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Three-component carboarylation of unactivated imines with arynes and carbon nucleophiles

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With 2-(trimethylsilyl)aryl triflates as aryne precursors, an unprecedented three-component carboarylation reaction of unactivated imines with arynes and carbon nucleophiles has been developed to access a variety of functionalized tertiary amines under transition metal-free conditions. Suitable carbon nucleophiles include chloroform, acetonitrile, and methyl propiolate.

Arynes are highly electrophilic species that serve as targets toward nucleophilic addition in a number of cascade reactions in the absence of transition metals, leading to complex organic molecules.¹ Notably, the scope of nucleophiles has been expanded to some unusual ones such as unactivated imines, addition of which to arynes provides convenient access to iminium zwitterions having activated carbon-nitrogen double bonds. In 2006, Yoshida, Kunai, and coworkers disclosed the use of iminium zwitterions to capture carbon dioxide to yield benzoxazinones (Scheme 1).² Recently, Hwu and coworkers reported that iminium zwitterions bearing electronwithdrawing groups could undergo proton transfer to generate azomethine ylides, which subsequently underwent [3+2] cycloaddition with the original imines or electron-deficient alkenes.³ In these cases, iminium zwitterion intermediates were intercepted by double bonds to yield nitrogen-containing heterocycles.^{4,5} Inspired by these reports, we envisioned that iminium zwitterions could deprotonate some nucleophiles and the resulting activated nucleophiles would undergo addition to the activated carbon-nitrogen double bonds (Scheme 1).⁶ Clearly, it constitutes a formidable challenge to minimize or even obviate the addition of nucleophiles to arynes in the proposed three-component reaction of unactivated imines with arynes and nucleophiles.



This work:



Scheme 1 Three-component reactions involving unactivated imines and arynes.

While chloroform, an inexpensive bulk chemical used frequently as a solvent, traditionally serves as a dichlorocarbene source under basic conditions, sporadic examples have shown that it can undergo deprotonation followed by addition to activated imines, such as N-sulfonyl imines and N-sulfinyl imines, to yield amine derivatives bearing a trichloromethyl group.7 It is noteworthy that the trichloromethyl group exists in a number of biologically relevant compounds.⁸ Consequently, we selected chloroform as a nucleophile to develop the three-component reaction proposed in Scheme 1. Using 2-(trimethylsilyl)phenyl triflate (2a) (1.2 equiv) as a benzyne precursor,⁹ we surveyed a few fluoride sources, such as cesium fluoride, potassium fluoride, sodium fluoride, and tetrabutylammonium fluoride, in the model reaction of imine 1a and chloroform in dry acetonitrile under nitrogen at 50 °C (eqn (1)) and found that the use of cesium fluoride afforded 2,2,2-trichloroethanamine 3a in the best yield (45%).¹⁰ Importantly, addition of chloroform to benzyne was not observed at all. The yield was not enhanced simply by screening a few other common solvents such as toluene, 1,2-dichloroethane, chloroform, and tetrahydrofuran. Elevating the temperature to 65 °C improved the yield to 68%,

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and moreover, increasing the amount of benzyne precursor 2a to 1.5 equiv further improved the yield to 81%.



A range of aliphatic and aromatic imines smoothly underwent three-component carboarylation with benzyne precursor 2a and chloroform in the presence of cesium fluoride to afford structurally diverse 2,2,2trichloroethanamines in moderate to good yields (Scheme 2, 3a-r). Both acyclic and cyclic unactivated imines served as suitable substrates. It is noteworthy that the reaction worked well with sterically bulky imines, aromatic imines bearing electron-donating groups, and unactivated imines bearing a variety of N-substituents such as an alkyl group, a benzyl group, an allyl group, a propargyl group, and an aryl group. In some cases the yields were moderate simply owing to unsatisfactory conversion of the starting imines judging by TLC analysis. On the other hand, the chemistry was extended to a few 2-(trimethylsilyl)aryl triflates bearing either electrondonating groups or electron-withdrawing groups (Scheme 2, 3s-x). It is noteworthy that the regioselectivity highly depends on the position of substituents in the in situ generated unsymmetrical arynes. While the reaction with 4methylbenzyne gave poor regioselectivity (Scheme 2, 3s and 3s'), a single regioisomer was obtained from the reaction with 3-methoxybenzyne (Scheme 2, 3w).²





Scheme 2 Three-component reaction of imines, arynes, and chloroform. ^a Reaction conditions: 1 (0.20 mmol), 2 (0.30 mmol), CsF (0.60 mmol), chloroform (0.3 mL), acetonitrile (0.3 mL), 65 $^{\circ}\text{C},$ 10 h. b Isolated yields were given. ^c Aryne precursors for the synthesis of **3s-x**: 4-methyl-2-(trimethylsilyl)phenyl triflate (2b), 4,5-dimethyl-2-4,5-dimethoxy-2triflate (trimethylsilyl)phenyl (2c), (trimethylsilyl)phenyl triflate (2d), 4,5-difluoro-2-(trimethylsilyl)phenyl triflate (2e), 3-methoxy-2-(trimethylsilyl)phenyl triflate (2f), and 3-(trimethylsilyl)naphthalen-2-yl triflate (2g).

In contrast, 2,2-dichloroethenamines rather than 2,2,2trichloroethanamines were obtained from the reaction with aromatic imines bearing electron-withdrawing groups such as a trifluoromethyl group, a cyano group, a sulfonyl group, and a nitro group (Scheme 3). In most cases the yields were moderate due to unsatisfactory conversion of the starting imines. Notably, the reaction was highly sensitive to the position of an electron-withdrawing group on the benzene ring. While para- and meta-substituted aromatic imines reacted well with benzyne precursor 2a and chloroform to 2,2-dichloroethenamines, afford the desired the corresponding reaction with an ortho-substituted one just provided a complex mixture probably because of the steric hindrance imposed on the formation of the carbon-carbon double bond.



To gain insights into the reaction mechanism, we treated imine 1a and benzyne precursor 2a with deuterated chloroform under the standard conditions and observed complete deuterium incorporation at the ortho-position of the phenyl group in the desired product **3a-D1** according to ¹H NMR spectroscopic analysis and HRMS spectrometric analysis (eqn (2)).¹⁰ This result substantially supports that the iminium

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zwitterion shown in Scheme 1 abstracts a proton from chloroform during the reaction. While no 2.2dichloroethenamine product was obtained from the threecomponent reaction with an aromatic imine bearing an electron-donating group such as a methoxy group, we found that treatment of 2,2,2-trichloroethanamine 3d with 2 equiv of fluoride led to the formation cesium of 2.2dichloroethenamine 4g in 81% yield (eqn (3)). These results, along with those shown in Scheme 3, suggest that electronwithdrawing groups on the aromatic rings greatly accelerate the elimination of HCl from 2,2,2-trichloroethanamines generated during the reaction.



On the basis of the above experimental results and previous studies, we proposed a reaction pathway as depicted in Scheme 4. Nucleophilic attack of imine 1 on aryne 5, generated in situ from 2-(trimethylsilyl)aryl triflate 2 in the presence of cesium fluoride, gives iminium zwitterion $6^{2,3}$ which activates chloroform by deprotonation to yield iminium 7. The resulting trichloromethyl anion undergoes nucleophilic addition to iminium 7 to afford 2,2,2-trichloroethanamine 3. When the starting imine is an aromatic one having an electron-withdrawing group, elimination of HCl occurs readily under the standard conditions to afford 2,2-dichloroethenamine 4.



A few other types of carbon nucleophiles were examined in the three-component reaction with unactivated imines and arynes. To our delight, acetonitrile and methyl propiolate served as suitable carbon nucleophiles and the corresponding three-component reaction afforded functionalized tertiary amines in moderate yields (Scheme 5). Nevertheless, the three-component reaction was not applicable to bromoform, nitromethane, acetone, activated methylene compounds such as diethyl malonate, ethyl 3-oxobutanoate, and malononitrile, and electron-rich aromatic compounds such as indole and 2naphthol under the standard conditions.



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In summary, we have developed an unprecedented threecomponent carboarylation reaction of unactivated imines with arynes and carbon nucleophiles. A range of aliphatic and imines underwent carboarylation with 2aromatic (trimethylsilyl)aryl triflates and chloroform in the presence of cesium fluoride to afford structurally diverse 2,2,2trichloroethanamines in moderate to good yields. In the case of aromatic imines having electron-withdrawing groups, elimination of HCl occurred readily to afford 2,2dichloroethenamines. The scope of carbon nucleophiles for the three-component reaction was successfully extended to acetonitrile and methyl propiolate. These three-component reactions are operationally simple and provide access to a variety of functionalized tertiary amines under transition metal-free conditions.

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