylsulfide \textit{10a} as the minor product formed through 1,3-dithiolation/aromatization (Fig. 3, entry 2), showing the beneficial effect of TMSCl on the formation of \textit{3aa}.

Whereas, under identical conditions as in Fig. 3, entry 1 but at room temperature, \textit{3aa} was produced in high yield (Fig. 3, entry 3). Similar result was obtained by using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as the additive (Fig. 3, entry 5). Lowing the loading of In(OTf)_3 (Fig. 3, entry 6) or the reaction temperature (Fig. 3, entry 4), resulted in the decrease of the yields of \textit{3aa}. Among the solvents tested, DCE gave the highest yield of \textit{3aa} (Fig. 3, entry 3) in comparison with dichloromethane (DCM, Fig. 3, entry 7), acetonitrile (Fig. 3, entry 8) or THF (Fig. 3, entry 9). With the optimal conditions (Fig. 3, entry 3) in hand, the scope of the three-component, double nucleophilic 1,3-carbothiolation/aromatization reaction of 4-(\textit{trifluoromethyl})-\textit{p}-quinol silyl ether \textit{1a} with 1-dodecanethiol as S-nucleophile (\textit{Nu1}) and active methylenes \textit{2} as C-nucleophiles (\textit{Nu2}) were next examined and the results are summarized in Fig. 4. As shown in Fig. 4, various acyclic aliphatic ketones \textit{2a–g} can be applied as the C-nucleophiles to give the desired functionalized trifluoromethyl arenes (Fig. 4, entries 1–7), despite the yield of \textit{3ae} was low due to the steric hindrance of 3,3-dimethylbutan-2-one \textit{2e} as the C-nucleophile (Fig. 4,
entry 5). In comparison, the less hindered 3-methylbutan-2-one 2d can react smoothly to enable the formation of 3ad in high yield (Fig. 4, entry 4) and has an excellent regioselectivity with preferred C–C bond formation at the more substituted carbon of aliphatic ketones 2 (see Fig. 4, entries 2, 4, 6 and 7) via a double nucleophilic 1,3-carbothiolation/aromatization sequence.

In the cases of cyclic aliphatic ketones 2h–l as the C-nucleophiles, the desired product 3al, was obtained in high yield by using cycloheptanone 2l as the Nu2 component in the presence of 50 mol% of In(OTf)3 (Fig. 4, entry 12). Whereas, the corresponding 3ah–3aj and 3ak/3ak′ were produced in low to moderate yields under identical conditions (Fig. 4, entries 8–11) because cyclohexanone is structurally more rigid than either cycloheptanone and acyclic aliphatic ketones, which makes cyclohexanone less reactive towards the C–C bond formation41–43.

The three-component reaction mentioned above provides a convenient access to α-aryl ketones41,42,44–49 having a trifluoromethyl group on the aryl ring (Fig. 1)24,27 in a single operation50–55. Various methyl aryl ketones including acetophenone 2m, methyl aryl ketones bearing either electron-donating (2n and 2o) and electron-withdrawing groups (2p and 2q), 1-(thiophen-2-yl)ethanone 2r, and 2-chloro-1-phenylethanone 2s were proven the suitable

Figure 2. Synthesis of trifluoromethylated arenes based on “aromatic to be" strategy.
C-nucleophiles for the three-component reaction to deliver the desired products 2m–2s in good to high yields in most cases (Fig. 4, entries 13–19). In addition, trifluoromethylated 2-aryl-1-phenylpropan-1-ones 3at–3av (Fig. 4, entries 20–22) were prepared in good yields by using propiophenone 2t and propiophenones 2u and 2v possessing either an electron-rich (2u) and an electron-poor aryl group (2v) as the C-nucleophiles, respectively. Furthermore, the corresponding formal α-arylation products 3aw–3aa2 of 1-arylpropan-2-ones (2w and 2x as C-nucleophiles) and a variety of β-dicarbonyl compounds (acetoacetone 2y, ethyl acetoacetate 2z, ethyl 3-oxopentanoate 2a1, and 3-methyl acetoacetone 2a2 as C-nucleophiles) were obtained in moderate to excellent yields, respectively (Fig. 4, entries 23–28).

The above three-component reactions (Fig. 4) showed the generality of the active methylene components as the C-nucleophiles (Nu2) for their reactions with 1a as the 1,3-dielectrophile and 1-dodecanethiol as the S-nucleophile (Nu1). It was proved that phenylmethanethiol is also an efficient S-nucleophile for the above reaction (Fig. 4, entries 29 and 30). As an extension of the 4-(trifluoromethyl)-p-quinol silyl ether components 1, the desired trifluoromethylated arene products, such as trifluoromethylated naphthalene 3ba and 3bc, trifluoromethylated 2-aryl-pentan-3-one 3cc and 3dc bearing 3-tBu and 3-methyl group respectively on the benzene ring were prepared in good to high yields under similar reaction conditions using 4-(trifluoromethyl)-p-quinol silyl ethers 1b, 1c and 1d as the 1,3-dielectrophiles, respectively (Fig. 4, entries 31–34). In addition, pentafluoroethylated 2-aryl-pentan-3-one 3ec was also prepared in high yield from the reaction of 4-(pentafluoroethyl)-p-quinol silyl ether 1e as the 1,3-dielectrophile with 1-dodecanethiol and pentan-3-one 2c (Fig. 4, entry 35).

Three-component, double nucleophilic carbothiolation/aromatization reactions using electron-rich arenes as C-nucleophiles. The regioselective double nucleophile 1,3-addition/aromatization reaction mentioned above provides an easy access to a broad range of α-(ortho-trifluoromethyl/pentafluoroethyl-aryl) carbonyl compounds 3 using various active methylene compounds as C-nucleophiles (Fig. 4). Fortunately, when the double nucleophilic addition/aromatization reaction was performed using electron-rich aromatic compounds 4 as the C-nucleophiles (π-nucleophiles), trifluoromethylated biaryls28,29 were obtained under similar reaction conditions for the synthesis of 3, whereas at elevated temperatures (Fig. 5).

Although numerous trifluoromethylated aromatic compounds have been prepared1–13,24–26,28–30, few of them are trifluoromethylated biaryls (Fig. 1)3,11,12,28–30,56–61, which were usually synthesized, for example, by cross-coupling of the corresponding biarylhalides1,11,12,56 or biaryl boronic acids37 with related trifluoromethylated species, Suzuki–Miyaura coupling of trifluoromethylphenylboronic acid with aryl bromides38, and direct arylation of trifluoromethyl benzene with aryl bromides to give a mixture of para- and meta-products59,60, respectively.

It was found that, under the optimal conditions (Fig. 3, entry 3) but at 60 °C, a mixture of trifluoromethylated biaryls 3aa and 3aa′ was produced in excellent overall yields by the three-component reaction of 1a, 1-dodecanethiol as the S-nucleophile and 1,3,5-trimethoxybenzene 4a as the C-nucleophile via double...
nucleophilic additions at the 1,3- and 1,2-positions of 1a, respectively (Fig. 5, entry 1). Similar results were obtained by using phenylmethanethiol as the S-nucleophile (Fig. 5, entry 2). Under identical conditions as above, the desired trifluoromethylated biaryl compounds 5ba/5ba', 5ab/5ab', 5ac/5ac', and 5bf/5bf' were also prepared in moderate to high yields (Fig. 5, entries 3–8). The structure of 5ad/5ad' was confirmed by Nuclear Overhauser Enhancement Spectroscopy (for details, please see the supplementary information). In comparison, trifluoromethylated biaryls 5ag was produced in moderate yield by using mesitylene (20 equiv) 4g as the C-nucleophile, (Fig. 5, entry 9). In this case, no the corresponding regioisomer 5ag', could be observed. The

Figure 4. The scope of active methylenes as C-nucleophiles. Reaction conditions: 4-((trifluoromethyl)-p-quinol silyl ether 1a (0.6 mmol), RSH (0.5 mmol), 3 (1.5 mmol), In(OTf)3 (0.15 mmol), TMSCl (1.0 mmol), DCE (3 mL), 25 °C, 6–8 h. (A) 0.25 mmol of In(OTf)3 was used.
above results (Fig. 5) showed that the readily available 4-(trifluoromethyl)-p-quinol silyl ethers 1 can also act as the “aromatic to be” precursors of trifluoromethylated biaryl compounds.

**Pseudo three-component, double nucleophilic addition/aromatization reactions using electron-rich arenes as C-nucleophiles.** In the case of using 1,3-dimethoxybenzene 4i as the C-nucleophile and performing the reaction of 1a with 4i (6 equiv) at 80 °C for 5 h in the absence of a thiol, the double nucleophilic addition/aromatization products, m-terphenyl compound, 6 and 6' were obtained in good overall yield as a 1:1 mixture (Fig. 6)[62]. This pseudo-three component reaction provides an efficient route to trifluoromethylated m-terphenyl and o-terphenyl compounds, respectively (Fig. 1).

**Three-component, double nucleophilic 1,3-carboamination/aromatization reactions.** Promoted by the successful synthesis of functionalized trifluoromethyl arenes 3 (Fig. 4), trifluoromethylated biaryl compounds 4 (Fig. 5), and trifluoromethylated terphenyls 6 (Fig. 6), the three-component reaction using an amine component 7 as the N-nucleophiles (Nu1) was examined. Optimization of the reaction conditions for the model reaction of 1a, 4-methylbenzenesulfonamide 7a (TsNH2), and pentan-3-one 2c led to the formation of the desired product, benzenesulfonamide 8aa, in good yield (Fig. 7, entry 1), while 8aa was obtained in 28% isolated yield without the addition of TMSCl (2.0 equiv) as the additive. In comparison, trifluoromethylated sulfonamides 8ba–8da were obtained in relatively lower yields by using methanesulfonamide 7b, benzenesulfonamide 7c, and 4-chlorobenzenesulfonamide 7d as the N-nucleophiles, respectively (Fig. 7, entries 2–4). Furthermore, the desired trifluoromethylated sulfonamides 8ab/8ab', 8ac, and 8ad were prepared in moderate to high yields (Fig. 7, entries 5–7).

**Reaction mechanism.** To our knowledge, there have been no reports so far of 1,3-carboamination reaction[33,63–67]. To understand the mechanism for the formation of 8, the reaction of 1a with TsNH2, 7a was performed under the identical conditions as used for the synthesis of 8 (Fig. 7) but in the absence of a C-nucleophile. As a result, imine 9 was produced in 35% yield along with 4-(trifluoromethyl)-p-quinol in 32% yield (Fig. 8a). Furthermore, it was proven that 8aa could be formed by the reaction of 9 with pentan-3-one 2c (Fig. 8b),

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**Figure 5. Synthesis of trifluoromethylated biaryl compounds.** Reaction conditions: 4-(trifluoromethyl)-p-quinol silyl ether 1a (0.6 mmol), RSH (0.5 mmol), 4 (1.5 mmol), In(OTf)3 (0.15 mmol), TMSCl (1.0 mmol), DCE (3 mL), 60 °C, 4–6 h. (A) 20 equiv of mesitylene 4h was used.
indicating that imine 9 or the 1,2-adduct of 7 with 1a (Fig. 9) might be the intermediate for the formation of 8aa in the three-component, 1,3-carboamination/aromatization reactions (Fig. 7).

Accordingly, a possible mechanism for the formation of 8 was proposed (Fig. 9), with the reaction of 1a with 7a (RNH₂) and 2c (Nu₂) as an example, which involves (1) formation of complex I from 1a, In(OTf)₃ and RNH₂ along with the release of HOTf; (2) 1,2-addition of RNH at the carbonyl group of I in a pseudointramolecular manner to give intermediate II along with the regeneration of the catalyst, In(OTf)₃; (3) attack of the π-nucleophile 2c′...
(generated in-situ from ketone 2c with TMSCl) at C3 of II in a S$_3$2' manner with the release of TMSOH to afford intermediate III$^{43}$, and finally, (4) the release of TMSOH driven by aromatization gives 8 (Fig. 9)$^{32,43}$.

The proposed mechanism (Fig. 9) tells that the regioselective nucleophilic 1,2-addition (I $\rightarrow$ II) is the crucial step for the three-component, double nucleophilic addition/aromatization reaction$^{32}$. On the other hand, the addition of TMSCl as an additive is important (Fig. 3) for the activation of ketones through the formation of siloxyalkenes (Figs 4 and 7)$^{43,63-67}$. Therefore, the formation of trifluoromethylated terphenyls 6 using 1,3-dimethoxybenzene 4i as Nu1 should follow a similar mechanism, in which, the 1,2-addition of 4i at the carbonyl group of complex IV (Fig. 10) is to be involved. In this case, complex IV should be formed at first and this mechanism can also be used to interpret the formation of $\sigma$-terphenyl product 6' by the generation of complex V.
Furthermore, the formation of trifluoromethylated biaryls 5′ (Fig. 5) via 1,2-carbothiolation/aromatization is easy to understand.

In summary, it has been found that the readily available and relatively stable 4-trifluoromethyl-p-quinol silyl ethers are useful dielectrophiles in tandem and/or multi-component reactions. The three-component reactions of 4-trifluoromethyl-p-quinol silyl ethers with two nucleophiles provide a convenient access to a wide variety of trifluoromethylated arenes in a single operation under mild reaction conditions. The regioselective nucleophilic 1,2-addition of a nucleophile (Nu1) to a 4-trifluoromethyl-p-quinol silyl ether enables the formation of a highly reactive electrophilic intermediate, and thus create a useful template for further elaboration to highly functionalized arenes in a concise process. Further works focused on the synthetic applications of these dielectrophiles and analogues are in progress.

Methods

Detailed experimental procedures, analytical and spectral data for all the new compounds and crystallographic data, see Supplementary Information.

General procedure for the synthesis of 3,5,6,8 (taking 3aa as an example). To the solution of 4-(trifluoromethyl)-4-((trimethylsilyl)oxy)cyclohexa-2,5-dienone 1a (150 mg, 0.60 mmol) and propan-2-one 2a (111 μL, 1.5 mmol) in DCE (1 mL) was added TMSCl (126 μL, 1 mmol) and In(OTf)₃ (85 mg, 0.15 mmol). Then, DCE solution (2 mL) of dodecan-1-thiol (120 μL, 0.5 mmol) was added dropwise within 40 min. After the reaction was finished as indicated by TLC (reaction time, 8 h), the resulting mixture was poured into water (20 mL) and extracted with DCM (CH₂Cl₂, 20 mL × 3). The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (EtOAc/PE = 1: 120) to afford 3aa (145 mg, 72%) as a white solid (m.p. 57–58 °C).

1H NMR (500 MHz, CDCl₃): δ 0.88 (t, J = 7.0 Hz, 3H), 1.26–1.30 (m, 16H), 1.40–1.45 (m, 2H), 1.65–1.71 (m, 2H), 2.19 (s, 3H), 2.95 (t, J = 7.5 Hz, 2H), 3.85 (s, 2H), 7.11 (s, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H).

13C NMR (125 MHz, CDCl₃): δ 14.1, 22.7, 28.6, 28.8, 29.1, 29.3, 29.4, 29.5 (2), 29.6 (2), 31.9, 32.0, 47.2, 124.9 (CF₃, q, J = 271.4 Hz), 125.1, 125.2 (q, J = 30.1 Hz), 126.4 (q, J = 5.4 Hz), 130.6, 133.1, 143.2, 204.2. HRMS (ESI-TOF) Calcd for C₂₂H₃₄F₃OS (M + H)⁺ 403.2277. Found 403.2284.

Figure 10. Proposed mechanism for the formation of 6′.
6. Chu, L. & Qing, F.-L. Oxidative trifluoromethylation and trifluoromethylthiolation reactions using (trifluoromethyl)trimethylsilane as a nucleophilic CF₃ source. Acc. Chem. Res. 47, 1513–1522 (2014).
7. Merino, E. & Nevado, C. Addition of CF₃ across unsaturated moieties: a powerful functionalization tool. Chem. Soc. Rev. 43, 6598–6608 (2014).
8. Charpentier, J., Fruh, N. & Togni, A. Electrophilic trifluoromethylation by use of hypervalent iodin reagents. Chem. Rev. 115, 650–682 (2015).
9. Ni, C., Hu, M. & Hu, J. Good partnership between sulfur and fluorine: sulfur-based fluorination and fluoroalkylation reagents for organic functionalization. Chem. Rev. 115, 765–825 (2015).
10. Fujimura, Y. et al. Practical and innate carbon-hydrogen functionalization of heterocycles. Nature 492, 95–99 (2012).
11. Tomashenko, O. A. & Grushin, V. V. Aromatic trifluoromethylation with metal complexes. Chem. Rev. 111, 4475–4521 (2011).
12. Wu, X.-F., Neumann, H. & Beller, M. Recent developments on the trifluoromethylation of (hetero)arenes. Chem. Asiam J. 7, 1777–1784 (2012).
13. Sato, A. et al. Introducing a new radical trifluoromethylation reagent. Chem. Commun. 51, 5967–5970 (2015).
14. Ruppert, I., Schlich, K. & Volbach, W. Die ersten CF₃-substituierten organyl(chlor)silane. Angew. Chem. Int. Ed. 53, 1324–1327 (2014).
15. Satanschi, N. & Gilmour, R. The (not so) ephemeral trifluoromethanide anion. Angew. Chem. Int. Ed. 53, 11414–11415 (2014).
16. Liu, X., Xu, C., Wang, M. & Liu, Q. Trifluoromethyltrimethylsilane: nucleophilic trifluoromethylation and beyond. Chem. Rev. 115, 683–730 (2015).
17. Sato, A. et al. Introducing a new radical trifluoromethylation reagent. Chem. Commun. 51, 5967–5970 (2015).
18. Dilman, A. D. & Levin, V. V. Nucleophilic trifluoromethylation of C=S bonds with terminal alkyne to α,α'-unsaturated carbonyl compounds. Org. Lett. 15, 6242–6245 (2013).
19. Dong, J., Pan, L., Xu, X. & Liu, Q. Palladium-catalyzed insertions of aryne into C–S bond: synthesis of functionalized 2-quinolinoines. Angew. Chem. Int. Ed. 53, 3442–3446 (2014).
20. Zeng, Y. et al. Silver-mediated trifluoromethylation–iodination of arynes. J. Am. Chem. Soc. 135, 2955–2958 (2013).
21. Zeng, Y. & Hu, J. Silver-catalyzed formal insertion of arynes into R=I bonds. Chem. Eur. J. 20, 8866–8870 (2014).
22. Pan, L., Bi, X. & Liu, Q. Recent developments of ketene dithioacetal chemistry. Chem. Soc. Rev. 42, 1251–1286 (2013).
23. Zhang, L., Dong, J., Xu, X. & Liu, Q. Chemistry of ketene N,S-acetals: an overview. J. Org. Chem. 81, 3121–3124 (2016).
24. Owton, W. M. The synthesis of quinones. J. Chem. Soc. Perkin Trans. 1, 2409–2420, doi: 10.1039/A707426C (1996).
25. Abraham, I., Joshi, R., Pardasani, P. & Pardasani, R. T. Recent advances in 1,4-benzoquinone chemistry. J. Braz. Chem. Soc. 22, 385–421 (2011).
26. Shalty, G. P. & Bell, D. R. A new method for synthesis of trifluoromethyl-substituted phenols and anilines. J. Org. Chem. 54, 2873–2877 (1989).
27. Liu, X. et al. 1,3-Carbothiolation of (trifluoromethyl)-p-quinoins: a new access to functionalized (trifluoromethyl)arenes. Org. Lett. 15, 6242–6245 (2013).
28. Dong, J., Liu, R., Chen, P., Liu, Q. & Wang, M. Palladium-catalyzed insertion of aryne into C–S bond: synthesis of functionalized 2-quinolinoines. Angew. Chem. Int. Ed. 53, 3442–3446 (2014).
29. Nishide, K., Ohsugi, S., Shiraki, H., Tamakita, H. & Node, M. Use of odorless thios equivalent: formal asymmetric Michael addition of hydrogen sulfide to α,α'-unsaturated carbonyl compounds. Org. Lett. 3, 3121–3124 (2001).
30. Huang, X., Patil, M., Fares, C., Thiel, W. & Maulide, N. Sulfur(VI)-mediated transformations: from ylide transfer to metal-free arylation of carbonyl compounds. J. Am. Chem. Soc. 115, 7312–7323 (2013).
31. Huang, X. & Maulide, N. Sulfide-mediated α-arylation of carbonyl compounds. J. Am. Chem. Soc. 133, 8510–8513 (2011).
32. Guo, X. & Mayr, H. Functionalization of the ambient electrophilicities of halogen-substituted quinones. J. Am. Chem. Soc. 136, 11499–11512 (2014).
33. Bellina, F. & Rossi, R. Transition metal-catalyzed direct arylation of substrates with activated sp³-hybridized C–H bonds and some of their synthetic equivalents with aryl halides and pseudohalides. Chem. Rev. 110, 1082–1146 (2010).
34. Wu, G., Deng, Y., Wu, C., Zhang, Y. & Wang, J. Near-IR-triggered, remote-controlled release of metal ions: a novel strategy for caged ions. Angew. Chem. Int. Ed. 53, 10678–10681 (2014).
35. Yu, Z. et al. Highly site-selective direct C–H bond functionalization of phenols with α-aryl-α-diazoacetates and diazo oxindoles via gold catalysis. J. Am. Chem. Soc. 136, 6904–6907 (2014).
36. Ia, Z. et al. An alternative to the classical C–H activation: the transfer of an intact 2-iodosilyl from Ar[O(2,4,6-CCF₃)]₂. Angew. Chem. Int. Ed. 53, 11298–11301 (2014).
37. Murphy, S. K., Bruch, A. & Dong, V. M. Substrate-directed hydroacylation: rhodium-catalyzed coupling of vinylphenols and nonchelating aldehydes. Angew. Chem. Int. Ed. 53, 2453–2459 (2014).
38. Alemán, J., Cabrera, S., Maerten, E., Overgaard, J. & Jørgensen, K. A. Asymmetric organocatalytic α-arylation of aldehydes. Angew. Chem. Int. Ed. 46, 5520–5523 (2007).
39. Dömling, A., Wang, W. & Wang, K. Chemistry and biology of multicomponent reactions. Chem. Rev. 112, 3083–3135 (2012).
40. Tietze, L. E. Domino reactions in organic synthesis. Chem. Rev. 96, 115–136 (1996).
41. Zhu, J. & Bienaymé, H. Multicomponent reactions (WILEY-VCH, 2005).
42. Dömling, A., Wang, W. & Wang, K. Chemistry and biology of multicomponent reactions. Chem. Rev. 112, 3083–3135 (2012).
43. Tietze, L. E. Domino reactions in organic synthesis. Chem. Rev. 96, 115–136 (1996).
44. Zhu, J. & Bienaymé, H. Multicomponent reactions (WILEY-VCH, 2005).
45. Ramón, D. J. & Yus, M. Asymmetric multicomponent reactions (AMCRs): the new frontier. Angew. Chem. Int. Ed. 44, 1602–1634 (2005).
46. Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem. Rev. 106, 17–89 (2006).
55. Tejedor, D. & García-Tellado, F. Chemo-differentiating ABB′ multicomponent reactions. Privileged building blocks. *Chem. Soc. Rev.* **36**, 484–491 (2007).
56. Dubinina, G. G., Furutachi, H. & Vicic, D. A. Active trifluromethylation agents from well-defined copper(I)–CF₃ complexes. *J. Am. Chem. Soc.* **130**, 8600–8601 (2008).
57. Chu, L. & Qing, F. L. Copper-mediated oxidative trifluoromethylation of boronic acids. *Org. Lett.* **12**, 5060–5063 (2010).
58. Walker, S. D. et al. Development of a scalable synthesis of a GPR40 receptor agonist. *Org. Process Res. Dev.* **15**, 570–580 (2011).
59. Wang, Y.-N. et al. Pd(OAc)₂ catalyzed direct arylation of electron-deficient arenes without ligands or with monoprotected amino acid assistance. *Chem. Commun.* **48**, 10437–10439 (2012).
60. Zhou, Q. et al. Imino-N-heterocyclic carbene palladium(II) complex-catalyzed direct arylation of electron-deficient fluoroarenes with “on and off” chelating effect assistance. *Organometallics* **34**, 1021–1028 (2015).
61. Guo, X.-Q., Zhu, X.-H., Li, Z.-M. & Hou, X.-F. An efficient one-pot two-step three-component process for the synthesis of perfluorooalkylated biphenyls. *Tetrahedron* **71**, 820–825 (2015).
62. Sosnovskikh, V. Y., Korotaev, V. Y., Barkov, A. Y., Kutyashv, I. B. & Safrygin, A. V. One-pot domino synthesis of polyfunctionalized benzophenones, dihydroxanthones, and m-terphenyls from 2-(polyfluoroalkyl)chromones. *Eur. J. Org. Chem.* 1932–1944 (2015).
63. Schulz, D. M. & Wolfe, J. P. Recent developments in palladium-catalyzed alkene amination/arylation reactions for the synthesis of nitrogen heterocycles. *Synthesis* **44**, 351–361 (2012).
64. Shi, J., Qiu, D., Wang, J., Xu, H. & Li, Y. Domino aryle precursor: efficient construction of 2,4-disubstituted benzoazoles. *J. Am. Chem. Soc.* **137**, 5670–5673 (2015).
65. White, D. R. & Wolfe, J. P. Synthesis of polymeric nitrogen heterocycles via cascade Pd-catalyzed alkene carboamination/Diels–Alder reactions. *Org. Lett.* **17**, 2378–2381 (2015).
66. Hopkins, B. A. & Wolfe, J. P. Enantioselective synthesis of tetrahydroquinolines, tetrahydroquinoloxalines, and tetracyclodiquinolines via Pd-catalyzed alkene carboamination reactions. *Chem. Sci.* **5**, 4840–4844 (2014).
67. Yoshino, Y., Kurahashi, T. & Matsubara, S. Nickel-catalyzed decarboxylative carboamination of alkynes with isatoic anhydrides. *J. Am. Chem. Soc.* **131**, 7494–7495 (2009).
68. Zhang, J. et al. A variation of the Fischer indolization involving condensation of quinone monoketals and aliphatic hydrazines. *Angew. Chem. Int. Ed.* **52**, 1753–1757 (2013).

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**Author Contributions**

Q.L. and L.P. conceived, designed, supervised the project and wrote the paper. J.D. and L.S. undertook the experimental work. J.D., X.X., L.P. and Q.L. analyzed the results.

**Additional Information**

Accession codes: The X-ray crystallographic data of 5ba′, 6 and 8aa have been deposited at the Cambridge Crystallographic Data Centre with CCDC number 1404120–1404122, which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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