Squaramide/Li⁺-Catalyzed Direct S$_N$1-Type Reaction of Vinyl Triflates with Difluoroenoxysilanes through Vinyl Cations

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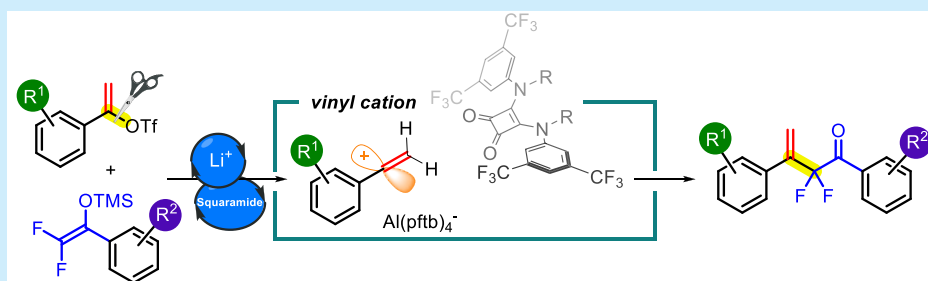
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ABSTRACT: Difluoromethylene-skipped enones have been readily obtained from arylvinyltriflates and aryldifluoroenoxysilanes. While these useful compounds are difficult to synthesize by the classical aldol/dehydration approach, the use of a squaramide/Li⁺ catalyst allows their direct formation via a vinyl carbocation paired with a weakly coordinating perfluorinated alkoxyaluminate. This strategy makes possible a reaction between a typically weak electrophile and a weak nucleophile. Control experiments and DFT computations shed light on the mechanism of this transformation.

Difluoromethylene-skipped enones are useful precursors of fluorinated alcohols, sugars, and fragments of natural products.[1] Only a few methods allow the one-step synthesis of such molecules. One way is to condense 1,1-difluoroallyl-lithium (obtained from 3,3-difluoro-3-bromopropene and BuLi) on an ester at −100 °C (Scheme 1, eq 1).[1a,2] Three transition-metal-catalyzed reactions have also been described, all starting from iododifluoroketones (eqs 2−4).[3] We report herein the lithium-catalyzed direct coupling of arylvinyltriflates with aryldifluoroenoxysilanes (eq 5). Our strategy is based on the formation of a vinyl carbocation by abstraction of the triflate anion promoted by the lithium salt and trapping of the latter by the fluorinated enol ether. The main challenge with this approach is that vinyl carbocations are sluggish electrophiles because of the high intrinsic barrier for sp ↔ sp² rehybridization.[4] Moreover, because of the strong electron-withdrawing ability of two fluorine atoms, difluoroenoxysilanes are relatively weak nucleophiles.[5] In recent years, synthetic methodologies exploiting the enhanced reactivity of vinyl carbocations paired with weakly coordinating anions have emerged.[6] For instance, using the Li⁺ salt of the perfluorinated alkoxyaluminate [Al{OC(CF₃)₃}₄]⁻,[7] we could efficiently generate vinyl carbocations from vinyl triflates and react them with arenes.[6c,8]

We were thus curious to know whether vinyl carbocations could be tamed in such a way that they can react with difluoroenoxysilanes.[9] This would represent the first Lewis-acid-catalyzed direct synthesis of difluoromethylene-skipped enones.

Our investigation began with the use of substrates **1a** and **2a** to synthesize difluoroenone **3a** (Table 1). Various lithium salts were tested as catalysts (5 mol %) in DCE at 40 °C (entries 1−5). As an encouraging result, a 44% NMR yield was obtained with the perfluorinated alkoxyaluminate [Al{OC(CF₃)₃}₄]⁻ (entry 5), which is the least coordinating anion of the series.[10] Changing the solvent proved deleterious (entries 6−8). Several additives were introduced in the reaction mixture (10 mol %), including ureas and squaramides **A−F** (entries 9−20).

Ureas deprotonated by LiHMDS have been used previously as weak coordination counterions of vinyl carbocations in Li-catalyzed C−H bond functionalization.[6d] Although the present case is different since no base is used, we nonetheless observed a positive effect with some of these additives. While the use of 1,3-diphenylurea **A** and 1,3-bis(3-(trifluoromethyl)phenyl)urea **B** decreased the yield (entries 9 and 10), a slight improvement was observed with 1,3-bis(3,5-bis(trifluoromethyl)phenyl)urea **C** (48%, entry 11). The corresponding thiourea **D** proved much less efficient (entry 12). Employing the pentafluoro-phenyl-substituted squaramide **E** allowed us to reach 59% yield (entry 13). Remarkably, squaramide **F** exhibiting 3,5-

Scheme 1. Synthesis of Difluorinated β,γ-Enones[a]
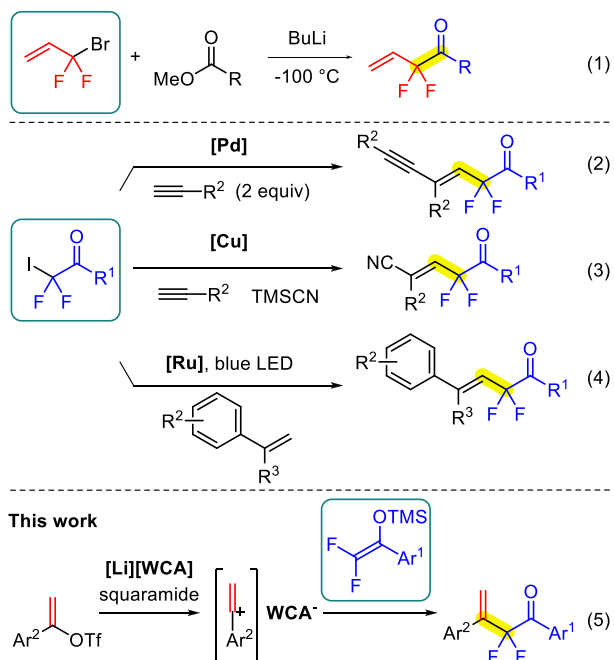
[a]WCA = weakly coordinating anion.

Table 1. Catalyst Screening and Optimization[a]

entry	WCA	additive	solvent	yield (%)[b]
1	OTf	-	DCE	16
2	BF₄	-	DCE	16
3	PF₆	-	DCE	20
4	SbF₆	-	DCE	20
5	[Al{OC(CF₃)₃}₄]	-	DCE	44
6	[Al{OC(CF₃)₃}₄]	-	DFB	11
7	[Al{OC(CF₃)₃}₄]		toluene	0
8	[Al{OC(CF₃)₃}₄]		pentane	10
9	[Al{OC(CF₃)₃}₄]	A	DCE	12
10	[Al{OC(CF₃)₃}₄]	B	DCE	30
11	[Al{OC(CF₃)₃}₄]	C	DCE	48
12	[Al{OC(CF₃)₃}₄]	D	DCE	24
13	[Al{OC(CF₃)₃}₄]	E	DCE	59
14	[Al{OC(CF₃)₃}₄]	F	DCE	98 (85)[c]
15	-	F	DCE	0
16	[Al{OC(CF₃)₃}₄]	F	DFB	61
17	[Al{OC(CF₃)₃}₄]	F	toluene	0
18	[Al{OC(CF₃)₃}₄]	F	pentane	0
19	[Al{OC(CF₃)₃}₄]	F	THF	0
20	[Al{OC(CF₃)₃}₄]	F	MeCN	0

[a]Reaction conditions: 1a (0.1 mmol), 2a (0.3 mmol), DCE (1 mL). [b]NMR yield using CH_2Br_2 as an internal standard. [c]Isolated yield. WCA = weakly coordinating anion; DCE = 1,2-dichloroethane; DFB = o-difluorobenzene.
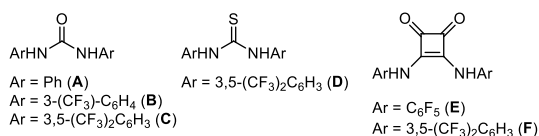
bis(trifluoromethyl)phenyl groups led to an excellent 98% NMR yield (85% isolated; entry 14). Of note, **F** alone is not able to catalyze the formation of the product (entry 15). With the [Li][Al{OC(CF₃)₃}₄]/**F** catalytic mixture, no other solvents proved competitive compared to DCE (entries 16–20). Attempts to lower the temperature, to change the proportions of the lithium salt/**F** mixture, or to use **F** with other Lewis acids (AlCl₃, GaCl₃, InBr₃, FeBr₂, etc.) resulted in much lower yields. Changing the **1a**:**2a** ratio also strongly affected the efficiency of the reaction. For instance, an NMR yield of 69% (vs 98%) was obtained using 2 equiv of **2a** instead of 3 (Table S4).

The optimized conditions proved efficient in the synthesis of a variety of difluoromethylene-skipped enones from arylvinyltriflates and aryldifluoroenoxysilanes (Scheme 2).

The presence of electron-donating or -withdrawing groups at the ortho-, meta-, or para-positions of the aryl groups was tolerated, and the products were usually obtained in good isolated yields. Some incompatible substrates, such as

Scheme 2. Scope of the Reaction[a,b]
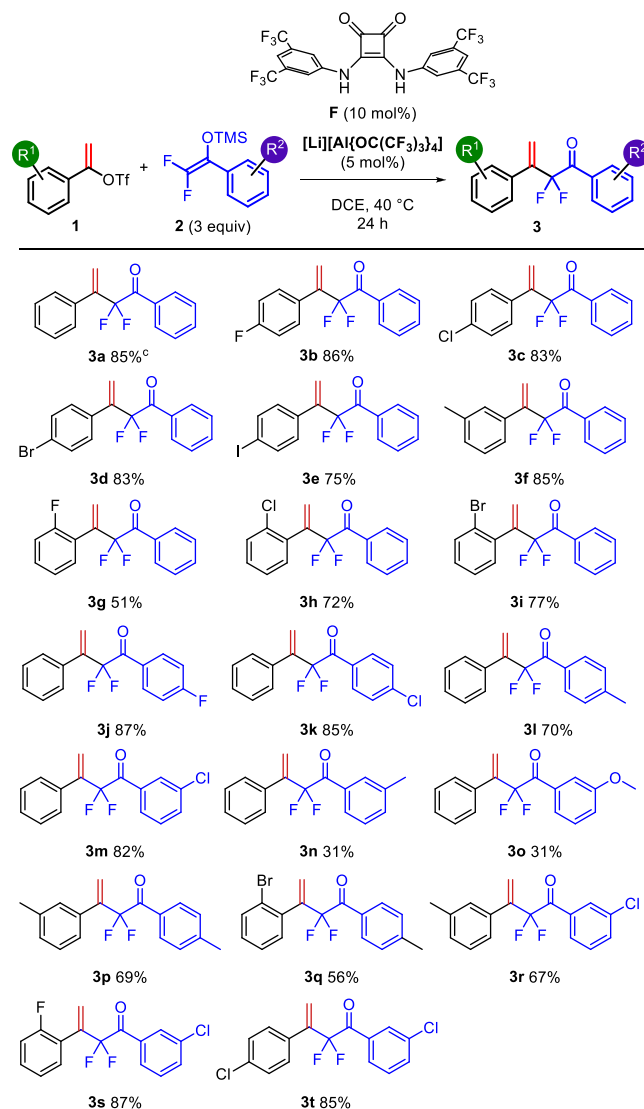
[a]Reactions performed on a 0.1 mmol scale. [b]Isolated yields. [c]86% isolated yield (222 mg) on a 1 mmol scale.

heteroaryl-substituted difluoroenoxysilanes, are indicated in Table S6 (Supporting Information). Of note, alkyl-substituted or cyclic vinyl triflates are not reactive under the developed conditions.

Intrigued by the role of the squaramide in the dramatic increase of the reaction efficiency, we monitored the reaction of **F** with 2 equiv of enoxysilane **2u** by NMR (Scheme 3, eq 1).

Scheme 3. Control Experiments
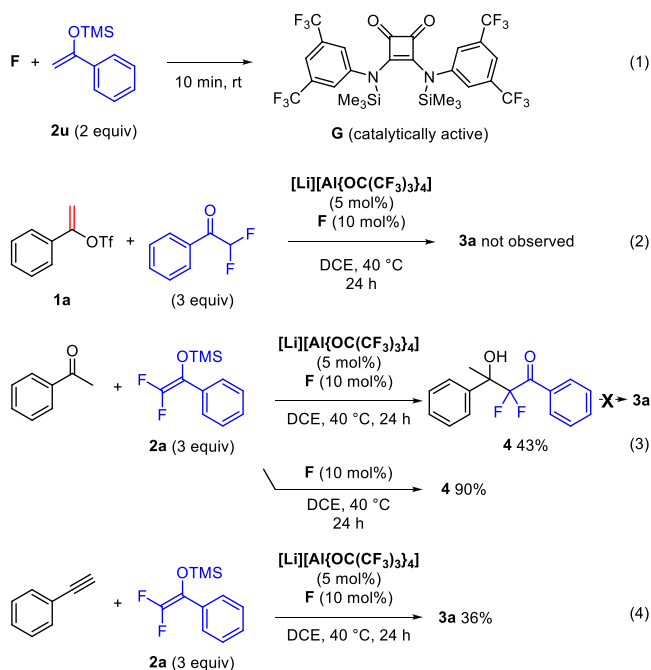
We observed the rapid disappearance at room temperature of the NH protons of **F** and the appearance of the typical signals of 2,2-difluoroacetophenone. This agrees with the reported protodesilylation of enoxysilanes promoted by squaramides, which results in N-silylated species such as **G**.[11,12] While this species could not be isolated in pure form, using it as an additive instead of **F** provided **3a** in virtually the same yield (82% vs 85% with **F**). We believe the squaramide plays the role of a ligand to improve the solubility of the lithium salt. In fact, $[Li][Al\{OC(CF_3)_3\}_4]$ is only slightly soluble in DCE.[7a] Squaramide **F** is also hardly soluble in this solvent. However, adding **F** to a mixture of $[Li][Al\{OC(CF_3)_3\}_4]$ and enoxysilanes **2a** clearly helps dissolve the materials. This is likely due to the in situ transformation of **F** into **G**, which is much more soluble due to the TMS groups.

As shown in eq 2, 2,2-difluoroacetophenone is not a likely reaction intermediate as it does not provide **3a** when reacted with **1a**. Acetophenone itself, which might arise from the adventitious hydrolysis of **1a**, is also not a likely precursor. Its reaction with **2a** led to aldol **4** in 43% yield (eq 3).[13] This yield is increased to 90% when squaramide **F** is the only catalyst. This test also demonstrates that an aldol such as **4** is not an intermediate toward **3a** by elimination. In fact, E1 eliminations of alcohols exhibiting a vicinal *gem*-difluoro substitution pattern are difficult to achieve since the corresponding carbocations would be destabilized by the electron-withdrawing ability of the fluorine atoms.[14] E2 approaches are also known to be difficult,[15] which give credit to the present methodology compared to classical aldol/dehydration ap-

proaches. Finally, we tested the reaction of phenylacetylene, which could form after elimination of TfOH from **1a** (eq 4). However, the yield of **3a** in this case was very modest (36%). Besides, repeating the same reaction under the same conditions but adding 1 equiv of TfOH (which might form during vinyl triflate elimination toward phenylacetylene) lowered the yield of **3a** to 17%.

Thus, the above experiments support a direct reaction between **1a** and **2a**, which could be explained by the formation of a vinyl carbocation. To support this proposal, putative intermediates and transition states were computed at the ωB97-XD/6-31+G(d,p) level of theory (Figure 1; see the SI for details).
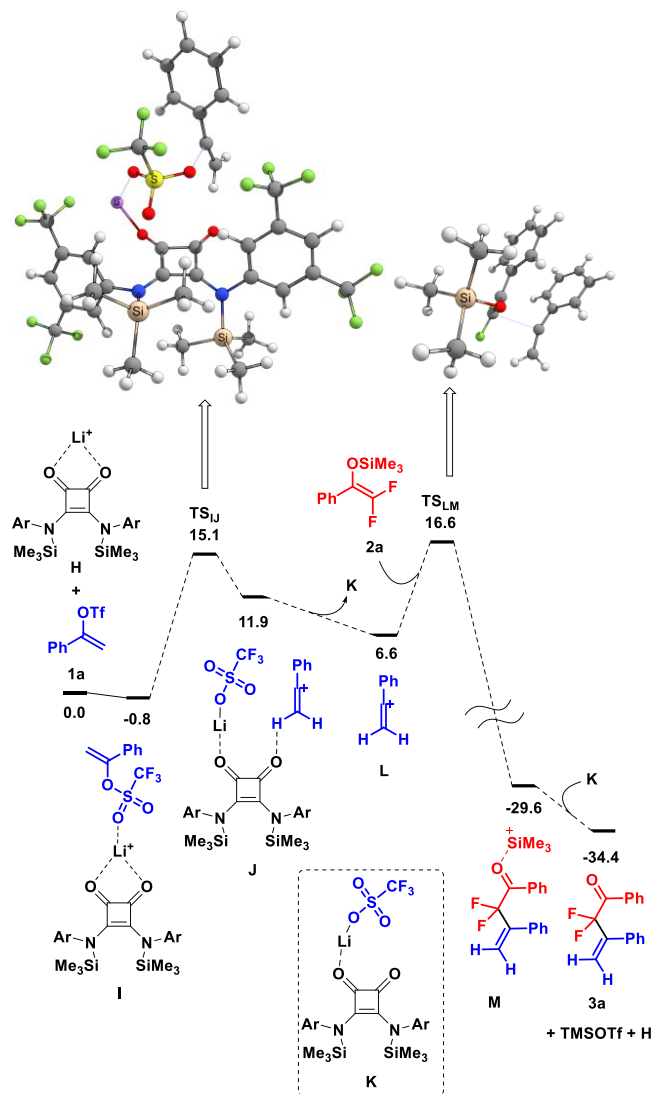
**Figure 1.** Computed free energy profile (ΔG, kcal/mol; Ar = 3,5-$(CF_3)_2C_6H_3$).

The silylated squaramide and Li^+ converged as complex **H** as the most stable species. In **H**, the lithium ion is chelated by the two carbonyl oxygen atoms. The vinyl triflate **1a** binds to Li^+ via a sulfonyl oxygen to give **I**, which lies at −0.8 kcal/mol on the free energy surface. Cleavage of the C−O bond to give vinyl cation **J** (11.9 kcal/mol) requires 15.9 kcal/mol of free energy of activation (**TS$_{IJ}$**; 15.1 kcal/mol). This step is endergonic by 12.7 kcal/mol. The vinyl cation fragment is

connected to the squaramide by hydrogen bonding (O···H 1.96 Å). However, dissociation of the vinyl cation **L** from the squaramide·LiOTf complex **K** releases 5.3 kcal/mol. Formation of the C−C bond between the vinyl cation and enoxysilane **2a** takes place at **TS$_{LM}$** (16.6 kcal/mol). The resulting silylium adduct **M** is more stable than the reference system by 29.6 kcal/mol. Lithium/silicon exchange to deliver enone **3a** and TMSOTf as the side product and regenerate **H** further liberates 9.5 kcal/mol of free energy (−34.4 kcal/mol). Overall, the free energy profile corroborates the catalytic activity of the Li$^+$/squaramide complex **H**. The computed rate-determining step, which corresponds to **TS$_{KL}$**, is consistent with a reaction requiring 24 h at 40 °C.

Because the reactivity of **3a** is limited to a single control experiment in the literature,[1h] we tested a few transformations (Scheme 4). Using NaBH$_4$ or catalytic hydrogenation

Scheme 4. Transformations of Compound 3a
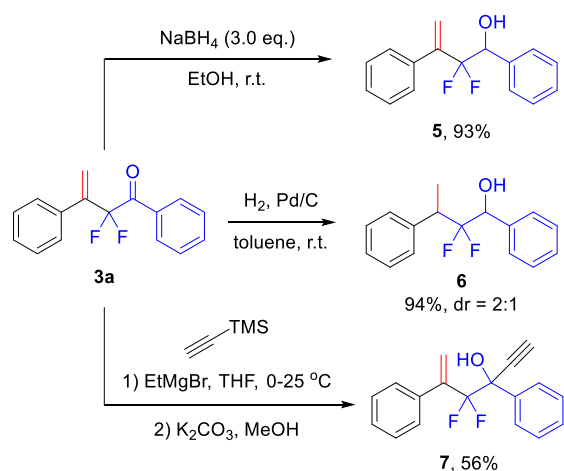
conditions, the expected difluorinated secondary alcohols **5** and **6** were obtained in excellent yields of 93% and 94%, respectively. The tertiary propargyl alcohol **7** was also readily obtained from trimethylsilylacetylene in 56% yield.

In summary, we have devised an efficient lithium-catalyzed coupling protocol toward difluoromethylene-skipped enones. The vinyl cation generated from an arylvinyltriflate and a lithium salt of a weakly coordinating perfluorinated alkoxyaluminate is reactive enough to undergo the addition of weak nucleophiles such as difluoroenoxysilanes. The success of this strategy is based on the use of a squaramide ligand, which greatly improves the solubility of the lithium species after in situ trimethysilylation of the nitrogen atoms.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02793.

> Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra, coordinates, and energy of the computed species (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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