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Synthetic Methods

A Transition-Metal-Free Synthesis of Fluorinated Naphthols

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Abstract: Herein, we describe a transition-metal-free protocol for the conversion of simple 2-allyl-3-(trifluoromethyl)-phenols into substituted 5-fluoronaphthalen-1-ols. The key events of this reaction include the selective activation of two C–F bonds and formation of an intermediate hexatriene system, which undergoes a 6π electrocyclization, followed by rearomatization. This concept enables the rapid conversion (three steps) of various commercially available 3-(trifluoromethyl)phenols into novel fluorine-containing naphthols, which are difficult to prepare by previous methods. The reported sequence was also extended to a one-pot transformation of 3-(trifluoromethyl)phenols into 5-fluoronaphthalen-1-ols.

Introduction

The naphthalene structural motif can be found in several pharmaceuticals, natural products, dyes, and fluorophores, in addition to privileged catalyst structures (Figure 1). The particular functional groups present and their substitution pattern determine the biological, physical, and chemical properties of these compounds. For instance, incorporation of fluorine substituents into arenes and heteroarenes[1] has led to many novel drugs, which show improved bioavailability, greater metabolic stability, and increased lipophilicity.[2] Fluorine substitution also has a profound influence on the HOMO and LUMO levels of aromatic systems, such as fluorophores, and facilitates "electron injection",[3] hence allowing the excitation and emission wavelengths to be tuned. In recent years, much progress has been made towards the selective introduction of fluorine atoms into aromatic structures.[4] However, despite these advances, practical and efficient synthetic routes towards higher-substituted fluorinated polycyclic aromatic hydrocarbons (PAHs) are not available.[5] This is surprising in view of the numerous bioactive small molecules containing polycycles such as naphthalene. The direct fluorination of PAHs (mono-substituted naphthalene has seven vacant sites) leads to complex product mixtures.[6] Other methods rely on multi-step sequences starting from mono- and bisfluorinated arenes, require expensive transition metals, and often lack regiocontrol.[7,8]

Currently, researchers have a continuously growing selection of commercially available fluorinated molecules at their disposal, and the installation of fluorine atoms, for instance as a CF_3 group, has advanced to become a common operation.[4] The progress in this area allowed for a reverse approach to access fluorinated molecules. The transition-metal-catalyzed activation of aromatic, aliphatic, and olefinic C–F bonds has attracted many research groups in recent years.[9] However, most of the reported methods are limited to reductive C–F bond cleavage

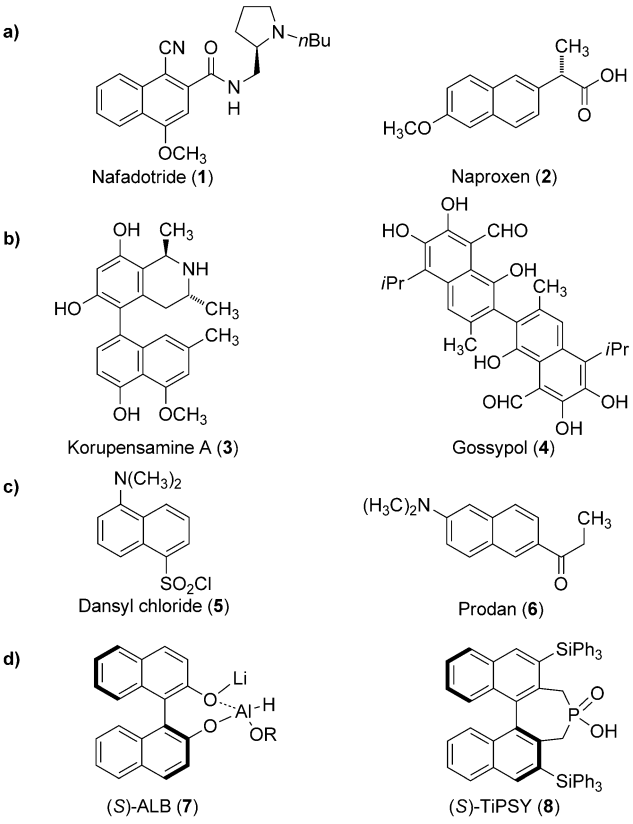

Figure 1. The naphthalene structural motif can be found in a) pharmaceuticals, b) natural products, c) fluorophores, and d) privileged catalyst structures.

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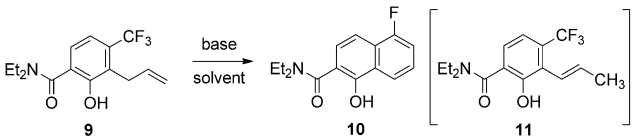
(hydrodefluorination), in which C–C bonds are not formed.[10] This might be partially due to the fact that C–F bonds are exceptionally strong (DH_{298} CH_3–F = 481 kJ mol^{-1}, DH_{298} Ph–F = 532 kJ mol^{-1})[11] and unreactive. In general, highly reactive catalysts that are usually not compatible with other functional groups are required for the activation of C–F bonds.[12] However, allylic trifluoromethyl[13] and difluoromethyl groups[14] display a lower activation barrier and can undergo substitution with carbon and nitrogen nucleophiles through a S_N2' mechanism. For instance, difluoroallenes[15] and β,β-difluorostyrenes[16] were reported to be versatile substrates for the preparation of fluorine-substituted PAHs and 3-fluorinated isoquinolines.

The application of the CF_3 group in medicinal chemistry was first reported in seminal work by Kiselyov and Strekowski et al.[17] This enabled the synthesis of aromatic (e.g. naphthalene and aniline)[18] and heteroaromatic (e.g. quinoline, isoquinoline, and quinolinone)[19] compounds. Activation of the trifluoromethyl group could be accomplished in ethereal solvents (tetrahydrofuran and diethyl ether) by using non-nucleophilic bases (e.g. lithium *N*,*N*-diisopropylamide, lithium hexamethyldisilazane, and potassium *tert*-butoxide) at temperatures typically ranging between −78 and 23 °C. In many cases, displacement of the postulated *ortho*-difluoroquinone methide intermediate preceded intramolecular cyclization to afford the heteroatom-substituted arenes. In a few cases, the fluorinated product could be isolated, but no correlation between substitution pattern and reaction pathway could be found. With the aim to identify a substrate class that exclusively leads to the fluorine-containing product, we decided to investigate this transformation in more detail.

Results and Discussion

Herein, we report the use of readily available 2-allyl-3-(trifluoromethyl)phenols for the synthesis of 5-fluoronaphthalen-1-ols. At the outset of this study, model substrate **9**, prepared from inexpensive 4-(trifluoromethyl)salicylic acid in three steps, was exposed to various reaction conditions beginning with a set of different bases (Table 1). Upon treating a solution of **9** in dimethyl sulfoxide (DMSO, 1 M) with an excess of potassium *tert*-butoxide (entry 1) or potassium hexamethyldisilazane (KHDMS, entry 2) at 120 °C, naphthol **10** could be isolated in 58 and 55% yield, respectively. In this context, we also observed a strong counterion effect, with potassium and cesium ions (entry 3) being more efficient than lithium (entry 4) and sodium ions (entry 5). Previous studies on carbanion formation in dimethyl sulfoxide by using alkali metal *tert*-butoxides showed a similar overall order of reactivity.[20,21] Sublimed potassium *tert*-butoxide, which exists in a cubane-like tetrameric structure [KO*t*Bu]$_4$, promoted the reaction with equal efficiency.[22] Nelson et al. reported that a suspension of potassium *tert*-butoxide in dimethyl sulfoxide contains low concentrations of potassium dimsyl (KDMSO).[23] On the basis of these results, we speculated that potassium dimsyl might be the active promoter. However, when **9** was exposed to a suspension of potassium dimsyl, freshly prepared from dimethyl sulfoxide and potassium hydride, only decomposition of the starting material

Table 1. Screening of reaction conditions for the cyclization of 2-allyl-3-(trifluoromethyl)phenols.



9 **10** **11**

	Solvent[a]	Base	Equiv	*T* [°C]	*t* [h][c]	**10** [%][c]	**11** [%][c]
1	**DMSO**	**KO*t*Bu**	**5.0**	**120**	**1.0**	**58**	**–**
2	**DMSO**	**KHMDS**	**5.0**	**120**	**1.0**	**55**	**–**
3	DMSO	CsO*t*Bu	5.0	120	1.0	43	15
4	DMSO	LiO*t*Bu	5.0	120	0.5	13	62
5	DMSO	NaO*t*Bu	5.0	120	0.5	14	55
6	DMSO	KDMSO	5.0	120	0.5	–	–
7	DMSO	Cs_2CO_3	5.0	120	1.0	–	66
8	DMSO	KO*t*Bu	5.0	23	6.0	–	79
9	DMSO	KO*t*Bu	5.0	60	60	12	58
10	DMSO	KO*t*Bu	5.0	160	0.5	44	–
11	DMSO	KO*t*Bu	3.0	120	1.0	22	–
12	DMSO	KO*t*Bu	2.5	120	6.0	39	24
13	**sulfolane**	**KO*t*Bu**	**7.0[b]**	**120**	**7.0**	**58**	**–**
14	DMF	KO*t*Bu	5.0	120	3.0	31	–
15	HMPA	KO*t*Bu	5.0	120	0.5	37	2
16	NMP	KO*t*Bu	5.0	120	0.5	–	11
17	DMPU	KO*t*Bu	5.0	120	0.5	–	28
18	dioxane	KO*t*Bu	5.0	120	0.5	30	–
19	toluene	KO*t*Bu	5.0	120	0.5	11	–
20	*t*BuOH	KO*t*Bu	5.0	120	1.0	–	55

[a] 1 M solution. [b] One equivalent of base was added per hour. [c] Isolated yields.

was observed (entry 6). Using inorganic bases, such as cesium carbonate (entry 7), or Schwesinger's P_1-*t*Bu base[24] (not shown) led to partial isomerization of the double bond, but no product was obtained. We then examined the influence of temperature, time, and substrate to base ratio. When the reaction was performed at 23 °C (entry 8), no cyclization product was formed, whereas only trace amounts were detected at 60 °C (entry 9). At higher temperatures (160 °C), the reaction was less clean and the yield decreased to 44% (entry 10). Reactions were generally complete in one hour for **9**. Reducing the equivalents of base (entry 11 and 12) resulted in incomplete conversion even after prolonged reaction times (entry 12).

A solvent screen using the model system, **9**, revealed that the reaction proceeded most efficiently in dry dimethyl sulfoxide or sulfolane (entry 13).[25,26] A sluggish reaction was observed when the dipolar, non-protic solvents *N*,*N*-dimethylformamide (DMF, entry 14), hexamethylphosporamide (HMPA, entry 15), *N*-methyl-2-pyrrolidone (NMP, entry 16), and *N*,*N*′-dimethylpropyleneurea (DMPU, entry 17) were used, though some of these solvents are known to break down the oligomeric structures of potassium *tert*-butoxide to produce a highly basic media.[26c] Toluene (entry 18) and dioxane (entry 19) also gave lower yields, and the polar protic solvent *tert*-butanol (entry 20) only led to partial isomerization (55% yield).

When samples were taken out of the reaction mixtures after 6, 12, 18, and 24 min, and analyzed by ^{19}F NMR spectroscopy (1 M in $CDCl_3$, C_6F_6 internal standard), we noticed that **9** (δ = −62.9 ppm) was immediately consumed, and smoothly con-

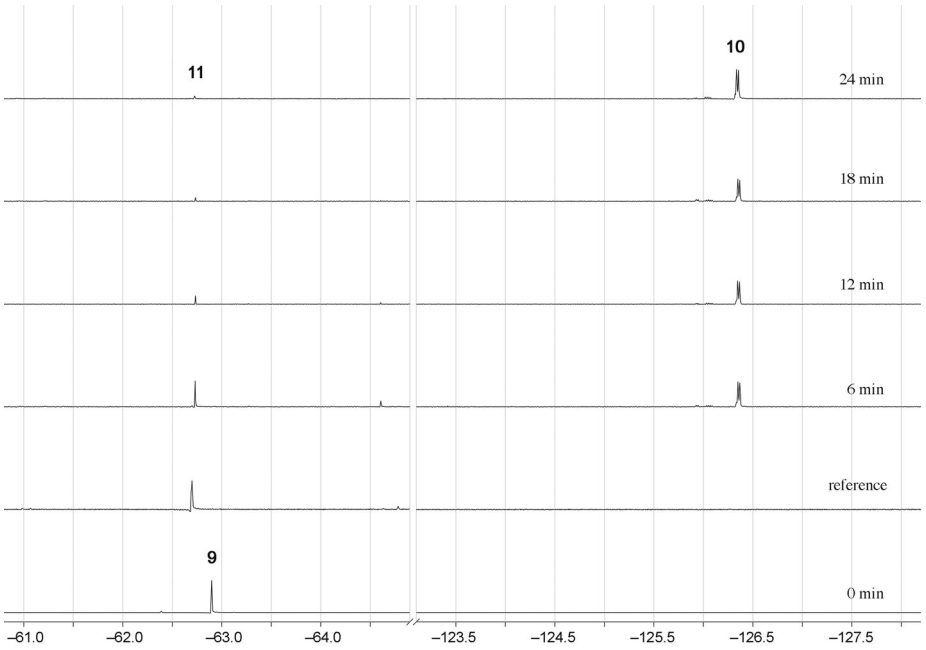
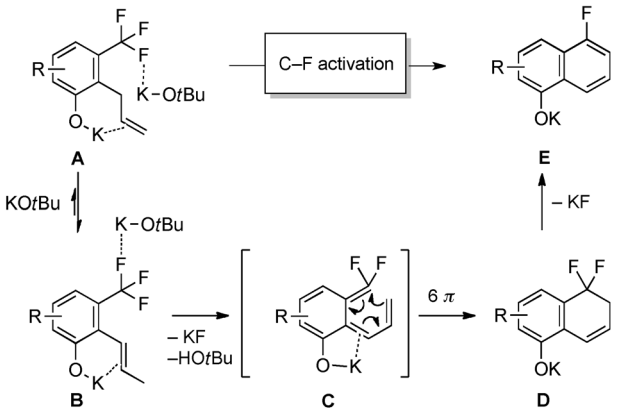


Figure 2. Monitoring the transformation of **9** into **10** by ^{19}F NMR spectroscopy (DMSO, 120 °C, 24 min).

verted into naphthol **10** ($\delta = -126.4$ ppm), within less than 30 min (Figure 2). Isolation and characterization of the rapidly formed species, which appeared in the spectrum at $\delta = -62.7$ ppm, showed that the transformation proceeded via intermediate **11**. Exposure of pure **11** to the same reaction conditions also produced the cyclized product **10** (52% yield), but no intermediate **9** could be detected (see the Supporting Information).

To explore the scope of the reaction we subjected a variety of readily available 2-allyl-3-(trifluoromethyl)phenols to the experimental reaction conditions (Table 2, see the Supporting Information for further details). This led to the formation of several di-, tri-, and tetra-substituted naphthalenes in up to 58% yield. Electron-rich as well as electron-poor substrates underwent the transformation. The presence of halogen substituents [Cl (**16**, and **23**), F (**18**, **19**, **20**, **22**, and **25**)], ethers [OCH_3 (**15**), SCH_3 (**26**)], amides [$CONEt_2$ (**10**)], and acids [COOH (**24**)] were tolerated. For the synthesis of **13**, **14**, and **15**, a larger excess of base (conditions b) was required, whereas for the chlorine-substituted product, **16**, four equivalents (conditions c) were enough to observe full conversion. The exchange of potassium *tert*-butoxide for potassium hexamethyldisilazane (conditions d) increased the yield of **17** from 47 to 56%. Esters and substrates containing a nitro group were unstable under the reaction conditions and complex mixtures were formed. Byproducts resulting from heteroatom substitution of fluorine atoms (F→O*t*Bu) were not isolated. The inherent free phenol is an ideal handle for the derivatization of the substrates and enables the further functionalization of the products. In addition, it might also play a crucial role for the cyclization. Paquin et al. speculated that the presence of a free hydroxy group in close proximity to the fluoro substituents is necessary for the displacement of certain C–F bonds (no examples given).[14] To validate this hypothesis, we prepared two substrates lacking the free phenol. When a solution of methoxymethyl derivative **27** or 1-allyl-2-(trifluoromethyl)benzene (**28**) were subjected to the standard protocol, we only observed complex mixtures. Surprisingly, even temperatures as low as 0 °C were not tolerated and the desired fluoronaphthalenes were never isolated. The exact role of the phenol is still unclear, but we believe that coordination of the alkali metal phenoxide to the double bond and activation of the trifluoromethyl group plays a critical role.

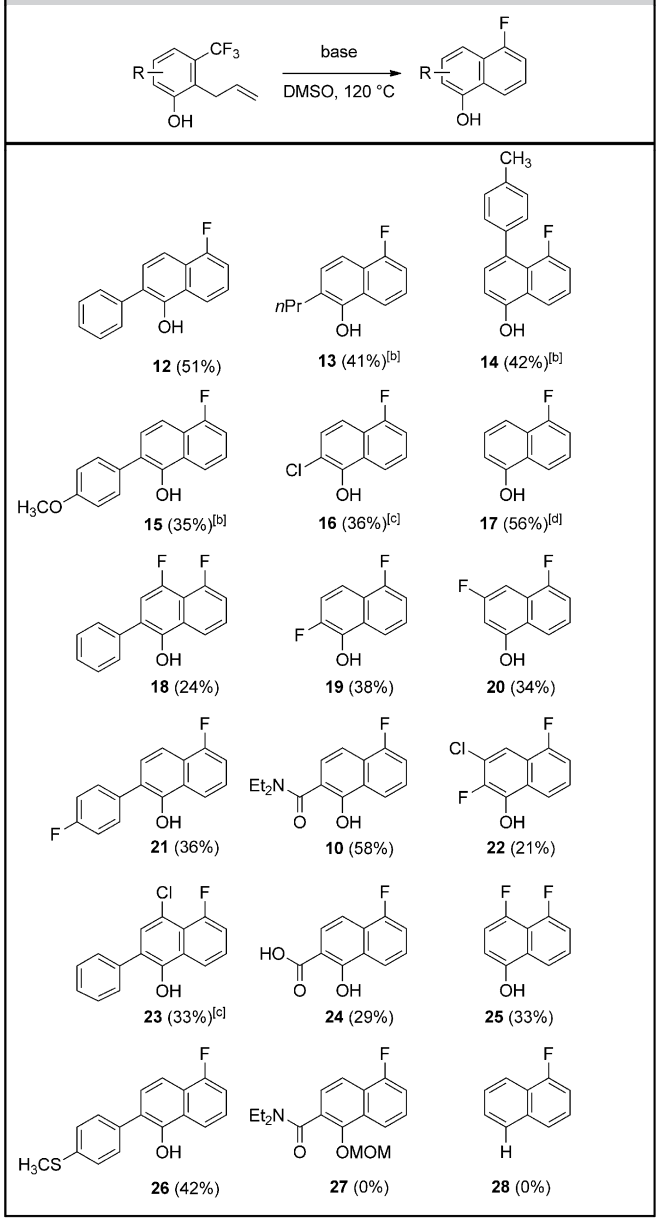
A plausible reaction pathway is depicted in Scheme 1. In the presence of potassium *tert*-butoxide, **A** is in equilibrium with its vinyl isomer **B** (characterized for



Scheme 1. Proposed reaction mechanism for the formation of 5-fluoronaphthalen-1-ols.

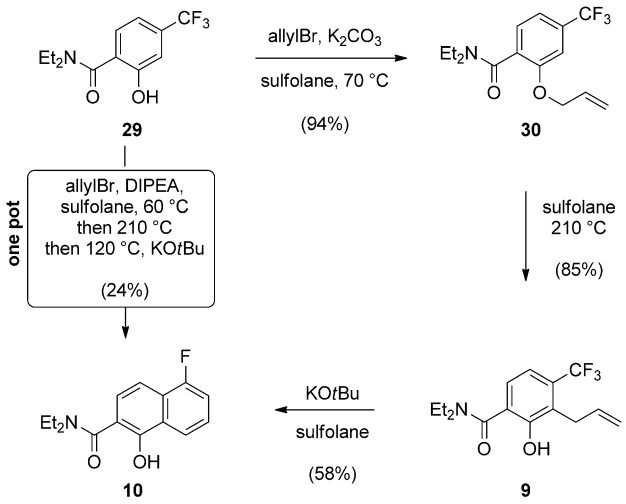
$R^3 = CONEt_2$). For both isomers, potassium ions might activate the trifluoromethyl group[27] and coordinate to the double bond,[28] thus enhancing the acidity of the methylene group of **A** and the terminal methyl group of **B**. In the presence of excess base (5 equiv KO*t*Bu), deprotonation and formation of a short-lived π-allyl potassium complex[29] occurs, and collapses to **C**. Intermediate **C** (not directly detectable) contains a *gem*-difluorohexatriene motif, which undergoes a 6π electrocyclization to produce **D**.[30] Although general studies regarding the influence of fluorine substituents on 6π electrocyclizations are not available, it is known that fluoroorganic compounds show increased reaction rates for many pericyclic reactions.[31] However, the opposite effect was observed for the thermal rearrangement of polyfluorinated substrates, such as 9,10-bis(trifluorovinyl)pheanthrene.[32] Loss of a second equivalent of potassium fluoride and rearomatization gives **E**. For the conver-

Table 2. Substrate scope for the synthesis of fluorinated napthols.



sion of **9** into **10**, the ^{19}F spectrum at 6 min (Figure 2) shows that **9** is rapidly converted into **11**, and **10** is continuously formed. Monitoring the cyclization of pure **11** (see the Supporting Information) showed that the cyclization into **10** proceeds faster than the cyclization from **9**. Even though the fluoride ion is generally regarded as a poor leaving group, we believe that the increase in leaving-group ability results from a beneficial C-F-K interaction,[27] which leads to an additional polarization of the C–F bond. According to Pearson's HSAB (hard and soft acids and bases) principle,[33] both fluorine and potassium can be classified as hard atoms and thus should associate strongly. A radical mechanism cannot be excluded, though addition of radical scavengers, such as 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO), provided the product in similar yield.

For the synthesis of 5-fluoronaphthalen-1-ols, commercially available 3-(trifluoromethyl)phenols were first allylated and then subjected to a Claisen reaction to give the cyclization precursors, 2-allyl-3-(trifluoromethyl)phenols. We hypothesized that the experimental procedure could be further simplified by combining the overall process into a single flask. To develop a one-pot protocol, each step en route to **10** was investigated independently (Scheme 2), and, after extensive experimentation, sulfolane emerged as the optimal solvent. Of note is the observation that the Claisen rearrangement in sulfolane (**30** to **9**) went to completion within 3 h (210 °C) compared with 24 h when this reaction was performed neat at 220 °C. Surprisingly, the use of dimethyl sulfoxide was only tolerated for steps 1 (allylation) and 3 (cyclization), and no conversion was observed for the Claisen reaction after 3 h at 185 °C.



Scheme 2. One-pot conversion of **29** into **10**.

When the individually optimized steps were initially combined into one single flask, **10** was not formed. Instead, the free phenol of **9** underwent a 5-*exo* cyclization onto the adjacent allyl group to give the corresponding dihydrobenzofuran (see the Supporting Information for further details). Further experiments showed that potassium carbonate promoted this unusual cyclization, whereas a base screen (DBU, proton sponge, NaH, 2,6-lutidine, 1,1,3,3-tetramethylguanidine, and DIPEA) revealed that only *N*,*N*-diisopropylethylamine (DIPEA) could prevent this side reaction. Finally, when a solution of **29** in sulfolane was exposed to the optimized reaction conditions, **10** was obtained in 24% yield (62% yield per step).

Conclusion

In summary, we have reported a practical method for the synthesis of 5-fluoronaphthalen-1-ols starting from readily available 2-allyl-3-(trifluoromethyl)phenols. We believe that the reaction includes the sequential activation of two C–F bonds, and that the cyclization proceeds through a 6π electrocyclization. This transformation benefits from inexpensive reagents

(potassium *tert*-butoxide) and solvents (dimethyl sulfoxide and sulfolane). Notably, it was discovered that a free hydroxy group adjacent to the allyl unit is required for the reaction to occur. Additionally, no transition metals are required, and there is no need for a low-temperature set-up. We are currently trying to extend this methodology by exchanging the oxygen functionality for nitrogen and sulfur functionalities. A large number of phenol, thiophenol, and aniline building blocks are commercially available for this purpose. The developed protocol will enable the synthesis of novel aromatic scaffolds for medicinal and biological chemistry (e.g. fluorophores for cellular imaging). Finally, we demonstrated that the three-step conversion of 3-(trifluoromethyl)phenols to 5-fluoronaphthalen-1-ols can be combined into a single flask.

Experimental Section

General procedure for the synthesis of 5-fluoronaphthalen-1-ols

Potassium *tert*-butoxide (5.0 equiv) was added to a solution of the 2-allyl-3-(trifluoromethyl)phenol (1 equiv) in dimethyl sulfoxide (1.0 M) at 23 °C. The mixture was heated to 120 °C in a sealed pressure vessel under an argon atmosphere and the reaction was monitored by thin-layer chromatography until completion (1–3 h). Upon consumption of the starting material, the reaction mixture was allowed to cool to 23 °C, diluted with water, and acidified with aqueous hydrochloric acid (1 M). The aqueous layer was extracted with ethyl acetate (3×50 mL), the combined organic layers were washed with water (50 mL) and saturated aqueous sodium chloride (50 mL), and the washed organic solution was dried over sodium sulfate. The dried solution was filtered, the filtrate was concentrated, and the residue was purified by flash column chromatography on silica gel (ethyl acetate in hexanes, or dichloromethane) to afford the corresponding 5-fluoronaphthalen-1-ol.

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Keywords: C–F bond activation · fluorinated substituents · halogen compounds · naphthalene · one-pot reactions

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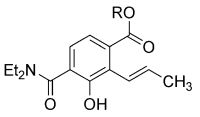
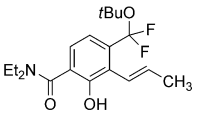
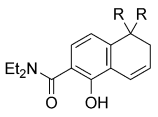
[30] Evidence for the intermediacy of **C** was obtained from the cyclization of **9** into **10**. Analysis of a reaction aliquot by mass spectrometry after 6 min showed **10** together with the following intermediates:



R = *t*Bu, ESI $[M+H]^+$ = 334.2
R = H, ESI $[M+H]^+$ = 278.1



ESI $[M+H]^+$ = 356.2



R = O*t*Bu, ESI $[M+H]^+$ = 390.3
R = F, ESI $[M+H]^+$ = 282.2

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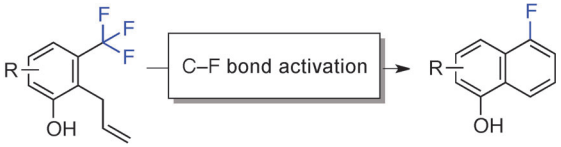

A synthetic platform for fluoronaphthols: The base-promoted cyclization of 2-allyl-3-(trifluoromethyl)phenols leads, by means of two sequential C–F bond activations, to the formation of substituted 5-fluoronaphthalen-1-ols (see scheme).

Synthetic Methods

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A Transition-Metal-Free Synthesis of Fluorinated Naphthols