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Copper-mediated intramolecular aminofluorination of 1,3-dienes by using nucleophilic fluorine reagent

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A copper-mediated intramolecular aminofluorination of 1,3-dienes is disclosed, in which both AgF and Et_3N•3HF can be used as the fluorine source. This protocol provides a variety of pyrrolidines bearing allylic fluorides with excellent regioselectivities and good diastereoselectivities.

Organofluorine compounds are abundant in medicinal and agricultural chemistry due to the unique properties of fluorine.[1] Therefore, significant progress has been made in the development of new approaches for the synthesis of fluorinated compounds.[2] Recently, transition metal-catalyzed fluorination reactions have been proved to be the powerful approaches for directly introducing fluorine into organic molecules.[3] Among them, the aminofluorination of alkenes represents one of the most efficient pathways to the synthesis of fluorinated amine derivatives, which are valuable synthons.[4] However, the related reaction of dienes has not yet to be described.

Allylic fluorides are prevalent in many insecticides, herbicides, and prostanoid analogues.[5] Traditional methods for access to these compounds via dehydroxyfluorination and nucleophilic fluorination usually suffer from harsh conditions and poor functional group compatibility.[6] Recently, transition metal-catalyzed allylic fluorinations have received much attention (Scheme 1).[7-10] For instance, Doyle and co-workers reported the first Pd-catalyzed fluorination of allylic halides.[7a,b] Nguyen disclosed the Ir-catalyzed regioselective fluorination of allylic trichloroacetimidates.[8a,b] Our group developed a Cu-catalyzed fluorination of allylic halides (Scheme 1a).[9] Recently, significant progress on the Pd-catalyzed allylic C-H fluorination of terminal alkenes has been discovered by Doyle and coworkers.[11] In these reactions, a nucleophilic fluorination of π-allyl metal complexes was involved to form C-F bonds.

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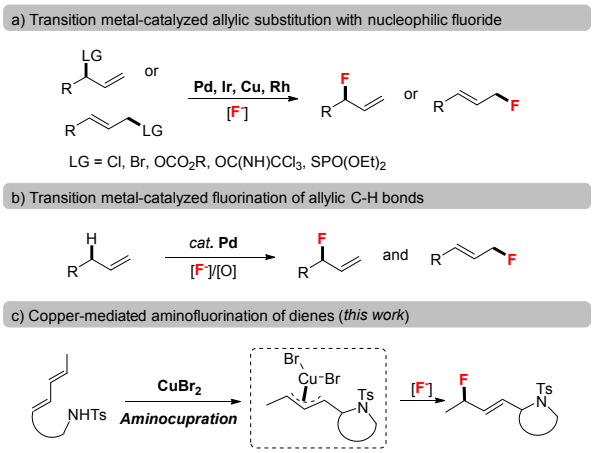
In the last few decades, Cu(II)-catalyzed/mediated difunctionalization of alkenes initiated by an aminocuperation has been extensively studied for the synthesis of nitrogen-containing heterocycles.[12] We reasoned that, a similar protocol should be suitable for the amination of 1,3-dienes, and an active allylic copper complex might be involved as the key intermediate.[13] Herein, we report a copper-mediated aminofluorination of 1,3-dienes by using nucleophilic AgF or Et_3N•3HF as the fluorine sources to deliver the 1,4-addition products regiospecifically (Scheme 1c).



Scheme 1. Metal-catalyzed/mediated allylic fluorination.

To test our hypothesis, we began our investigation by examining the intramolecular aminofluorination of 1,3-dienes **1a** with tethered sulfamides (Table 1). First, various copper salts were screened in the presence of silver fluoride as a fluorine source. To our delight, the reactions with both $CuCl_2$ and $CuBr_2$ stoichiometrically provided the 1,4-aminofluorination product **2a** with excellent regioselectivity and moderate diastereoselectivity (entries 1-2). And $CuBr_2$ showed better reactivity to give the allylic fluorination product **2a** in 50% yield. However, CuF_2 proved to be an inert catalyst (entry 3). Meanwhile, other copper(II) salts (eg. CuO and

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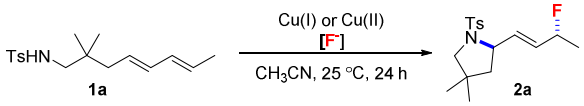
$Cu(OAc)_2$) and copper(I) salts (eg. CuCl and CuBr) were ineffective (entries 4-7). Adjusting the loading of $CuBr_2$ demonstrated that the best result was obtained with 2.5 equivalent of $CuBr_2$ (77% yield) (entry 8-10). Next, investigation on various fluorine sources indicated that NaF and KF were invalid fluorinating reagents, while other nucleophilic fluorinating reagents such as CsF, Et_3N•3HF and TBAF could deliver the desired product **2a,** but in lower yields (entries 11-15). Furthermore, either increasing or decreasing the amount of AgF reduced the product yield (see SI). We speculated that the formation of CuF_2 from $CuBr_2$ and AgF may be the key reason for the excess loading of $CuBr_2$. In order to retard the formation of CuF_2, further optimizing reaction condition by employing Et_3N•3HF as the fluorine source was conducted. Interestingly, decreasing the amount of $CuBr_2$ improved the yield of product, and the reaction using 1.1 equivalent of $CuBr_2$ with Et_3N•3HF (3.0 equiv) gave the desired product **2a** in 53% yield (entries 16-17). However, no desired product was detected in the catalytic reaction of **1a** with 20 mol% $CuBr_2$ and both fluoride sources. Notably, the choice of acetonitrile as a solvent is crucial for the successful fluorination (see SI), and moderate to good diastereoselectivities (4~9:1) were observed in above reactions.

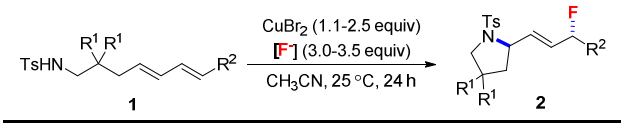
Table 1 Optimum Conditions[a]

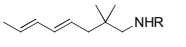
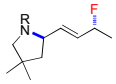
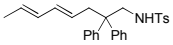
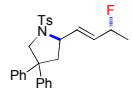
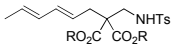
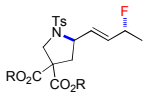
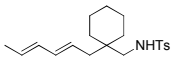
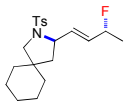
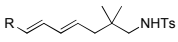
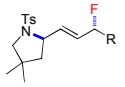
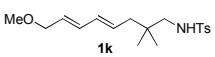
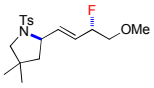
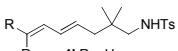
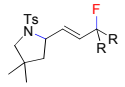


Entry	Cu (equiv)	[F⁻] (equiv)	Yield (%)[b,c]
1	$CuCl_2$ (2.0)	AgF (3.5)	25 (7:1)
2	$CuBr_2$ (2.0)	AgF (3.5)	50 (7:1)
3	CuF_2 (2.0)	AgF (3.5)	0
4	CuO (2.0)	AgF (3.5)	0
5	$Cu(OAc)_2$ (2.0)	AgF (3.5)	0
6	CuBr (2.0)	AgF (3.5)	0
7	CuCl (2.0)	AgF (3.5)	0
8	$CuBr_2$ (1.5)	AgF (3.5)	35 (4:1)
9	$CuBr_2$ (2.5)	AgF (3.5)	77 (7:1)
10	$CuBr_2$ (4.0)	AgF (3.5)	45 (7:1)
11	$CuBr_2$ (2.5)	NaF (3.5)	0
12	$CuBr_2$ (2.5)	KF (3.5)	0
13	$CuBr_2$ (2.5)	CsF (3.5)	50 (9:1)
14	$CuBr_2$ (2.5)	Et_3N·3HF (3.0)	27 (5:1)
15	$CuBr_2$ (2.5)	TBAF (3.5)	12 (4:1)
16	$CuBr_2$ (1.5)	Et_3N·3HF (3.0)	43 (6:1)
17	$CuBr_2$ (1.1)	Et_3N·3HF (3.0)	53 (7:1)

[a] Reaction conditions: **1a** (0.1 mmol) and fluoride source in CH_3CN (0.5 mL). [b] Yields determined by ^{19}F-NMR spectroscopy with N,N-dimethyltrifluoroacetamide as an internal standard. [c] The dr values given in the parentheses were determined from the crude ^{19}F NMR spectrum.

Table 2 Substrate Scope [a]



Entry	Substrate	Product	Yield of **2** (%)[b,c]
1	 **1a**, R = Ts; **1b**, R = Ns; **1c**, R = Ms		**2a** **A**: 83 (8:1) **B**: 56 (7:1)
2			**2b** **A**: 70 (8:1) **B**: 65 (8:1)
3			**2c** **A**: 51 (6:1) **B**: 44 (5:1)
4	 **1d**		**2d** **A**: 62 (6:1) **B**: 60 (5:1)
5	 **1e**, R = Me		**2e** **A**: 64 (10:1) **B**: 50 (9:1)
6	**1f**, R = Et		**2f** **A**: 71 (6:1) **B**: 61 (7:1)
7	 **1g**		**2g** **A**: 71 (15:1) **B**: 46 (8:1)
8	 **1h**, R = Et		**2h** **A**: 68 (11:1) **B**: 50 (10:1)
9	**1i**, R = *n*Pr		**2i** **A**: 70 (12:1) **B**: 67 (11:1)
10	**1j**, R = n-C_5H_{11}		**2j** **A**: 75 (12:1)
11	 **1k**		**2k** **A**: 48 (22:1)
12	 **1l** R = H		**2l** **A**: trace
13	**1m** R = Me		**2m** **A**: trace

[a] Reactions were run with 0.2 mmol scale. Condition **A**: $CuBr_2$ (0.5 mmol), AgF (0.7 mmol), stirred in CH_3CN (1.0 mL) for 24 h under rt; Condition **B**: $CuBr_2$ (0.22 mmol) and Et_3N•3HF (0.6 mmol), stirred in CH_3CN (1.0 mL) for 24 h under rt. [b] Isolated yield. [c] The dr values given in the parentheses were determined from the crude ^{19}F NMR spectrum.

With the optimized reaction conditions in hand, we next investigated the substrate scope with AgF (condition A) and Et_3N•3HF (condition B) as the fluorine sources, respectively (Table 2). First, substrates with different protecting groups on nitrogen were surveyed (entries 1-3). Sulfonyl protecting groups (**1a-1c**) were compatible with the reaction conditions, and the reactions under both condition A and B afforded the corresponding products **1a-1c** in moderate to good yields with excellent regioselectivities (entries 1-3). In general, the product yields of condition B were slightly lower than that of condition A. Furthermore various *gem*-disubstituented substrates were suitable for the reaction. The reaction of substrates with bis-phenyl and bis-ester groups proceeded smoothly under both conditions A and B affording the corresponding products **2d-2f** in good yields (62-71% under condition A and 50-61% under condition B). Interestingly, the spiro-products **2g** could be obtained in 71% yield under condition A, while 46% under condition B. Then various terminal substituents on the

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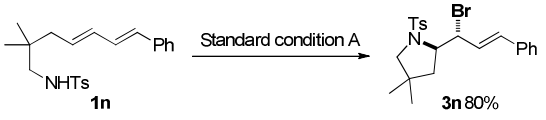
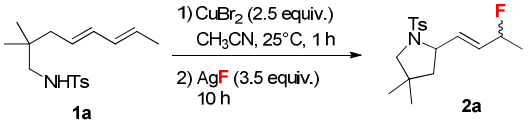
conjugate dienes were surveyed (entries 8-13). Changing the methyl group into ethyl group caused a slight lower yield of the product **2h** (68% under condition A). Further increasing the carbon chain did not affect the reaction much and still afforded the desired products **2i** and **2j** in 70-75% yields. Substrate **1k** with a methoxymethyl group at the terminal diene was also compatible with condition A and the reaction gave the product **2k** in moderate yield (48%). However, terminal diene **1l** and dimethyl substituted diene **1m** were inactive substrates for this reaction. It is worthy to noting that excellent regioselectivities were observed for all these reactions, combined with moderate to good diastereoselectivities.

To our surprise, the reaction of substrate **1n** under the standard condition A did not give the desired product **2n**, instead bromide **3n** was isolated in 80% yield (eq 1). A similar result was obtained in the absence of AgF. We speculated that the bromide species might be the key intermediate, which could be successfully transferred to corresponding fluoride product in the presence of CuBr catalyst.[9] In order to test this possibility, substrate **1a** was treated by 2.5 equivalents $CuBr_2$ in acetonitrile for 1 hour; then AgF was sequentially added to the solution. The sequential process gave the similar result (68% yield, dr 7:1) as the standard process (entry 9, table 1). When the solution of the first step was passed through a short silica gel column, and the filtrated solution was then treated by AgF, however, the reaction provided **2a** in poor yield (16%) and poor diastereoselectivity (*dr* = 1:1) (eq 2). Meanwhile, only 16% brominating product **3a** (*dr* = 1:1) was obtained in the first step.[14] These observation indicated that, the allyl-copper species might be generated in situ, which acts as a key intermediate to react with nucleophilic fluoride to give fluorination product. In contrast, the brominating product is less likely to be the key intermediate.



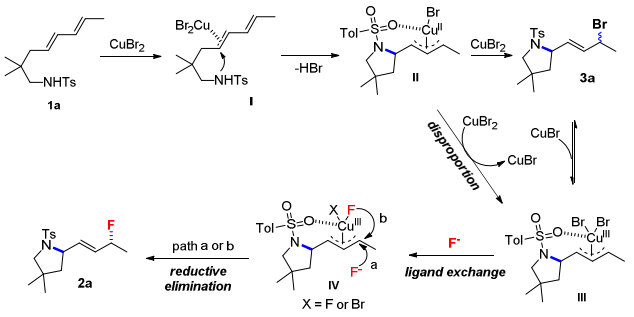
(1)



(2)

sequential steps 1 & 2	68% (*dr* 7:1)
after step 1, removal Cu catalyst by SiO_2 column; then step 2	16% (*dr* 1:1)
only step 1	15% bromination product

On the basis of the above analysis, a plausible mechanism was proposed in Scheme 2. The reaction was initiated by an intramolecular aminocupration of 1,3-dienes to generate a Cu(II) intermediate **II**, which can be oxidized by excess amounts of $CuBr_2$ to give the allyl-Cu(III) intermediate **III**. The following ligand exchange affords the allyl-Cu(III)-F intermediate **IV**, which could undergo reductive elimination to give the desired allylic fluoride **2a** via either path a or b. Alternatively, the fluorination of brominating product **3a**, generated from intermediate **II**, may also contribute to the fluorination product in small portion.[9] However, the detailed mechanism is unclear at this stage.



Scheme 2 Plausible mechanism

Furthermore, alkyl copper species is prone to undergo radical-based functionalization.[12c] In order to test the possibility of radical fluorination, some radical scavengers were added to the standard reaction. Addition of BHT or tempo (0.5 equiv) did not influence the reaction. However, the yield of **2a** was slightly decreased with 1.5 equivalent of tempo, accompanied with the small amount of oxidation byproduct (see SI). Therefore, a radical pathway for the formation of C-F bond is less likely.

In conclusion, a copper-mediated intramolecular aminofluorination of 1,3-dienes was disclosed in which both AgF and $Et_3N{\bullet}3HF$ can be used as the fluorine source. This reaction can afford a variety of valuable pyrrolidines bearing allylic fluorides. In addition, excellent regioselectivities and good diastereoselectivities were observed in this reaction. Further copper-catalyzed fluorination reactions are in progress.

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Conflicts of interest

There are no conflicts to declare.

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