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Direct Access to Aryl Bis(trifluoromethyl)carbinols from Aryl Bromides or Fluorosulfates via a Pd-Catalyzed Carbonylation

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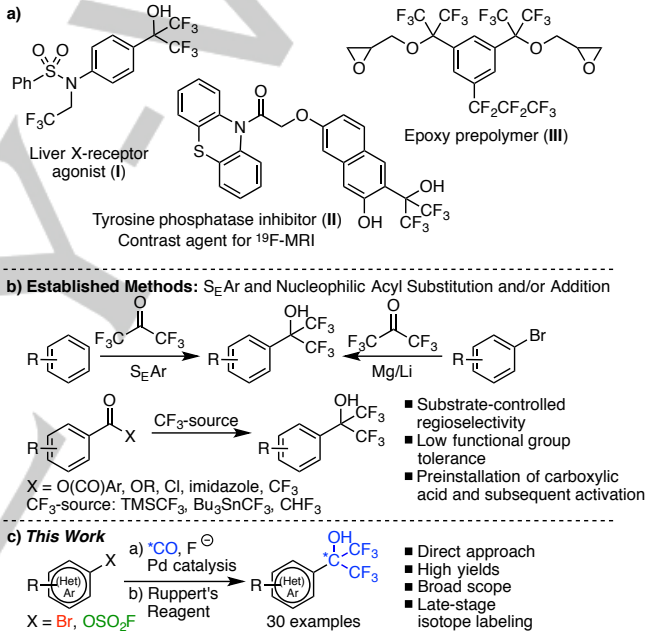
Abstract: *A Pd-catalyzed carbonylative approach for the direct conversion of (hetero)aryl bromides into their α,α-bis(trifluoromethyl)carbinols is described, applying only stoichiometric amounts of carbon monoxide and trifluoromethyltrimethyl-silane. In addition, aryl fluorosulfates proved highly compatible to these reaction conditions. The method is tolerant of a diverse set of functional groups, and it is adaptable to late-stage carbon isotope labeling.*

The introduction of a fluorine atom into bioactive molecules can strategically alter their chemical and biological properties.[1] In recent years, an increasing number of fluorine-containing drugs have been launched, justifying the need for new synthetic methodologies centered on the incorporation of fluorine-containing motifs.[1a] One of these privileged motifs is the α,α-bis(trifluoromethyl)carbinol group. Compounds containing this substructure have shown biological activity against cancer, diabetes, hepatitis C, dyslipidemia and inflammation (Scheme 1a).[2] An interesting feature of this motif is the presence of a large number of fluorine atoms, which renders them as promising contrast agents for ^{19}F-MRI.[3] This technique allowed *in vivo* target identification of carbinol **II**, a tyrosine phosphatase inhibitor.[3a] Furthermore, aryl α,α-bis-(trifluoromethyl)carbinol-containing polymers display excellent material properties, as well as high thermal stability and flame resistance.[4] The hexafluoroisopropanol group can also be found in ligand design, either by merit of its inductive electron withdrawing properties or as a bulky substituent.[5] Other applications include their use for the detection of nerve agents[6] and as precursors for the synthesis of Martin's spirosilanes.[7]

Despite the multidisciplinary impact of this fluorinated motif, only few synthetic strategies have been reported for its installation (Scheme 1b). Most procedures rely on electrophilic aromatic substitution or the use of organolithium or -magnesium reagents in the presence of hexafluoroacetone.[8] Alternatively, α,α-bis(trifluoromethyl)carbinols can be prepared from the corresponding carboxylic acid derivatives or from trifluoroacetophenones using a nucleophilic CF_3-source (Scheme 1b).[9] Nevertheless, these methods are limited by substrate biased regioselectivity, low functional group tolerance, the use of toxic reagents[10] and/or the need of extra steps for preliminary introduction or activation of the carbonyl functionality.



Scheme 1. Examples of bis(trifluoromethyl)carbinol-containing bioactive molecules and polymer materials, and previous strategies for the introduction of this functional group.

Herein, we wish to report a general and mild protocol for the direct conversion of aryl bromides or fluorosulfates into (hetero)-aryl α,α-bis(trifluoromethyl)carbinols applying a Pd-catalyzed carbonylative transformation. The latter class of starting materials indirectly allows phenols as substrates for this transformation. Furthermore, the developed methodology is suitable for direct and late-stage carbon isotope labeling of the target compound.[11]

We started our investigation by optimizing the carbonylation of 4-bromoanisole **1a** with a nucleophilic CF_3-source, using a two-chamber system and the ex situ generation of carbon monoxide from COgen.[11a,12] After thorough evaluation of the reaction parameters, the desired α,α-bis(trifluoromethyl)carbinol **2a** was successfully isolated in an 81% yield (Table 1, entry 1). The

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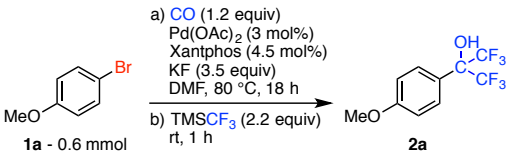
Table 1. Optimization of the reaction conditions.[a]



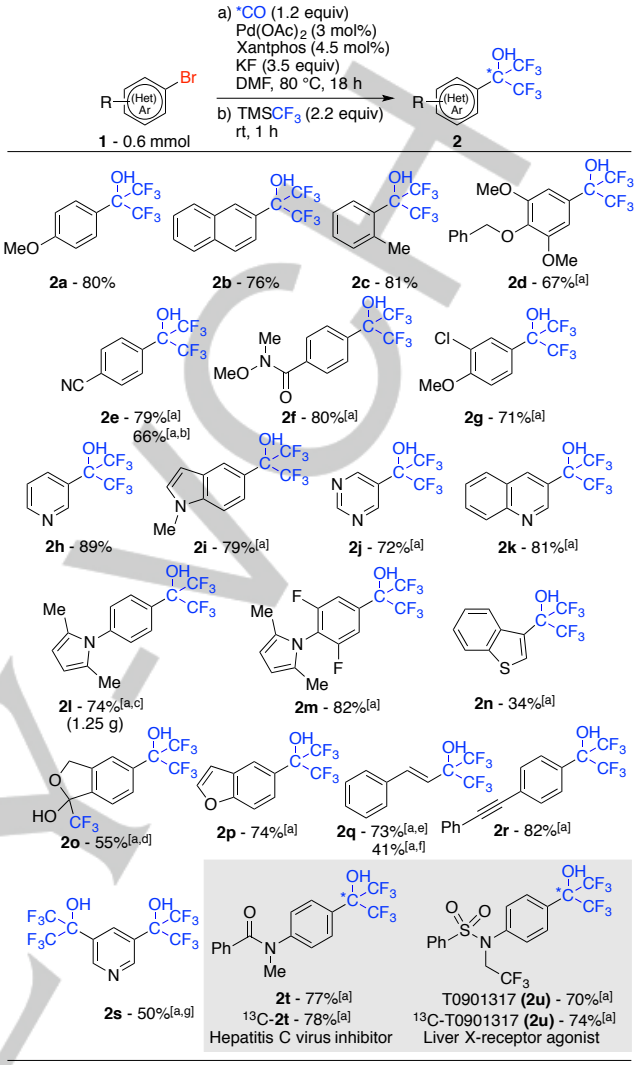
1a - 0.6 mmol **2a**

Entry	Deviation from standard conditions	**Yield of 2a** [%][b]
1	None	89 [81][c]
2	Xantphos-Pd-G4 instead of $Pd(OAc)_2$ and Xantphos	89
3	$Pd(dba)_2$ instead of $Pd(OAc)_2$	0
4	Dppf instead of Xantphos	76
5	DPEPhos instead of Xantphos	83
6	MeCN instead of DMF	38
7	Dioxane instead of DMF	0
8	CsF instead of KF	47
9	$[Me_4N]F$ instead of KF	0
10	KF (2.1 equiv)	83
11	No KF	0
12	$TESCF_3$ instead of $TMSCF_3$	74
13	$TMSCF_3$ (2.05 equiv)	77
14	$TMSCF_3$ (1.0 equiv)	22

[a] All reactions were performed in a two-chamber setup. CO was released from a solid precursor in one chamber; see Supporting Information for full details. [b] Yields determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield. The carboxylic acid was observed as the major side-product.

optimized reaction conditions composed of the aryl bromide with $Pd(OAc)_2$ (3 mol%), Xantphos (4.5 mol%), CO (1.2 equiv), and KF (3.5 equiv), heated in DMF for 18 h, followed by the addition of Ruppert's reagent at room temperature in a one-pot fashion. We suspect the reaction initially generates an acyl halide intermediate,[13] which subsequently reacts with $TMSCF_3$.

Performing the carbonylative coupling with the Xantphos-Pd-G4 precatalyst[14] instead of $Pd(OAc)_2$ provided a similar reaction outcome (entry 2). In contrast, no conversion was observed with $Pd(dba)_2$, and the starting material **1a** was fully recovered (entry 3). Substituting Xantphos with other bidentate phosphine ligands resulted in a slightly lower yield (entries 4 and 5). Next, several other solvents were screened, however, they provided moderate to no conversion of the model substrate 1a (entries 6 and 7). Optimization of the fluoride source revealed that CsF and n-Bu_4NF were inferior to KF. When the amount of KF was lowered to 2.1 equiv., a slight decrease in yield was observed. In the absence of a fluoride source, no product was formed, and the starting material was fully recovered (entries 8–11), whereas replacement of Ruppert's reagent with $TESCF_3$ led to a drop in yield (entry 12). Conducting the Pd-catalyzed carbonylative coupling in the presence of $TMSCF_3$ had a detrimental effect on the reaction outcome, as only starting material could be recovered (results not shown). The Marshall group has previously reported that the CF_3-anion can interchange with Xantphos on the metal center possibly exerting a hampering effect in the catalytic cycle.[15] Efforts to lower the amount of Ruppert's reagent, provided only lower conversions to **2a** (entries 13 and 14). Noteworthy, in the presence of one equivalent of $TMSCF_3$, a mixture of *p*-methoxy trifluoroacetophenone and α,α-bis(trifluoromethyl)carbinol **2a** was observed, indicating that



Scheme 2. Scope of aryl bromides. All reactions were performed in a two-chamber setup. CO was released from a solid precursor in one chamber (see Supporting Information for full details). Yields are isolated and are the average of duplicates. [a] 1.5 equiv of KF were initially added, followed by 2.5 equiv of KF after the carbonylation step. [b] Reaction performed on the corresponding Ar-Cl at 120 °C. [c] Reaction performed on a 5.0 mmol scale. [d] Starting from 5-bromophthalide using 3.2 equiv of $TMSCF_3$. [e] From an approx. 4:1 mixture of (*E*)- and (*Z*)-bromostyrene. [f] From (*Z*)-bromostyrene. [g] The reaction was performed with 0.3 mmol of the aryl dibromide and 4.4 equiv of $TMSCF_3$.

selective formation of the trifluoroacetophenone could not be achieved under the applied reaction conditions. Finally, we observed that performing the reaction with a balloon of CO instead only led to a 6% yield of **2a.**[16]

With the optimized conditions in hand, we commenced an investigation on the generality of this transformation (Scheme 2). Initially, it was established that aryl bromides containing either only electron rich (**2a**–**2c**) or electron poor (**2e** and **2f**) substituents could be efficiently transformed into the corresponding α,α-bis(trifluoromethyl)carbinols in high yields. The effect of *o*-substituents was not detrimental for the outcome of the reaction as shown for **2c**. At this point, a beneficial effect of splitting the

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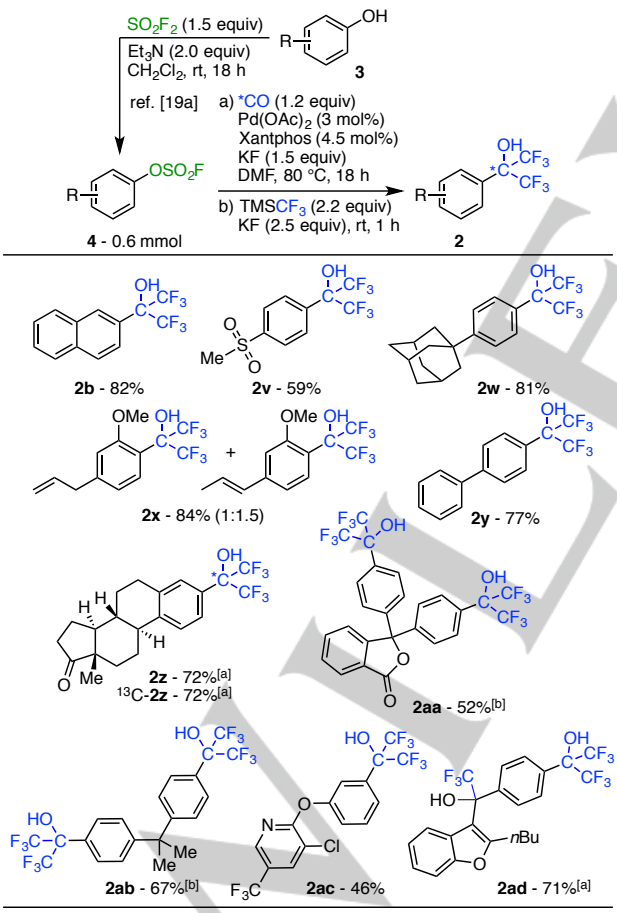
addition of KF was observed. This ensured that fluoride is present to activate Ruppert's reagent upon its addition. As shown with compounds **2g** and **2m**, halide substituents including chloride or fluoride were well tolerated, with the former representing a useful handle for possible post-functionalization of the carbinol product. Heteroaromatic bromides including pyridine, indole, pyrimidine, quinoline and benzothiophene were also applicable for the synthesis of α,α-bis(trifluoromethyl)carbinols (**2h**–**2k**, **2n** and **2s**). Even heterocycles as substituents or fused to the benzene ring were tolerated as exemplified by compounds **2l**, **2m**, **2o** and **2p**. Further adaptation to a gram scale synthesis was shown for the pyrrole substituted compound **2l**. Addition of a third trifluoromethyl group was observed with 5-bromophthalide involving the lactone carbonyl group to give **2o**. Both *cis*- and *trans*-bromostyrene were found to be viable substrates for this carbonylative coupling. Interestingly, the two stereoisomers led to the same *trans*-product **2q** in 73% and 41% isolated yields, resp.[17] An internal alkyne was tolerated under the applied reaction conditions as illustrated with **2r**. Finally, an activated aryl chloride was attempted, providing the corresponding bis(trifluoromethyl)carbinol **2e** in a 66% yield, though with a reaction temperature of 120 °C.

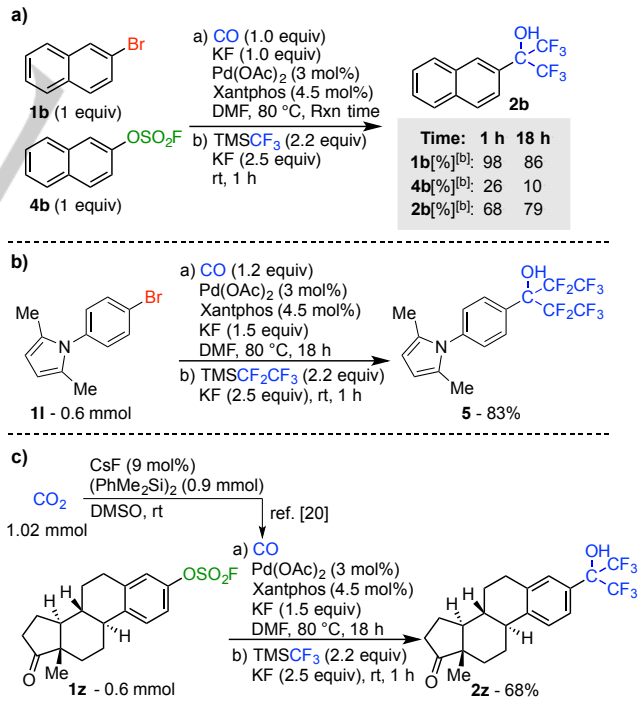
Our methodology could be adapted to the efficient preparation of two bioactive molecules, including late-stage ^{13}C-isotopic labeling.[12a] As such, the hepatitis C virus inhibitor **2t** was synthesized in two steps from 4-bromo-*N*-methylaniline with a 77% yield for the carbinol formation. Similarly, the liver X-receptor agonist T0901317 (**2u**) could be prepared in only three steps from 4-bromoaniline under mild reaction conditions. Importantly, a ^{13}C-isotope label could be introduced in the last step in similar yields as for their unlabeled counterparts applying ^{13}C-COgen.[11a,12]



Scheme 3. Scope of aryl fluorosulfates. All reactions were performed in a two-chamber setup. CO was released from a solid precursor in one chamber (see Supporting Information for full details). Yields are isolated and are the average of duplicates. [a] 3.2 equiv of $TMSCF_3$ was used. [b] The reaction was performed with 0.3 mmol of the aryl fluorosulfate and 4.4 equiv of $TMSCF_3$.

Aryl fluorosulfates are easily prepared from phenols and have gained increased interest either as a robust connector in SuFEx click chemistry or as a leaving group.[19–21] We therefore investigated the possible application of these electrophilic substrates for the synthesis of aryl α,α-bis(trifluoromethyl)-carbinols. Initially, the aryl fluorosulfates were prepared from the corresponding phenols according to a recent procedure relying on the ex-situ generation of gaseous sulfuryl fluoride in the two-chamber set-up, COware.[21a] As depicted in Scheme 3, these electrophiles proved to be well-suited for the catalytic protocol providing the bis(trifluoromethyl)carbinols in good yield as shown for the introduction of one carbinol unit with products **2b**, **2v**–**2z**, **2ac** and **2ad**, and two units with **2aa** and **2ab**. Interestingly, some double bond migration was observed for the allylic benzene **2x**.[17] Finally, the bis(trifluoromethyl)carbinol obtained from estrone could easily be prepared with specific incorporation of a carbon-13 label (^{13}C-**2z**).

To conclude, additional experiments were performed to examine the comparative reactivity of aryl bromides and the fluorosulfates in the Pd-mediated carbonylation step. As can be



Scheme 4. Additional experiments with aryl bromides and aryl fluorosulfates. a) Competition experiments between aryl bromide **1b** and aryl fluorosulfate **4b**.[a,b] b) An example with pentafluoroethyltrimethylsilane.[a] c) An application with CO_2 as the CO source. [a] Reaction was performed in a two-chamber setup. CO was released from a solid precursor in one chamber (see Supporting information for full details). [b] Yields determined by GC using dodecane as internal standard.

seen in Scheme 4a with **1b** and **4b** in equal amounts, the napthyl fluorosulfate proved to be substantially more reactive in the transformation to the bis(trifluoromethyl)carbinol **2b**. In a second experiment, we demonstrated that pentafluoroethyltrimethylsilane can be exploited for the generation of the bis(pentafluoroethyl)carbinols as illustrated in the transformation of **1l** to **5** in a satisfactory yield of 83% (Scheme 4b). Lastly, this protocol could be coupled up to the efficient disilane-mediated reduction of CO_2 to carbon monoxide for the conversion of the estronyl fluorosulfate **1y** to the corresponding bis(trifluoromethyl)-carbinol **2z** in a 68% yield (Scheme 4c).[22]

In summary, an efficient procedure for the direct formation of (hetero)aryl α,α-bis(trifluoromethyl)carbinols from the corresponding (hetero)aryl bromides and fluorosulfates has been demonstrated relying on Pd-mediated carbonylation with stoichiometric amounts of carbon monoxide and trifluoromethyltrimethylsilane. Particularly noteworthy with this protocol is its ease in operation, but also its suitability even in the presence of a wide range of other functional groups. This chemistry will undoubtedly allow for the rapid introduction of the bis(trifluoromethyl)carbinol unit into a wide variety of pharmaceutically relevant molecules.

Acknowledgments

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Keywords: • carbonylation • aryl bromides • palladium • bis(trifluoromethyl)carbinol • aryl fluorosulfates

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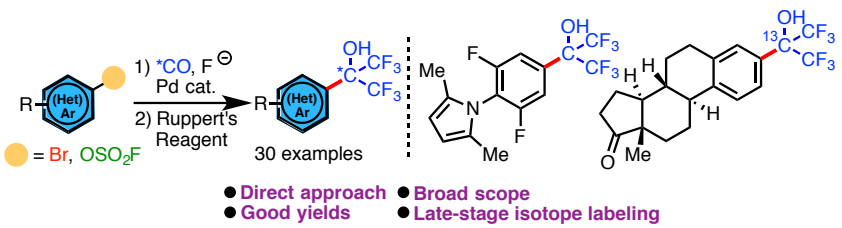

6 Fluorines are better than 3: The titled reaction allows for the direct synthesis of aryl bis(trifluoromethyl)carbinols from aryl bromides and fluorosulfates with stoichiometric carbon monoxide and two equivalents of trifluoromethyltrimethylsilane. The method exhibits good functional group tolerance and is suitable for carbon isotope labeling.

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