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Gold-Catalyzed Synthesis of 2-Aryl-3-fluoropyrroles

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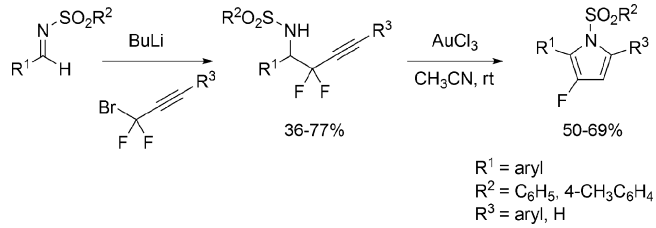
ABSTRACT



The gold-catalyzed cyclization and dehydrofluorination of *gem*-difluorohomopropargylamines provides a novel access to 2-aryl-3-fluoropyrroles. Difluorinated homopropargylamines are prepared by the addition of *gem*-difluoropropargyllithium reagents to arylated *N*-tosylimines.

Fluorine as a substituent can drastically affect the physical, chemical, and biological properties of a molecule. The use of fluorine substitution in drug design has resulted in enhanced binding efficiencies and selectivities of pharmaceuticals. These advantages led to a growing interest in organofluorine chemistry and stimulated the research for selective syntheses of fluorinated heterocyclic compounds.[1] In particular, fluorinated pyrroles represent a class of important structural units in pharmaceutical and agrochemical products such as drugs against cytokine-mediated diseases,[2] fungicides and bactericides,[3] porphyrins,[4] and antithrombosis agents.[5] In contrast to the large number of syntheses for nonfluorinated pyrroles, only limited synthetic pathways are available to synthesize 3-fluoropyrroles selectively.[6,7] Recently, our research group developed a convenient synthetic route to 2-aryl-3-fluoro-1*H*-pyrrole-5-carbaldehydes and 5-alkoxymethyl-2-aryl-3-fluoro-1*H*-pyrroles via electrophilic fluorination of the corresponding 1-pyrrolines.[7] Because of the importance of fluorinated pyrroles, the search for new and efficient synthetic pathways was continued. Therefore, the gold-catalyzed 5-*endo*-*dig* cyclization of 2,2-difluorobut-3-yn-1-amines **3** toward 3,3-difluoropyrrolines **4** was investigated. Dehydrofluorination of the obtained pyrrolines **4** should lead to 2,5-

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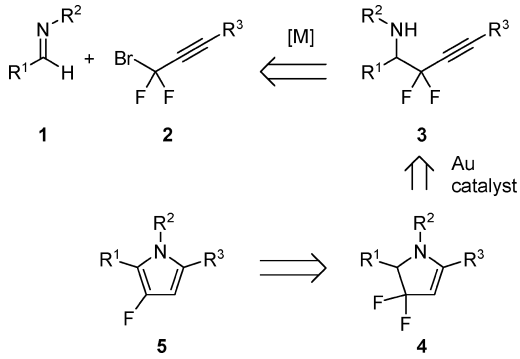
disubstituted 3-fluoropyrroles **5** in a mild and convergent way (Scheme 1).

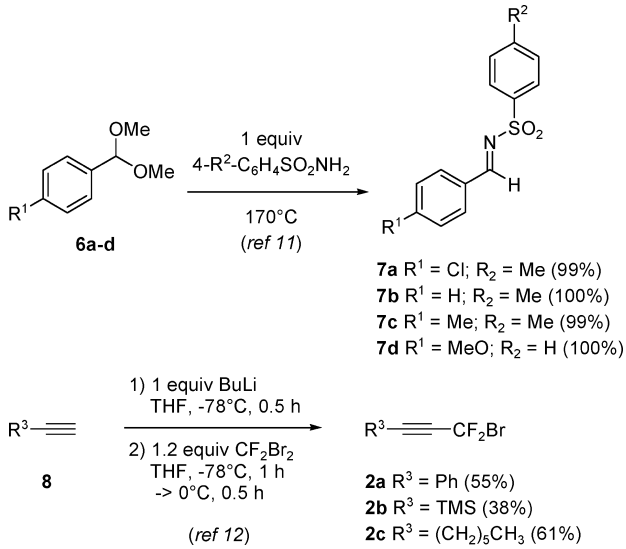
Scheme 1



Despite the successful application of homogeneous gold catalysis in organic synthesis for the preparation of heterocyclic compounds,[8] gold-catalyzed cycloisomerizations using fluorinated starting materials have been scarcely investigated. Recently, difluorinated dihydropyranones have been synthesized from β-hydroxy-α,α-difluoroynones via gold-catalyzed 6-*endo-dig* cyclization.[9]

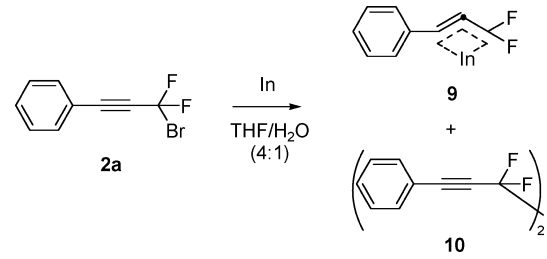
Only one example of a 2,2-difluorobut-3-yn-1-amine **3**, notably a silyl derivative, is known in literature (R^1 = Ph, R^2 = CH_2Ph, R^3 = Si(*i*-Pr)$_3$), and its synthesis consists of an indium-mediated propargyl-allene isomerization of (3-bromo-3,3-difluoroprop-1-ynyl)triisopropylsilane and subsequent attack to *N*-(phenylmethylidene)benzylamine.[10] For the synthesis of amines **3**, it was decided to use more activated *N*-sulfonylimines **7** that were easily prepared from (dimethoxymethyl)benzenes **6** via condensation with arylsulfonamides.[11] Substituted difluoropropargyl bromides **2** were synthesized via reaction of lithium acetylides, derived from alkynes **8**, with CF_2Br_2 (Scheme 2).[12]

Scheme 2



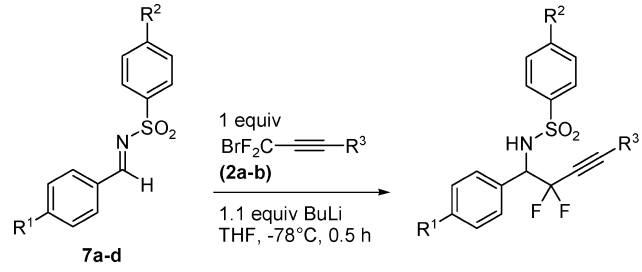
1-Bromo-1,1-difluoro-3-phenylprop-2-yne **2a** could be isomerized into the corresponding compound **9** using indium in THF/H_2O (1:4) at room temperature, but a substantial amount of dimerization product **10** (3,3,4,4-tetrafluoro-1,6-diphenylhexa-1,5-diyne) was formed after 2 h, making this solvent- and substrate-dependent route unattractive (Scheme 3).[10]

Scheme 3



In contrast to imines, the addition of difluoropropargyl bromides across aldehydes resulting in the corresponding alcohols is far more investigated in the literature. Therefore, the addition of difluoropropargyl bromide **2a** across *N*-tosylimine **7a** was investigated to establish a new entry toward fluorinated *N*-heterocycles. Unfortunately, the metal-mediated condensation of **2a** with *N*-tosylimine **7a** using indium,[13,14] tin,[15] magnesium,[12,16−18] or zinc[19−23] did not result in the corresponding addition product **11a** in acceptable yields. Finally, when difluoropropargyl bromide **2a** was transmetalated with 1.1 equiv of butyllithium (2.5 M in hexane) in THF at −78 °C, the organolithium reagent was reactive enough to attack *N*-tosylimine **7a** leading to sulfonamide **11a** in 100% conversion after 30 min without formation of byproducts (Scheme 4).

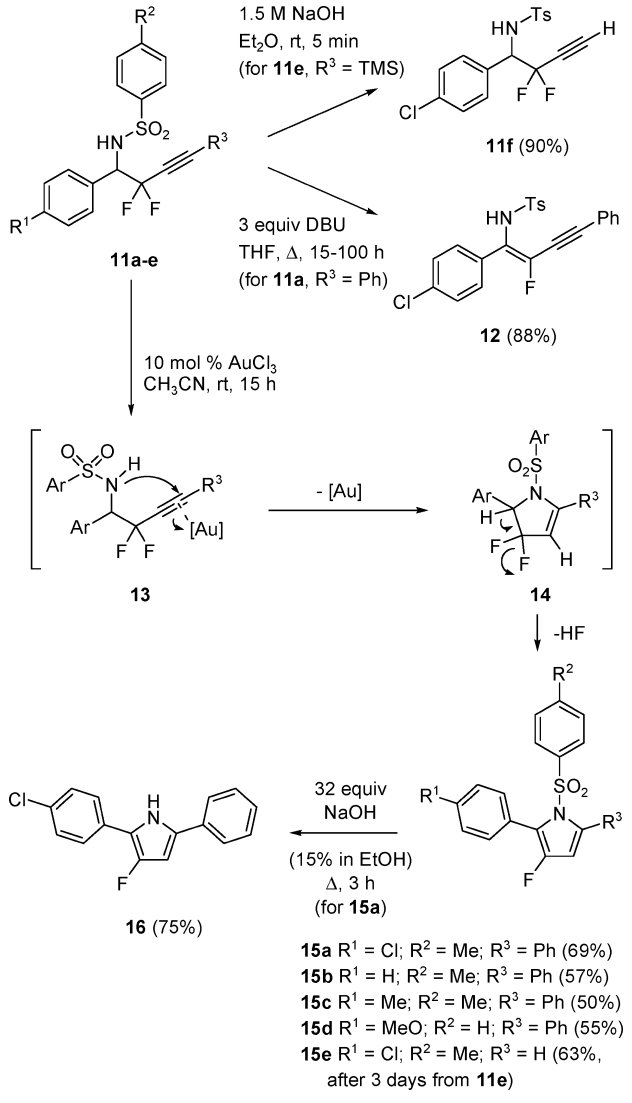
Scheme 4



To our knowledge, this is the first report on lithium−bromine exchange of *gem*-difluoropropargyl bromides, and it proceeds analogously to the synthesis of *gem*-difluoroallyllithium reagents.[24] Sulfonamide **11a** was easily purified

via crystallization without necessity of chromatography. Derivatives **11a**−**d** were prepared by reaction of (3-bromo-3,3-difluoroprop-1-yn-1-yl)benzene **2a** with various aromatic *N*-sulfonylimines **7a**−**d**, and the yields varied between 36% and 54% depending on the R^1-substitution pattern of the aromatic imine. Better yields were obtained when (3-bromo-3,3-difluoroprop-1-ynyl)trimethylsilane **2b** was treated with butyllithium and imine **7a** to form sulfonamide **11e** (77%). The trimethylsilyl group of sulfonamide **11e** was almost quantitatively hydrolyzed toward sulfonamide **11f** after 5 min of stirring in 1.5 M NaOH in diethyl ether at room temperature (Scheme 5).

Scheme 5



1-Bromo-1,1-difluoronon-2-yne **2c**, however, could not be coupled to imine **7a** under various reaction conditions.

Besides gold catalysts, silver(I) salts also form stable π-complexes with acetylenes. Silver(I)-promoted cyclizations of *N*-(2-hydroxybut-3-yn-1-yl)toluenesulfonamides to substituted pyrroles in excellent yields were reported previously.[25] 3-Fluoro-4,5-dihydrofurans were synthesized from *gem*-difluoropropargyl alcohols using $AgNO_3$ by Hammond et al.[26] Therefore, we tried to cyclize sulfonamide **11a** to pyrrole **15a** using 0.1 equiv of $AgNO_3$ in CH_2Cl_2 with or without NaOAc as a base, but unfortunately no reaction was observed. Recently, a DBU-promoted cyclization of *gem*-difluorohomopropargyl alcohols was reported for the synthesis of 2,5-disubstituted 3-fluorofurans.[27] However, the reaction of sulfonamide **11a** with 3 equiv of DBU in THF under reflux gave only dehydrofluorination product **12** that did not cyclize to fluorinated pyrroles even after 100 h. Finally, treatment of sulfonamides **11a**−**d** with 10 mol % $AuCl_3$ in acetonitrile at room temperature resulted in a smooth cyclization and in situ dehydrofluorination, forming 2,5-aryl-1-(aryl)-sulfonyl-3-fluoro-1*H*-pyrroles **15a**−**d** in 50−69% yield. The gold-catalyzed cyclization of [(trimethylsilanyl)butynyl]sulfonamide **11e** proved to be more difficult but could be driven to completion by reaction with $AuCl_3$ for 3 days. However, during this long reaction time the TMS group of **11e** was removed via protodesilylation, resulting in 2-(4-chlorophenyl)-3-fluoropyrrole **15e**. In order to determine the feasibility of removing the *N*-*p*-toluenesulfonyl group of pyrroles **15**, the hydrolysis of 2-(4-chlorophenyl)-3-fluoro-1-[(4-methylphenyl)sulfonyl]-5-phenyl-1*H*-pyrrole **15a** was carried out using NaOH in EtOH to provide 2-(4-chlorophenyl)-3-fluoro-5-phenyl-1*H*-pyrrole **16** in 75% yield.

In conclusion, a gold-catalyzed cyclization reaction of electron-deficient *gem*-difluorohomopropargylamines and simultaneous dehydrofluorination of intermediate difluoropyrrolines to new 2(,5)-(di)substituted 3-fluoropyrroles was developed. Difluorinated homopropargylamines, an almost unknown class of compounds, were successfully prepared via lithium bromine exchange of difluoropropargyl bromides and subsequent reaction with *N*-tosylimines.

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Supporting Information Available: General experimental conditions and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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