Cross-Coupling

Deutsche Ausgabe: DOI: 10.1002/ange.201600105
Internationale Ausgabe: DOI: 10.1002/anie.201600105

Synthesis of Aryldifluoroamides by Copper-Catalyzed Cross-Coupling

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Abstract: *A copper-catalyzed coupling of aryl, heteroaryl, and vinyl iodides with α-silyldifluoroamides is reported. The reaction forms α,α-difluoro-α-aryl amides from electron-rich, electron-poor, and sterically hindered aryl iodides in high yield and tolerates a variety of functional groups. The aryldifluoroamide products can be transformed further to provide access to a diverse array of difluoroalkylarenes, including compounds of potential biological interest.*

Fluorinated compounds are common in pharmaceuticals, agrochemicals, and materials because of their favorable biological and physical properties.[1] In medicinal chemistry, fluorinated substituents can alter the lipophilicity, metabolic stability, and overall activity of biologically active compounds relative to their nonfluorinated counterparts.[2] The difluoromethylene (CF_2) group has particular value because it is considered a bioisostere of carbonyl groups and ethers[3] and can modulate the pK_a value of neighboring functional groups such as amines.[4]

Aryldifluoroamides are present in several biologically active compounds, including the inhibitor of FKBP12[3] and the modulator of AMPAR[5] shown in Figure 1. Moreover, amides can be transformed into amines, alcohols, acids, esters, and ketones, thus making aryldifluoroamides versatile precursors to a variety of difluoroalkylarenes. Despite the biological and synthetic potential of this class of compound, current methods for the synthesis of difluoroamides are limited. Aryldifluoroamides can by prepared by deoxyfluorination of dicarbonyl compounds with diethylaminosulfur trifluoride (DAST) or related aminosulfur trifluorides.[6] However, these fluorinating reagents release toxic HF upon contact with water and can undergo explosive decomposition upon heating.

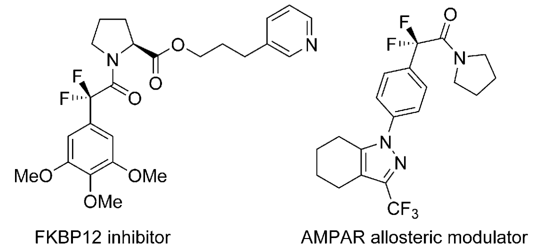

Figure 1. Bioactive compounds containing aryldifluoroamide groups.

The cross-coupling of aryl halides with difluorinated enolates would be a valuable approach to the synthesis of aryldifluorocarboxylic acid derivatives. Cross-coupling reactions of aryl nucleophiles, such as arylboronic acids, with difluorocarboxylic acid derivatives as electrophiles have been reported,[7] but reactions of the more widely accessible aryl halides with a carbonyl derivative as the nucleophile would constitute a more direct method from chemical feedstocks. A synthesis of aryldifluoroamides by the reductive coupling of aryl iodides and iododifluoroamides has been reported,[8] but the reaction requires excess copper (6 equiv) and displays limited scope and functional-group tolerance. For example, the reaction occurs in low yields with electron-rich or sterically hindered aryl iodides, and coupling reactions of heteroaryl iodides have not been reported. Our group recently reported a palladium-catalyzed coupling of aryl bromides with silyldifluoroamides.[9] This reaction has broad substrate scope, but it did not occur with many medicinally relevant heterocycles, such as 2-halopyridines. In addition, this reaction required palladium as the central metal of the catalyst, and we sought to develop a catalytic coupling reaction based on a cost-effective and earth-abundant first-row metal. Amii and co-workers reported a coupling of α-silyldifluoroesters with aryl iodides in the presence of stoichiometric CuI. The reaction also proceeded with catalytic CuI, but yields were variable (40–71 %), and the reaction was limited to electron-deficient substrates.[10] A related coupling of halopyridines was also reported, but required two equivalents of CuI.[11]

Herein, we report the cross-coupling of aryl halides with α-silyldifluoroamides in the presence of a catalytic quantity of CuOAc. The reactions encompass aryl and heteroaryl iodides containing a range of functional groups, as well as steric and electronic properties, and they occur with a commercially available copper catalyst without the need for any added ligand. Furthermore, we demonstrate that the aryldifluoroamide products are synthetically useful precursors to difluorinated analogues of biologically active compounds.

The arylation of α-silyldifluoroamide **2** with 1-butyl-4-iodobenzene (**1a**; see Table 1) was chosen as a model system to identify a copper catalyst and reaction conditions for the cross-coupling reaction. Compound **2** was synthesized from the corresponding chlorodifluoroamide, in analogy to a procedure for the synthesis of α-silyldifluoroesters reported by Amii and co-workers.[10] Compound **2** is an air-stable solid that can be prepared on multigram scale. By employing a preformed silyl amide enolate, we sought to avoid the strong base required to generate a difluoroamide enolate in situ by deprotonation of a difluoroamide. We envisioned that the silyldifluoroamide could be activated by a fluoride source under mild reaction conditions.

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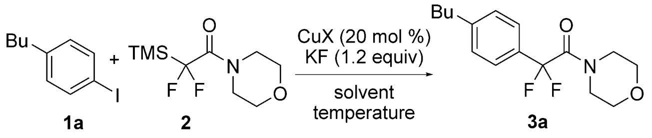
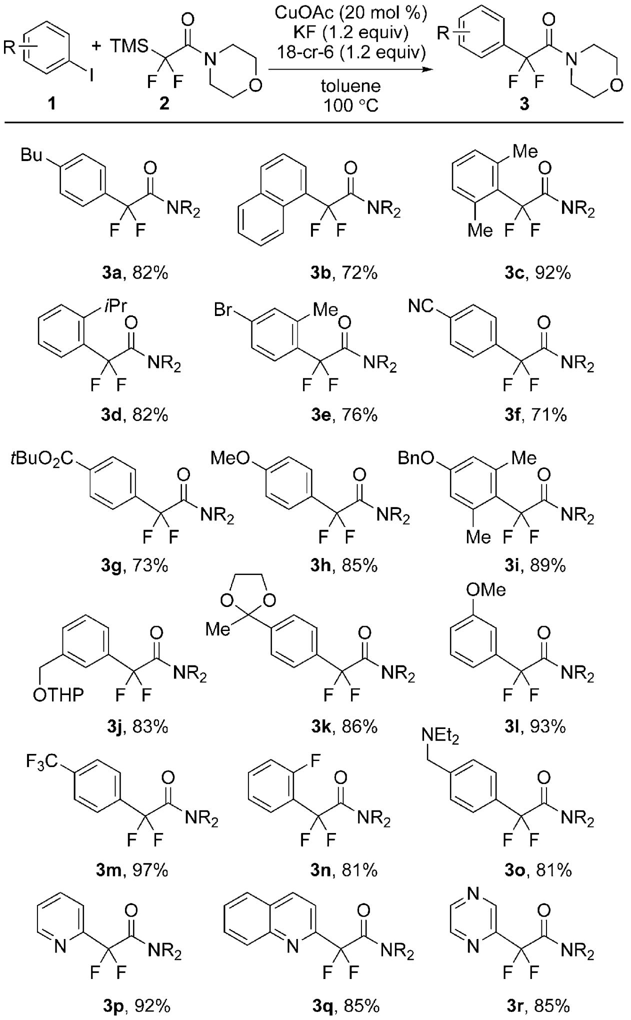
Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201600105.

Table 1: Effect of the reaction conditions on the coupling of **1a** with the α-silyldifluoroamide **2**.[a]



Entry	Solvent	T [°C]	CuX	Yield [%][b]
1	DMSO	80	CuCl	<5
2	DMSO	80	$CuBr{\cdot}SMe_2$	14
3	DMSO	80	CuI	18
4	DMSO	80	CuCN	12
5	DMSO	80	CuOAc	89
6[c]	toluene	100	CuOAc	87

[a] General reaction conditions: 0.100 mmol **1a**, 0.120 mmol **2**, and 0.0200 mmol CuX in 0.25 mL of solvent. [b] Yields were determined by ^{19}F NMR spectroscopy. [c] 1.2 equiv 18-cr-6 and 2.0 equiv **2**. DMSO = dimethylsulfoxide, TMS = trimethylsilyl.



Scheme 1. Yield is that of the isolated product. General reaction conditions: aryl iodide (0.400 mmol), **2** (0.800 mmol), CuOAc (0.0800 mmol), KF (0.480 mmol), and 18-cr-6 (0.480 mmol) in toluene (1 mL) at 100 °C for 24 h. THP = tetrahydropyran.

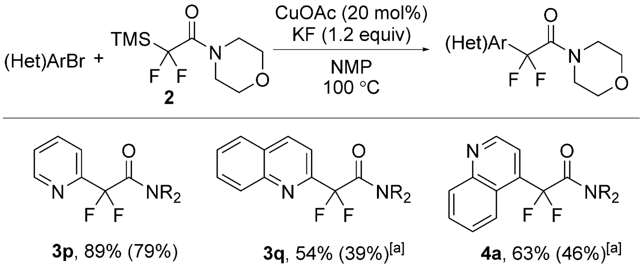
Various copper(I) sources were found to catalyze the coupling of **2** and **1a** (Table 1). Reactions catalyzed by CuOAc proceeded in higher yields than those catalyzed by CuI, $CuBr{\cdot}SMe_2$, CuCl, or CuCN. None of the copper(II) sources tested catalyzed the coupling process (see Table S1 in the Supporting Information). Reactions conducted with CuOAc without added ligand proceeded in higher yields than those conducted with added ligand (see Table S2). The reaction catalyzed by CuOAc (20 mol %) in toluene in the presence of KF and 18-crown-6 formed the coupled product in 87 % yield, as measured by ^{19}F NMR spectroscopy, and in 82 % yield upon isolation. The reaction of **1a** and **2**, conducted in DMSO in the absence of 18-crown-6 (Table 1, entry 5), proceeded in yields which are comparable to those from the reaction conditions described in entry 6. However, the conditions described in entry 6 were applicable to a wider range of substrates, and afforded the coupling products of electron-rich aryl iodides in higher yield than did the conditions described in entry 5.

Having identified reaction conditions for the coupling of **2** with **1a**, we investigated the conversion of a variety of aryl iodides into the corresponding aryldifluoroamides (Scheme 1). Electron-rich, electron-neutral, and electron-poor aryl iodides (**1**) coupled with **2** in high yield. In contrast to many copper-catalyzed coupling reactions, which occur in significantly lower yields with sterically hindered aryl iodides,[12] the reactions of **2** with aryl iodides containing mono- or disubstitution adjacent to the iodine atom (**1c**–**e**, **1i**, **1n**) occurred in high yield. The reaction conditions were found to tolerate ester (**1g**), nitrile (**1f**), tertiary amine (**1o**), ether (**1h**–**1l**), and aromatic bromide (**1e**) groups. Although free hydroxy groups, primary or secondary amines, and enolizable ketones were found to be incompatible with the reaction conditions, aryl iodides containing a protected alcohol (**1j**) and a ketone (**1k**) coupled in high yields.

Heteroarenes are ubiquitous in pharmaceuticals, agrochemicals, and materials,[13] but the metal-catalyzed coupling of basic heteroarenes can be challenging to effect because they can coordinate to and potentially deactivate transition-metal catalysts. However, electron-poor heteroaryl iodides, such 2-iodopyridine, 2-iodoquinoline, and 2-iodopyrazine, coupled with **2** in the presence of catalytic CuOAc to afford the corresponding heteroaryldifluoroamides **3p**–**r** in high yield.

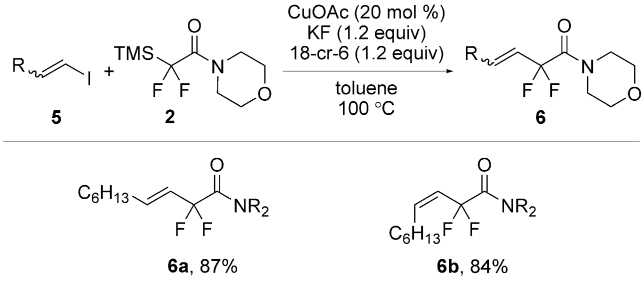
Recent studies in our group demonstrated that heteroaryl bromides react with $(phen)CuR_F$ complexes to form perfluoroalkylarenes in high yield,[14] and studies by other groups have shown that ligandless perfluoroalkyl copper compounds generated in situ also react with heteroaryl halides.[15] Therefore, we investigated the copper-catalyzed reactions of α-silyldifluoroamides with heteroaryl bromides to form α,α-difluoro-α-aryl amides.

Coupling of halopyridines and haloquinolines at the electron-poor 2- and 4-positions is challenging with palladium catalysts, often requiring high catalyst loadings and occurring in low yields and with limited scope. For example, 2-bromopyridine and 2-bromoquinoline did not undergo coupling with α-silyldifluoroamides under the palladium-catalyzed conditions previously reported by our group.[9] To investigate the reactivity of these substrates in the presence of a copper catalyst, the coupling of 2-bromopyridine with **2** was chosen as a model reaction. The reaction conditions identified for the coupling of **2** with iodoarenes resulted in only 21 % yield of **3p** from coupling of **2** with 2-bromopyridine. However, the reaction conducted with KF as an additive in NMP as solvent resulted in 79 % yield of the isolated product (**3p**) (Scheme 2). Other nitrogen-containing heteroaryl bromides, such as 2- and 4-bromoquinoline, coupled with **2** in moderate yield.



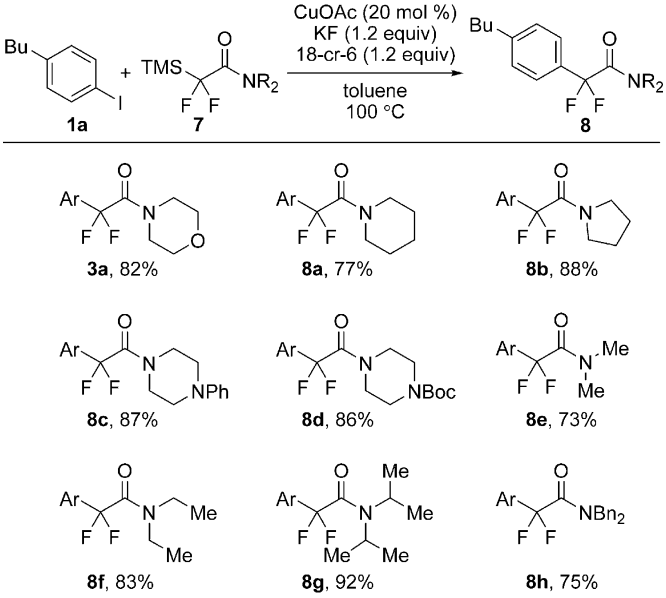
Scheme 2. Reactions were performed on a 0.100 mmol scale to determine yields by ^{19}F NMR spectroscopy. Yields of isolated products are shown within parentheses for reactions performed on a 0.400 mmol scale. General reaction conditions: aryl bromide (1 equiv), **2** (1.5 equiv), CuOAc (20 mol %), KF (1.2 equiv), 100 °C, 24 h. [a] Reactions performed using toluene as solvent and 18-cr-6 (1.2 equiv) as an additive. NMP = *N*-methylpyrrolidone.

Vinyl iodides also coupled with **2** in high yield (Scheme 3). The coupling reactions of both *trans*- and *cis*-vinyl iodides afforded the corresponding vinyldifluoroamides (**6a** and **6b**, respectively) as single stereoisomers with retention of the alkene geometry.



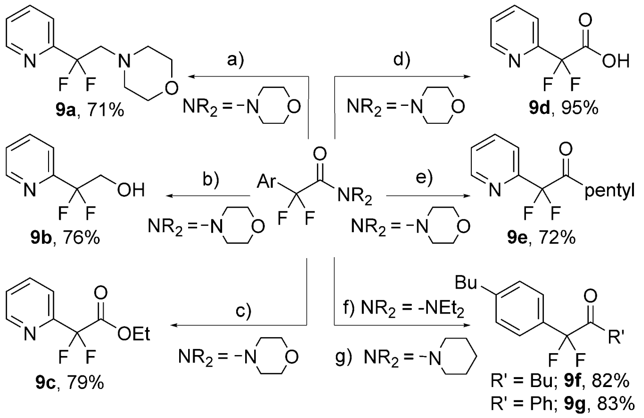
Scheme 3. Yield is that of the isolated product. General reaction conditions: vinyl iodide (0.400 mmol), **2** (0.800 mmol), CuOAc (0.0800 mmol), KF (0.480 mmol), and 18-cr-6 (0.480 mmol), in toluene (1 mL) at 100 °C for 24 h.

A variety of α-silyldifluoroamides (**7**) coupled with aryl iodides under the reaction conditions (Scheme 4). Tertiary amides containing both cyclic and acyclic groups on nitrogen atom coupled with **1a** in high yield. Varying degrees of steric bulk at the amide nitrogen atom were tolerated: dialkyl amides ranging from dimethyl- to diisopropylamides underwent coupling with **1a** in 73 to 92 % yield.



Scheme 4. Yield is that of the isolated product. General reaction conditions: **1** (0.400 mmol), α-silyldifluoroamide (0.800 mmol), KF (0.480 mmol), CuOAc (0.0800 mmol), and 18-cr-6 (0.480 mmol) in toluene (1 mL) at 100 °C for 24 h.

Aryldifluoroacetamides can serve as precursors to a variety of difluoroalkylarenes.[9] Because of the unique access to 2-pyridyldifluoroamides by this coupling chemistry, we investigated the transformation of compound **3p** into a range of 2-difluoroalkylpyridines. This 2-pyridyldifluoroamide underwent transformations under reaction conditions related to those we reported to occur with electron-neutral aryldifluoroamides (Scheme 5).[9] It was reduced to the amine **9a** with BH_3·THF in 71 % yield and to alcohol **9b** with excess sodium borohydride in 76 % yield. Compound **3p** also underwent addition of a single equivalent of an alkyl Grignard reagent in

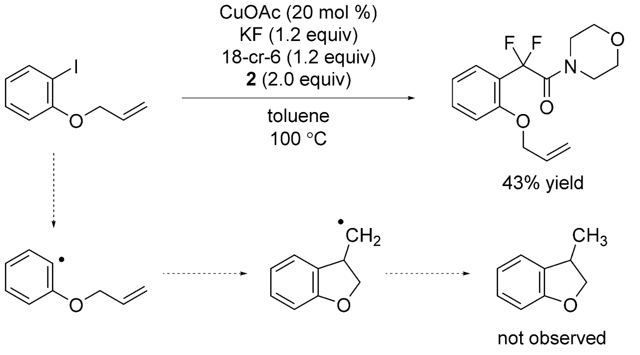


Scheme 5. Yield is that for product isolated from the reaction of 0.500 mmol **3p**, unless otherwise stated. a) BH_3·THF, THF, reflux. b) $NaBH_4$, EtOH, reflux. c) TMSCl, EtOH, reflux. d) NaOH, EtOH, RT. Yield was determined by ^{19}F NMR spectroscopy. e) Pentylmagnesium bromide, THF, −78 °C. f) Reaction of 0.300 mmol **8f**. *n*-Butyllithium, THF, −78 °C. g) Reaction of 0.300 mmol **8a**. Phenyllithium, THF, −78 °C.

72 % yield to afford a product (**9e**) equivalent to the unknown coupling of an aryl halide at the difluoromethyl group of the enolate of an alkyl difluoromethyl ketone. Monoaddition of alkyl- and arylmetal reagents is not limited to morpholinoamides: diethyl and piperidinyl amides were also converted into ketones (**9f** and **9g**) in high yield.

As noted in the introduction, the fluorine atoms in the α-position to the amide carbonyl group render the carbon center more electrophilic than that in a typical amide. Consistent with this hypothesis, hydrolysis or alcoholysis of **3p** to the corresponding carboxylic acid and ester occurred under mild reaction conditions in 95 and 79 % yield, respectively (Scheme 5). The reaction conditions for this hydrolysis were milder than those for hydrolysis of nonfluorinated amides, thus suggesting that selective hydrolysis of an aryldifluoroamide group in the presence of nonfluorinated amides is feasible.

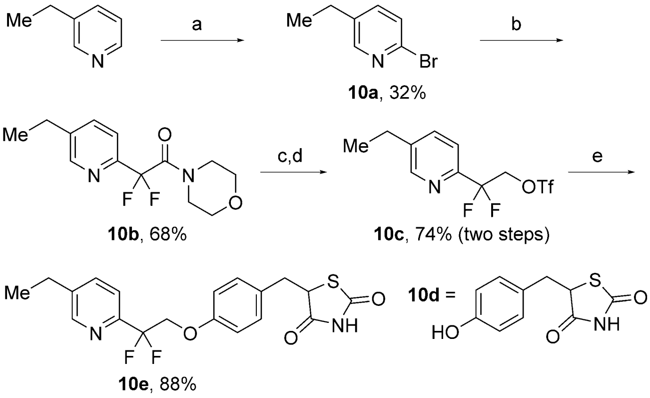
Copper-catalyzed enolate arylation reactions of aryl halides have been proposed in some cases to proceed via the intermediacy of aryl radicals,[16] and in other cases to proceed through a copper(I)/(III) cycle without the intermediacy of aryl radicals.[17] To investigate the potential that the coupling reactions of difluoroamide enolates occur through aryl radicals, we conducted the coupling reaction with 1-(allyloxy)-2-iodobenzene (Scheme 6). The corresponding aryl radical has been reported to undergo cyclization with a rate constant of $9.6\times10^{9}\,s^{-1}$.[18] The absence of 3-methyl-2,3-dihydrobenzofuran, which would be formed after hydrogen-atom abstraction from the solvent by the product of cyclization of the aryl radical, would provide evidence against the intermediacy of aryl radicals. The reaction of 1-(allyloxy)-2-iodobenzene under the standard CuOAc-catalyzed coupling conditions did not form cyclized products, thus implying that this reaction occurs, like other copper-catalyzed coupling reactions, without the intermediacy of an aryl radical. In addition, the coupling of (*Z*)-iodooctene proceeds with complete retention of the olefin geometry. If the reaction occurred through a vinyl radical, a mixture of *E* and *Z* stereoisomers of the coupled products would be expected to form.



Scheme 6. Probe for the intermediacy of aryl radicals.

Because of the versatility of both the copper-catalyzed coupling reaction and the transformations of the coupled products, we sought to apply our methodology to the synthesis of difluoro derivatives of biologically active compounds. Substituting fluorine atoms for hydrogen atoms at positions prone to oxidation has become a common strategy for increasing the metabolic stability of medicinal compounds.[2a] Because benzylic positions are common sites of metabolic oxidation, we targeted analogues of biologically active compounds containing two fluorine atoms at a benzylic position.

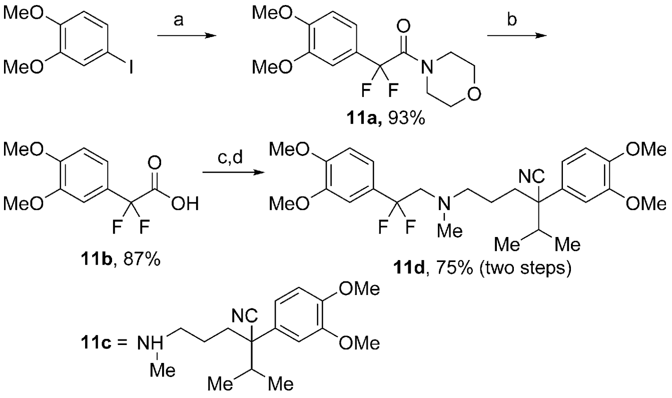
By the coupling chemistry in this work, we synthesized a difluorinated analogue of pioglitazone (**10e;** Scheme 7), a drug for the treatment of type 2 diabetes. The reaction of the 2-bromopyridine **10a** with **2** formed **10b**, which was reduced to the corresponding alcohol. The alcohol was converted into the corresponding tosylate, but the aryldifluoroalkyl tosylate was less reactive toward substitution than the unfluorinated analogue, and substitution with the phenol derivative **10d** did not occur. However, the alkyl triflate **10c** underwent Williamson etherification with **10d** to afford the difluoro pioglitazone analogue **10e** in 88 % yield.



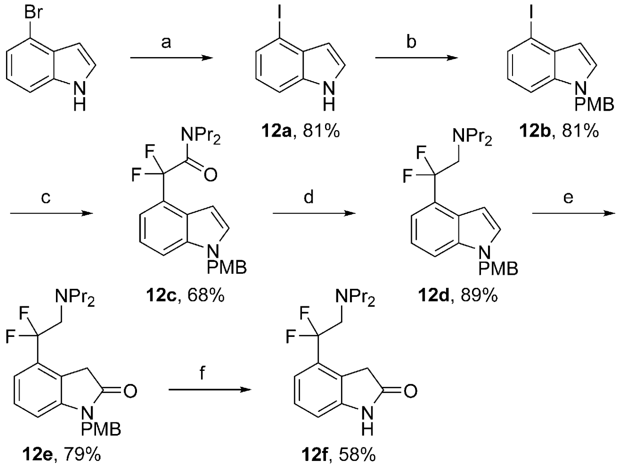
Scheme 7. Synthesis of a difluoro pioglitazone analogue (**10e**). a) *n*BuLi, $Me_2N(CH_2)_2OH$, CBr_4, hexanes, 0 °C→RT. b) CuOAc (20 mol %), KF (1.2 equiv), **2** (2 equiv), NMP, 100 °C. c) $NaBH_4$, EtOH, reflux. d) Tf_2O, pyr, CH_2Cl_2, RT. e) NaH, **10d**, DMF, 50 °C. DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

The copper-catalyzed reaction of an electron-rich aryl iodide with an α-silyldifluoroamide was exploited for the synthesis of a difluoro analogue of the cardiac drug verapamil (Scheme 8). 3,4-Dimethoxyiodobenzene coupled with **2** in the presence of CuOAc in 93 % yield. The compound **11a** was then converted into the corresponding acid in 87 % yield and coupled with amine **11c**. The resulting amide was reduced to the amine to afford the difluoro verapamil analogue **11d** in 75 % yield over the last two steps and in 61 % yield over the four-step sequence.

Finally, we synthesized a difluorinated analogue of ropinirole, a drug for the treatment of Parkinson's disease (Scheme 9). The protected indole **12b** participated in the copper-catalyzed coupling, which enabled the synthesis of the indole **12c**, which was then reduced to the amine **12d** in 89 % yield. Finally, oxidation of the indole into the corresponding oxindole **12e** and subsequent deprotection afforded the difluoro ropinirole analogue **12f**.



Scheme 8. Synthesis of a difluoro verapamil analogue (**11d**). a) CuOAc (20 mol %), KF (1.2 equiv), 18-cr-6 (1.2 equiv), **2** (2 equiv), toluene, 100 °C. b) NaOH, EtOH, 65 °C. c) CDI, DMAP, **11c**, CH_2Cl_2, RT. d) Zn-$(OAc)_2$, $HSiMe(OEt)_2$, THF, 65 °C. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, CDI = carbonyldiimidazole.



Scheme 9. Synthesis of a difluoro ropinirole analogue (**12f**). a) CuI, DMEDA, NaI, 1,4-dioxane, 110 °C. b) NaH, PMBCl, DMF, 0 °C→RT c) CuOAc (20 mol %), KF (1.2 equiv), 18-cr-6 (1.2 equiv), $TMSCF_2CONPr_2$ (2 equiv), toluene, 100 °C. d) $Zn(OAc)_2$, $HSiMe(OEt)_2$, THF, 65 °C. e) NCS, toluene/HCl, 100 °C. f) PhOMe, H_2SO_4, TFA, 100 °C. DMEDA = *N*,*N*′-dimethylethylenediamine, PMB = *p*-methoxybenzyl, TFA = trifluoroacetic acid.

In summary, we have developed a procedure for the synthesis of aryldifluoroamides from aryl halides and α-silyldifluoroamides. The reaction is catalyzed by commercially available CuOAc, does not require the addition of an exogenous ligand, and is applicable to the coupling of electron-rich, electron-poor, and sterically hindered aryl and heteroaryl iodides with a variety of α-silyldifluoroamides. We demonstrated that the aryldifluoroamide products can be converted into a range of difluoroalkylarenes that would otherwise be difficult to access, and that aryldifluoroamides serve as versatile intermediates for the synthesis of compounds of biological interest. Work is ongoing to develop general reaction conditions for the copper-catalyzed coupling of difluoroenolates with aryl bromides and to develop more general methods for the coupling of fluorinated nucleophiles.

Acknowledgements

The authors thank the NIH (GM058108) for support of this work. S.I.A. acknowledges the NSF for a graduate fellowship. We thank Dr. Patrick S. Fier for the synthesis of (*Z*)-iodooctene.

Keywords: amides · copper · cross-coupling · fluorine · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 4567–4572
Angew. Chem. **2016**, *128*, 4643–4648

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Received: January 5, 2016
Revised: February 11, 2016