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Ag-catalyzed difluorohydration of β-alkynyl ketones for diastereoselective synthesis of 1,5-diconboyl compounds

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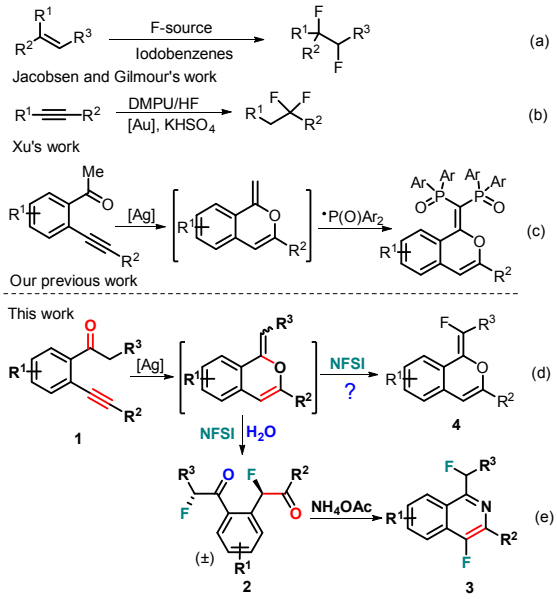
A new catalytic difluorohydration of β-alkynyl ketones using NFSI as the fluorinating reagent has been established, diastereoselectively furnishing a range of structurally diverse difluoride 1,5-dicarbonyl products through C(sp^3)-H fluorination. Notably, the sterically encumbered *t*-butyl functionality located at α-position of carbonyl group of substrates 1 behaved the excellent diastereoselectivity (up to >99:1 dr). The reaction enabled multiple bond-forming events including two C(sp^3)–F formation through Ag-catalysis to provide a high-efficient and practical method toward difluoride 1,5-dicarbonyls, some of which were successfully converted into difluorinated isoquinolines.

The incorporation of fluorine into organic molecules can modulate their abilities including lipophilicity, bioavailability and metabolic stability.[1] As a result, the fluorine-containing compounds have been widely applied in material science, chemical biology and pharmaceutical chemistry.[2] Furthermore, some fluorine-containing compounds behaved as key intermediates for the preparation of bioactive substances[3] and served as organocatalysts in catalytic chemistry.[4] With these attributes in mind, substantial effort aimed toward identifying general methods for the synthesis of these fluoric molecules has been made, mainly depending on the use of fluorination reagents, such as Selectfluor,[5] $Et_3N{\cdot}HF$,[6] *N*-fluoropyridinium salts,[7] diethylaminosulfur trifluoride,[8] *N*-fluorobenzenesulfonimide (NFSI).[9] With these fluorination reagents, the mono-fluorination involved the C(sp)–H, C(sp^2)–H or C(sp^3)–H functionalization has been extensively studied, providing an efficient strategy for the collection of fluorine-containing compounds.[10] Recently, chemists turned their attention to the dual fluorination for constructing difluoride molecules.[11] For instance, the group of Jacobsen[11e,f] and Gilmour[11g] independently reported a catalytic 1,2-difluorination of alkenes using suitable F-source and substituted iodobenzenes as a catalyst. Xu and co-workers described the synthesis of *gem*-difluoromethlylenes by gold-catalyzed dihydrofluorination of alkynes and DMPU/HF complex (Scheme 1b).[11h] Despite these significant advances, however, catalytic triple functionalization of β-alkynyl ketones involved difluorination for diastereoselective synthesis of difluoride 1,5-dicarbonyl compounds, to the best of our knowledge, has not been documented yet.



Scheme 1. Profile application of difluorination

Catalytic cyclization of β-alkynyl ketones has proven to be a exceptionally efficient methodology to construct synthetically significant cyclic compounds in a convergent manner.[12,13] Very recently, we reported silver-mediated *oxo*-cyclization and C(sp^3)–H biphosphinylation of β-alkynyl ketones to afford functional isochromenes. For this reaction, the *in-situ*-

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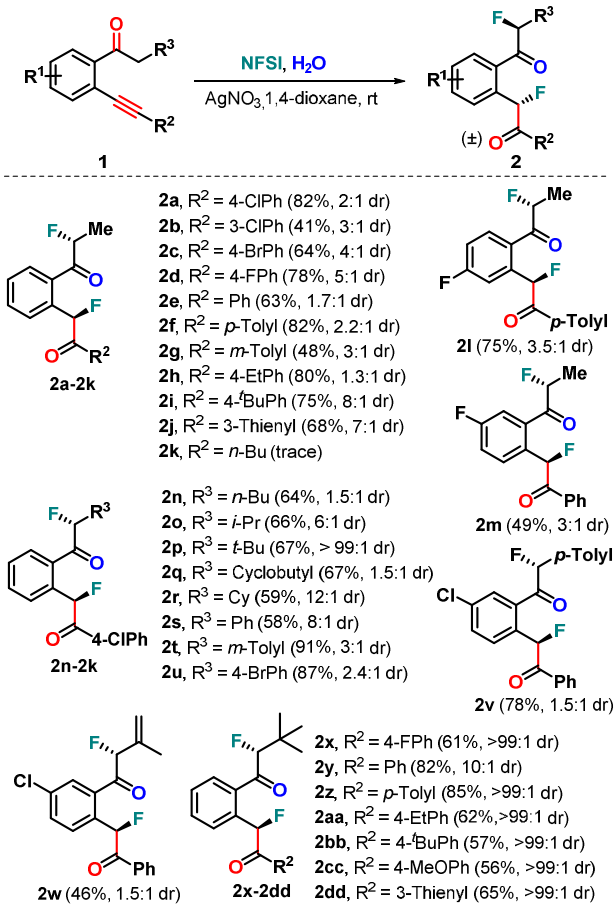
generation of methyleneisochromene intermediates is a key step to capture diarylphosphine oxide radicals to form the target products (Scheme 1c).[14] On the basis of the above successful transformation, we reasoned that under suitable catalytic conditions, β-alkynyl ketones are easily converted into electron-rich methyleneisochromenes, enabling electrophilic substitution with NFSI to give fluoride isochromenes **4** (Scheme 1d). Surprisingly, we found that the Ag-catalyzed reaction of the preformed β-alkynyl ketones **1** underwent unexpected difluorohydration process in the presence of H_2O, leading to the diastereoselective formation of difluoride 1,5-dicarbonyls. Herein, we would like to report this interesting transformation of catalytic difluorohydration involved C(sp^3)-H bond fluorination (Scheme 1c). The resulting 1,5-dicarbonyls were subjected to the reactions of ammonium acetate, allowing a facile dehydrated [5 + 1] aza-cyclization to access difluorinated isoquinolines with excellent yields.

Our initial investigation commenced with the reaction of β-alkynyl ketones **1a** with NFSI in a 1:2 mole ratio in the presence of water (2.0 equiv) using AgOAc (20 mol%) as a catalyst.[15] The reaction was performed in 1,4-dioxane solvent at room temperature under Ar conditions, delivering the unexpected difluoride product **2a** in 49% yield (Table 1, entry S1, See Supporting Information). After careful optimizations, we found that the reaction of **1a** with NFSI in a 1:3 mole ratio in 1,4-dioxane at room temperature together with 1.2 equivalents of water and 10 mol% of $AgNO_3$ as a catalyst was proven to be most effective, affording product **2a** in 82% yield (entry S18).

After determining the optimal reaction conditions, we then investigated the generality of this catalytic difluorohydration by examining β-alkynyl ketone components (Scheme 2). A variety of β-alkynyl ketones **1** readily reacted with NFSI to furnish the corresponding inseparably diastereoisomeric 1,5-dicarbonyls **2a–2dd** with generally good yields. With the ethyl group on the carbonyl anchor, various substituents on the arylalkynyl moiety (R^2), including Cl (**1a** and **1b**), Br (**1c**), F (**1d**), Me (**1f** and **1g**), Et (**1h**), and *t*-Bu (**1i**), can tolerate the catalytic conditions well, providing the 1,5-dicarbonyls **2a–2i** with 41%-82% yields and poor diastereoselectivity (1.3:1 to 8:1 dr). The presence of functional groups at the *para*-position of phenyl ring seemed to improve the reaction efficiency, as the corresponding products **2a** and **2f** could be obtained in higher yields than those resided at *meta*-position (Scheme 2, **2a** vs **2b**, **2f** vs **2g**). Alternatively, 3-thienyl substituted β-alkynyl ketone **1j** still showed high reactivity in current difluorohydration, giving access to the corresponding product **2j** with 68% yield and 7:1 dr. Unluckily, β-alkynyl ketone **1k** bearing *n*-butyl (*n*-Bu) group on the alkynyl moiety was not an adaptable reaction partner, as the reaction did not proceed at all under the standard conditions (Scheme 2, **2k**). The substrates **1** carrying fluoro functionality at 4- or 5-position of the internal arene ring can also lead to the formation of trifluoride product **2l** or **2m**, respectively. Next, we decided to change the substituents located at α-position of carbonyl group to expand its synthetic utility. As we had expected, a large variety of different substituents, including *n*-butyl, *i*-proply (*i*-Pr), *t*-butyl, cyclobutyl, cyclohexyl (Cy), aryl, and 2-propenyl, would be accommodated, confirming the efficiency of the reaction, as the corresponding **2n-2w** were generated with 46%-91% yields and up to >99:1 dr. Interestingly, the sterically bulky *t*-butyl counterpart **1p** was a good reaction component, delivering the diastereoenriched product **2p** as a single diastereoisomer in 67% yield (>99:1 dr). In view of this attractive outcome, we considered to exploit other *t*-butyl derivatives to evaluate the diastereoselectivity. To our delight, the purposefully preformed β-alkynyl ketones **1x-1dd** enabled Ag-catalyzed difluorohydration to exhibit the excellent diastereoselectivity (up to 99:1 dr), except for **1y**. In general, the current protocol represents a new and practical pathway for the diastereoselective construction of richly decorated 1,5-dicarbonyls. The structures of these 1,5-dicarbonyls **2** were characterized by their NMR spectroscopy and HRMS. Furthermore, stereoscopic structures of **2w** and **2z** were confirmed by carrying out single crystal X-ray diffraction (see Supporting Information).



Scheme 2 Substrate scope for forming products **2**. (*i*) Yields of isolated products based on β-alkynyl ketone **1**. (*ii*) dr value based on the analysis of ^{19}F NMR.

After the successful formation of difluoride 1,5-dicarbonyl products, we attempted to employ them as starting materials to react with ammonium acetate to investigate the dehydrated

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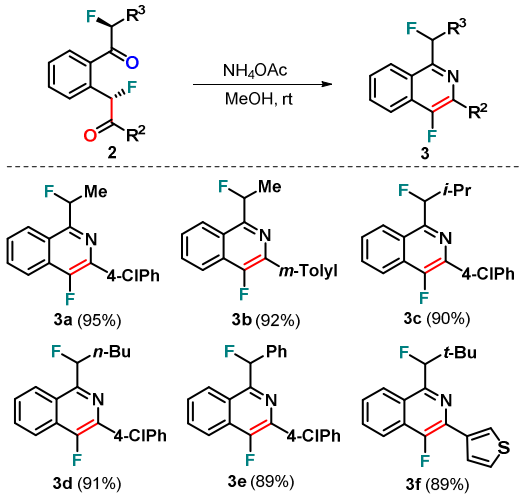
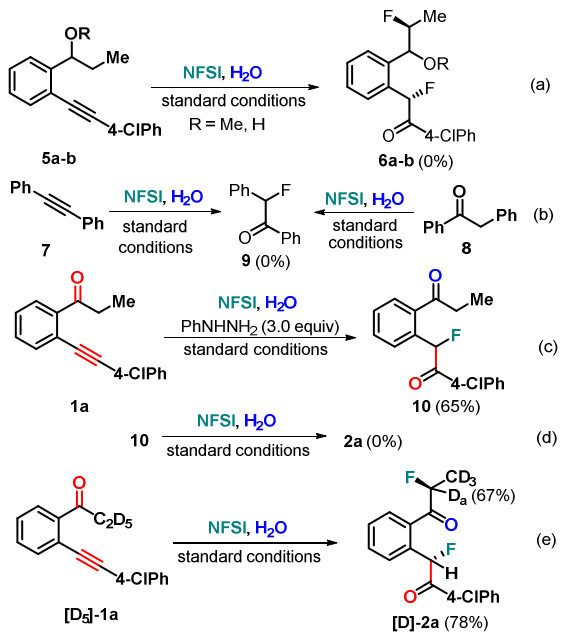
[5 + 1] aza-cyclization toward the expected difluorinated isoquinolines **3** since the fluorinated isoquinolines have been found to show a broad spectrum of biological activities.[16] Upon treatment with representative 1,5-dicarbonyls **2** with ammonium acetate proceeded readily in MeOH at room temperature under air conditions, providing access to the corresponding difluorinated isoquinolines **3a-3f** in 89%-95% yields (Scheme 3).

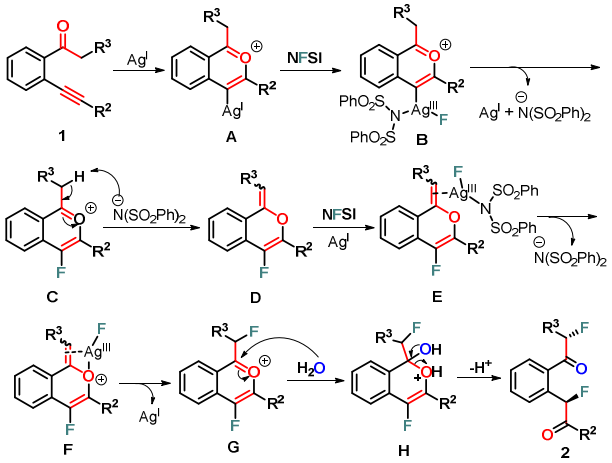


Scheme 3 Synthesis of difluorinated isoquinolines **2**. Yields of isolated products based on compounds **2**.



Scheme 4 Control experiments

To understand the reaction mechanism, several control experiments were conducted. Frist, *O*-protected or unprotected 1,2-diarylethynes **5** were subjected with the standard conditions, but no expected products **6** were observed with the starting materials **5** remaining (Scheme 4a), suggesting silver-catalyzed addition of carbonyl group into alkynyl unit to form isobenzopyrylium intermediate is a key step for the success of this transformation. The reaction of 1,2-diphenylethyne (**7**) failed to give the target product **9** (Scheme 4b), showing without carbonyl group at β-position of alkynyl moiety fluorohydration of 1,2-diphenylethyne did not work under the same conditions. In addition, the conversion of 2-phenylacetophenone (**8**) into product **9** did not proceed (Scheme 4b). In the presence of phenylhydrazine, substrate **1a** was converted into mono-fluoride 1,5-dicarbonyl compound **10** (Scheme 4c), but the transformation of compound **10** into product **2a** did not occur under the standard conditions (Scheme 4d). These results revealed that fluorination of alkynyl unit occurs prior to the hydration and the second C(sp^3)-H fluorination. The deuterium-labeling experiments based on the use of **1a** (Scheme 4e) indicated that a hydrogen atom of the new forming C-H bond was generated from H_2O.



Scheme 5. Plausible mechanism for forming **2**

Combining the above investigations and the literature precedents of silver-catalyzed redox system[17] and the oxygen transfer process,[12] we proposed a reasonable mechanism for this difluorohydration (Scheme 5). First, Ag-catalyzed 6-*endo-dig* *oxo*-cyclzation of *β*-alkynyl ketones generates isobenzopyrylium intermediate **A**, followed by oxidation with NFSI to afford vinyl–Ag^{III} fluoride **B** (detected by LC-MS, see Supporting Information). Next, intermediate **B** is converted into fluoride isobenzopyran **D** (detected by LC-MS) through reductive elimination and H-transfer, which undergoes oxidation-coordination with Ag^{I} and NFSI to afford Ag^{III} complex intermediate **E**, and the following ligand exchange and reductive elimination give difluoride isobenzopyrylium **G**. Finally, the ring-open of isobenzopyrylium **G** attacked by water diastereoselectively affords difluoride 1,5-dicarbonyl products **2**.

In conclusion, we have established a new silver-catalyzed difluorohydration of β-alkynyl ketones using NFSI as the fluorinating reagent, by which structurally diverse difluoride 1,5-dicarbonyl products can be diastereoselectively synthesized through C(sp^3)-H fluorination under mild catalytic oxidation conditions. Specifically, the sterically encumbered *t*-butyl functionality located at α-position of carbonyl group of

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substrates **1** behaved the excellent diastereoselectivity (up to 99:1 dr). The present transformation enables multiple bond-forming events including one C(sp^3)-H, two C(sp^3)–F and two C–O bond formation through Ag-catalysis, providing a high-efficient and practical protocol toward difluoride 1,5-dicarbonyls, and some of them were successfully converted into difluorinated isoquinolines *via* dehydrated [5 + 1] aza-cyclization. Further assessment of the biological activity of these difluoride compounds is underway in our laboratory.

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