Synthetic Methods

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Copper-Catalyzed Regioselective Fluorination of Allylic Halides**

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Dedicated to Professor Xiyan Lu on the occasion of his 85th birthday

Fluorination of organic molecules improves many of their properties, including solubility, bioavailability, and metabolic stability, and is therefore of great importance in pharmaceuticals and agrochemical industries.[1] The allylic fluoride motif exists in many insecticides, herbicides, and prostanoid analogues (Figure 1).[2] Compounds containing allylic fluoride moiety can also be used as synthetic intermediates for a large number of fluorinated compounds.[3] Thus, the synthesis and application of allylic fluorides have received much attention.[4] Generally, this functionality is assembled from dehydroxyfluorination of allylic alcohols and nucleophilic fluorination of allylic halides which suffers from narrow substrate scope and poor regioselectivity.[4,5]

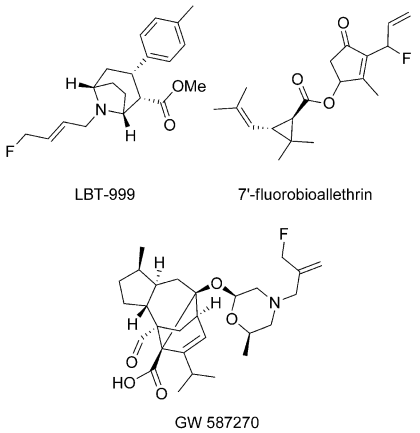
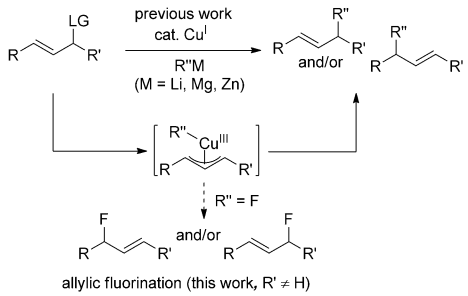


Figure 1. Significance of allylic fluorides.

Recently, transition metal catalyzed fluorination has been shown to be an efficient strategy to introduce fluorine into organic molecules, especially at a late stage of the synthesis.[6] For instance, the groups of Doyle, Gouverneur, and Wu reported palladium-catalyzed allylic fluorination under mild reaction conditions with good selectivity.[7] Nguyen[8a] and Gouverneur[8b] demonstrated that regioselective fluorination reactions could also be carried out by iridium catalysts. Despite these elegant approaches and the large number of reported allylations through C–C and C–X (X = heteroatom) bond formations, expansion of the tool box for metal-catalyzed allylic fluorination is still in great demand, especially by using metal catalysts which are abundant and cheap.

Copper catalysts have been extensively applied in organic transformations, and they often exhibit high reactivity.[9] For example, copper was proven to be one of the best metals for trifluoromethylation.[10] Unfortunately, copper-catalzyed fluorination reactions are quite rare. Copper-catalyzed allylic substitutions have been extensively studied by using relatively hard nucleophiles, such as organolithium, magnesium, or zinc reagents. Among these reactions, a copper(III) intermediate, generated from oxidative addition of alkylcuprate to allylic halide or ester, was proposed to mediate C–C bond formation.[11] Recently, the groups of Ribas and Wang independently reported that C–F bond formation could be achieved from reductive elimiantion of $ArCu^{III}F$ complexes containing triazamacromolecular ligands.[12,13] We reasoned that if the possible π-allylcopper(III) fluoride complex can be formed in situ, allylic C–F bond formation might be achieved (Scheme 1). Herein, we report the first example of copper-catalyzed fluorination of internal allylic bromides and chlorides using $Et_3N{\cdot}3HF$ as the fluorine source. It is worth noting that a functional group in substrate is required for the efficient transformation and high regioselectivity.



Scheme 1. Copper-catalyzed allylic fluorinations.

To test this hypothesis, initial investigations focused on the reaction of **1a**, bearing a proline skeleton, using stoichiometric amounts of the copper catalyst and AgF as the fluorine source (Table 1). Copper(I) salts proved to be good mediators to afford the allylic fluorination product **2a** as a single

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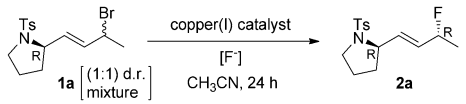
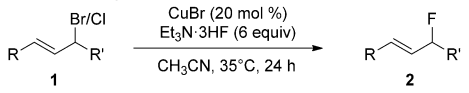
Table 1: Screening results.[a]

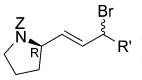
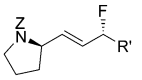
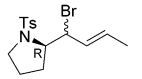
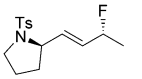
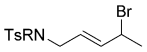
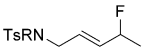
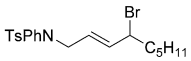
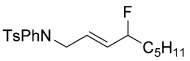
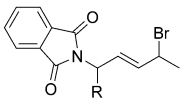
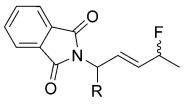
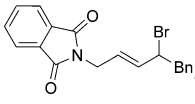
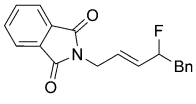
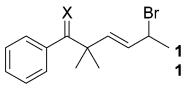
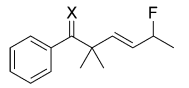
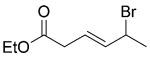
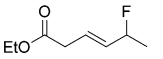
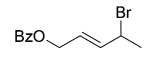
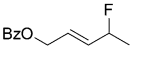
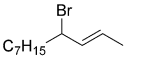
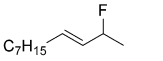
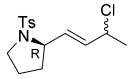
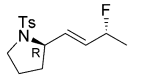
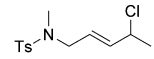
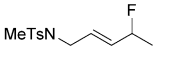
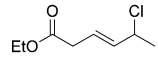
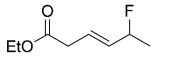


Entry	[Cu] (equiv)	[F⁻] (equiv)	*T* [°C]	Yield [%][b,c]
1	CuBr (1.0)	AgF (5.0)	RT	98 (5:1)
2	CuI (1.0)	AgF (5.0)	RT	90 (5:1)
3	CuCl (1.0)	AgF (5.0)	RT	79 (5:1)
4	CuTC (1.0)	AgF (5.0)	RT	0[e]
5	–	AgF (5.0)	RT	37 (1:1)[f]
6	CuBr (1.0)	$Et_3N{\cdot}HF$ (6.0)	RT	100 (5:1)
7	CuBr (1.0)	CsF (3.0)	RT	0
8	CuBr (1.0)	KF (3.0)	RT	0
9	CuBr (1.0)	NaF (3.0)	RT	0
10	CuBr (1.0)	KH_2F (3.0)	RT	0
11	CuBr (1.0)	Me_4NF (3.0)	RT	9 (n.d.)
12	CuBr (0.2)	$Et_3N{\cdot}HF$ (6.0)	RT	48 (5:1)
13	CuBr (0.2)	$Et_3N{\cdot}HF$ (6.0)	35	84 (4:1)
14	CuBr (0.2)	$Et_3N{\cdot}HF$ (6.0)	60	76 (3:1)
15	CuBr (0.2)	$Et_3N{\cdot}HF$ (3.0)	35	52 (4:1)
16[d]	CuBr (0.2)	$Et_3N{\cdot}HF$ (6.0)	35	82 (4:1)
17	–	$Et_3N{\cdot}HF$ (6.0)	35	0
18	$FeBr_2$ (0.2)	$Et_3N{\cdot}HF$ (6.0)	35	0
19	$CoCl_2$ (0.2)	$Et_3N{\cdot}HF$ (6.0)	35	0

[a] Reaction conditions: **1a** (0.1 mmol) in 0.5 mL of CH_3CN; [b] Yield determined by ^{19}F NMR spectroscopy using *N*,*N*-dimethyltrifluoroacetamide (DMA-CF_3) as an internal standard. [c] The d.r. value is given within parentheses and was determined by ^1H NMR spectroscopy, and (*R*,*R*)-**2a** was the major product. [d] TEMPO (1.0 equiv). [e] Reaction gave allylic esterification product. [f] Regioselectivity = 3:1. n.d. = not detected. Ts = 4-toluenesulfonyl.

Table 2: Substrate scope.[a]



Entry	Substrate	Product	Yield [%][b,c]
1 2 3	 **1a**:[e] Z = Ts, R' = Me **1b**:[e] Z = Ns, R' = Me **1c**: Z = Ts, R' = H		**2a**: 82 (4:1) **2b**: 89 (6:1) **2c**: trace
4	 **1d**[f]		**2a**: 78 (5:1)
5 6 7	 **1e**: R = Me **1f** Ph **1g** Bn		**2e**: 70 **2f**: 83 **2g**: 78
8	 **1h**		**2h**: 50
9 10 11	 **1i**: R = H **1j**[e] Me **1k**[e] Bn		**2i**: 92 **2j**: 81 (3:1) **2k**: 85 (4:1)
12	 **1l**		**2l**: 45
13 14	 **1m**: X = O **1n**: X = NOMe		**2m**: 54 **2n**: 59
15	 **1o**		**2o**: 49
16	 **1p**		**2p**: 18 (33)[g]
17	 **1q**		**2q**: 0[h]
18[d]	 **1r**[e]		**2a**: 64[i] (4:1)
19[d]	 **1s**		**2e**: 65
20[d]	 **1t**		**2o**: 51 (4:1)[j]

[a] All reactions were conducted on a 0.2 mmol scale. [b] Yield of isolated product. [c] The d.r. value is given within parentheses and was determined from the crude reaction mixture by ^1H NMR spectroscopy. [d] CuBr (30 mol%) at 50°C. [e] The mixture of isomers (d.r. = 1:1). [f] d.r. = 8:1. [g] CuBr (1 equiv). [h] The substrate **1q** was recovered quantitively at 35, 50, and 80°C. [i] 27% **1r** was recovered. [j] Regioselectivity. Bz = benzoyl, Ns = 4-nitrobenzenesulfonyl.

regioisomer and (*R*,*R*)-**2a** as major diastereoisomer (entries 1–3).[14] In contrast, the reaction with Cu(Tc) (Tc = 2-thiophenecarboxylic acid) afforded the allylic esterification product, rather than the fluorination product (entry 4). In the absence of the copper catalyst, the low yield (37%), poor regio- (3:1) and diastereoselectivity (1:1) confirmed that the copper catalyst is necessary for successful allylic fluorination (entry 5). Next, investigation on a variety of fluorine reagents demonstrated that $Et_3N{\cdot}3HF$ was an excellent fluorine source and gave the desired product **2a** in quantitative yield (entry 6). Other fluorine salts, such as CsF, KF, NaF, and KHF_2, were ineffective, and Me_4NF gave a very poor yield (entries 7–11). To our delight, the reaction afforded **2a** in moderate yield with a catalytic amount of CuBr (20 mol%, entry 12). Higher temperature was beneficial to the reaction yield but with slightly diminished diasteroselectivity. The best yield (84%) was obtained at 35°C (entries 12–14). Decreasing the amount of $Et_3N{\cdot}3HF$ reduced the reaction yield (entries 13 and 15). No significant inhibition effect was observed with the addition of the radical scavenger TEMPO, thus indicating that a radical process is less likely (entry 16). When $Et_3N{\cdot}3HF$ was employed as a fluorine source, no reaction occurred in the absence of copper catalyst (entry 17).[15] When CuBr was replaced by $FeBr_2$ or $CoCl_2$ as the catalyst, the reaction did not deliver the desired fluorination product (entries 18 and 19).

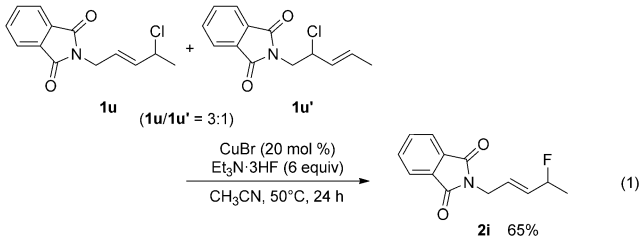
With optimized reaction conditions in hand, the substrate scope was investigated (Table 2). Different sulfonyl protecting groups on the nitrogen atom (**1a** and **1b**) were compatible with the reaction conditions, and the reactions afforded the corresponding products with excellent regioselectivities and in good yields (entries 1 and 2). However, the terminal allylic bromide substrate **1c** (R′ = H) did not give the product **2c** (entry 3). Under these reaction conditions, the substrate **1d**, a regioisomer of **1a**, provided the same product **2a** with

similar regio- and diastereoselectivity (entry 4). Other allylic bromide substrates bearing tosylamides were also suitable for this process and gave the products **2e–g** in good yields (entries 5–7). Replacement of the terminal methyl group with a pentyl group produced **1h** in a moderate yield (entry 8). In addition, the substrates **1i–k**, containing a phthalimide group, exhibited high reactivity and regioselectivity in this transformation (entries 9–11). The substrate **1l** with a benzyl group at the terminal carbon atom afforded the fluorination product **2l** in 45% yield, combined with a dehydrofluorination side product (entry 12). Further studies indicated that other functional groups, such as a ketone (**1m**), oxime ether (**1n**), and ester (**1o**), were also compatible under the reaction conditions to give fluorination products in high regioselectivity (entries 13–15). However, the substrate **1p** having an allylic ester was not compatible with the reaction conditions because of its instability. The yield was slightly increased to 33% when 1 equivalent of CuBr was used (entry 16). Finally, the allylbromide substrate **1q**, which lacks a heteroatom-containing functional group, did not show any reactivity under the standard reaction conditions, even at higher temperature (entry 17).

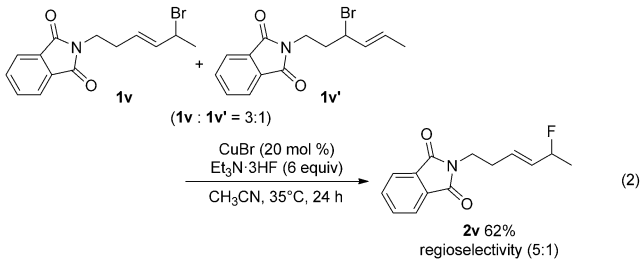
Fluorination of allylic chlorides was also conducted, and we found that this type of substrate presented similar regio- and diastereoselectivity, but slightly lower reactivity (Table 2, entries 18–20). For instance, the substrates **1r–t** could be smoothly transformed into the desired products in moderate yields under modified reaction conditions (elevated reaction temperature of 50 °C and a catalyst loading of 30 mol%). Compared to the allylbromide substrate **1o**, the reaction of **1t** gave a small amount of regioisomer, which possibly resulted from the slightly higher reaction temperature (entry 20). It is worth noting that most of substrates having functional groups exhibited excellent reactivities and regioselectivities, but there is a limitation when it comes to internal allylic halides.[16]

Interestingly, treatment of the mixture of regioisomers **1u** and **1u′** under the standard reaction conditions afforded the single isomer **2i** in 65% yield [Eq. (1)]. For the mixture of isomers **1v** and **1v′**, having one more carbon atom on the carbon chain, the reaction also proceeded smoothly to give the fluorinated product **2v** in moderate yield, but with a small amount of the regioisomer **2v′** [Eq. (2)]. For the homoallylic ester substrate, the mixture of **1w** and **1w′** also exhibited similar reactivity to afford the two isomers **2w** and **2w′**, respectively, but with a slightly diminished regioselectivity [Eq. (3)]. The decreased regioselectivity might be attributed to longer carbon chain separating the coordination site and the reactive center, thus weakening the coordination between the heteroatom and copper. Furthermore, the low regioselectivity of the substrate **1w** under standard reaction conditions might also result from weaker coordination of the ester and the copper(I) compared to the imide coordination for substrate **1v**.

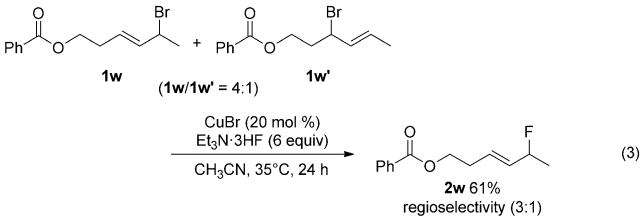
Although the mechanistic details of this transformation are not clear at the moment, preliminary observations provide some insight to this transformation. First, the reactions of the isomers **1a** and **1d** afforded the same product **2a** with similar reactivity and selectivity (Table 2, entries 1 versus 4). The mixture of **1u** and **1u′** gave the single isomer **2i** [Eq (1)].



(1)



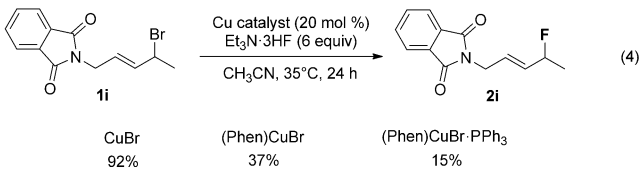
(2)



(3)

These observations indicate that either a π-allyl/Cu^{III} complex[17] or an allylic carbon cationic intermediate might be involved in the C–F bond formation. However, addition of carbon cationic scavengers did not influence the reaction yields.[18] Furthermore, compared to the 1:1 d.r. value in direct substitution fluorination of **1a** by AgF (Table 1, entry 5), an improved diastereoselectivity (4–5:1) was observed in the copper-catalyzed fluorination. The above data suggests that an allylic fluorination process involving a carbon cationic species is unlikely.

Additionally, the necessity of a functional group in the substrate for the success of the allylic fluorination indicates that precoordination of the functional group and the copper(I) catalyst plays an important role. Notably, instead of a simple CuBr catalyst, the ligated copper catalyst (Phen)-CuBr exhibited low reactivity (for **1i**), and the four-coordinated copper catalyst (Phen)CuBr·PPh_3 gave an inferior yield [Eq. (4)]. These results verified that the introduction of



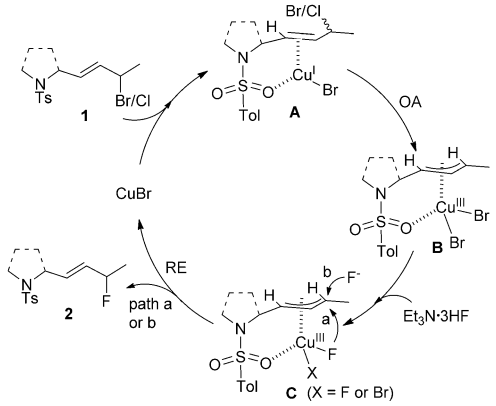
(4)

a ligand possibly reduces the precoordination of the substrate with the copper catalyst, and results in lower reactivity.

Finally, the mixture of $Et_3N{\cdot}3HF$ and CuBr did not provide a new fluorine signal,[19] thus suggesting that a CuF

species may not be a catalytically active species under the current reaction conditions.

Based on the above analysis, a mechanism is proposed (Scheme 2):[20] the reaction is initiated by the coordination of the functional group and the CuBr catalyst, and could



Scheme 2. Proposed mechanism.

promote oxidative addition of the allylic bromide to copper(I) to give the allyl/Cu^{III} complex **B**.[21,22] Sequential ligand exchange affords the allyl/Cu^{III} fluoride intermediate **C**, and the final reductive elimination gives the fluorination product.[23,24] For the C–F bond-formation step, both direct reductive elimination (path a) and S_N2-type nucleophilic attack (path b) of the allyl/Cu^{III} complex are possible, and cannot be differentiated at this stage.[25]

In summary, a novel copper-catalyzed fluorination of allylic halides has been developed using the readily available $Et_3N{\cdot}3HF$ as a fluorine source. In this transformation, the heteroatom functional group is necessary to give good reactivity and regioselectivity. Additional mechanistic studies are in progress.

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[14] For determination of the configuration of (*R*,*R*)-**2a**, see the Supporting Information.

[15] No reaction occurred in the absence of copper catalyst, either at room temperature or at 35 °C.

[16] The term of internal allylic halides is defined as two substituents on both sides of allylic moiety.

[17] When the reaction was monitored by ^{1}H NMR spectroscopy, the sharp, well-resolved peaks in the spectra argue against the formation of a paramagnetic copper(II) species.

[18] For details, see the Supporting Information.

[19] For a solution of $Et_3N{\cdot}3HF$ and CuBr, the broad single peak in the ^{19}F NMR spectra of $Et_3N{\cdot}3HF$ became a very sharp single peak, but with the same chemical shift ($\delta = -167$ ppm).

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[23] The Pearson rule-of-thumb (hard/soft-base/acid theory) predicted that the relative weak metal–fluoride interaction exists in the low-valent organotransition-metal complexes, and strong interaction in the high-valent organotrasition-metal complexes. For details, see Ref. [6a], and: a) N. M. Doherty, N. W. Hoffman, *Chem. Rev.* **1991**, *91*, 553; b) N. D. Ball, J. W. Kampf, M. S. Sanford, *Dalton Trans.* **2010**, *39*, 632.

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[25] The formation of (*R*,*R*)-**2a** as a major product could not provide more help to elucidate the stereochemistry of C–F bond step. Currently, the configuration of intermediate **C** is undefined, and the energy barrier of direct reductive elimination and S_N2-type nucleophilic attack is not clear. Thus, it is too early to define the stereochemistry of fluorination of allylic/Cu species.

