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A deoxyfluoroalkylation–aromatization strategy to access fluoroalkyl arenes†

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Fluoroalkyl arenes (Ar–R_F) are valuable substructures present in several FDA-approved drugs, patents, agrochemicals, and materials, and complementary strategies that enable access to a broad spectrum of Ar–R_F compounds benefit these applied fields. Herein, we report a deoxyfluoroalkylation–aromatization strategy to convert cyclohexanones into broad-spectrum Ar–R_F containing compounds. Generally, the fluoroalkyl sources were activated to participate in a 1,2-addition reaction followed by aromatization in a sequence that contrasts more common preparations of these Ar–R_F compounds, such as (i) transition-metal catalyzed cross-coupling reactions of aryl electrophiles and nucleophiles, and (ii) radical fluoroalkylation reactions of C–H bonds of arenes. Considering the range of cyclohexanone-derived substrates that could be prepared and used, this strategy can be creatively employed to deliver a broad spectrum of highly substituted fluoroalkyl arenes.

Fluoroalkyl arenes (Ar–R_F) are valuable for pharmaceutical, agrochemical, and material sectors as evidenced by their high prevalence in FDA-approved drugs, agrochemicals, materials, patents, and the literature.[1–3] In these realms, the Ar–R_F substructures can impart favorable physicochemical perturbations, such as thermal, chemical, and metabolic stability, lipophilicity, and basicity.[4–8] Common methods to access Ar–R_F compounds involve (i) transition-metal catalyzed cross-coupling reactions of aryl electrophiles and nucleophiles,[9–18] or (ii) radical perfluoroalkylation of C–H-containing arenes (Fig. 1A).[19–23] However, transition-metal catalyzed cross-coupling reactions require programmed substrates, limiting their utilities to access highly substituted derivatives, and radical perfluoroalkylation reactions have intrinsic issues with regioselectivity. To complement these strategies, a conceptually distinct deoxyfunctionalization/aromatization strategy can exploit non-aromatic cyclohexan(en)ones as substrates,[24,25] but has only recently been extended to deoxytrifluoromethylation reactions that convert cyclohexanone precursors to trifluoromethyl arenes (Ar–CF_3, Fig. 1B).[26] This strategy exploits cyclohexanone substrates that can be accessed in commercial libraries, prepared in annulation reactions, or accessed through the sequential decoration of cyclohexanone precursors. Subjection of the cyclohexanone substrate to a 1,2-addition reaction with a fluoroalkyl nucleophile and subsequent dehydration–aromatization delivers Ar–R_F compounds in a convenient 2–3 step sequence (Fig. 1C). This proof-of-concept study could be strategically adapted with readily available or pre-functionalized cyclohexanones to deliver previously unreported highly-substituted and valuable Ar–R_F products.

Accessing fluoroalkyl arenes via deoxyfluoroalkylation–aromatization. To adapt the previously reported deoxytrifluoromethylation–aromatization sequence to other fluoroalkyl groups (–R_F), adjustments would be needed to promote the 1,2-addition reactions. Using 4-phenyl-cyclohexanone as a model substrate, the 1,2-addition reaction was generally performed by activating an array of neutral fluoroalkyl precursors to generate a fluoroalkyl nucleophile (–R_F) using one of a series of strategies *via*: (i) F^- induced activation of TMS–R_F reagents, (ii) addition of Grignard reagent (R–Mg–X), (iii) addition of Reformatsky reagent (R–Zn–X), (iv) Li–halogen exchange reactions with MeLi, (v) base-mediated deprotonation of H–R_F, or (vi) Mukaiyama aldol addition of α,α-difluoro silyl enol ethers (Tables 1 and 2). In most cases, a quick workup was performed to quench the reagents and separate the 1,2-addition product in semi-pure form, though no workup was required for reactions involving F^- induced activation of TMS–R_F reagents. The 1,2-addition product was then subjected to dehydration–aromatization conditions previously reported with either: (i) a one-step procedure using *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) as aromatizing

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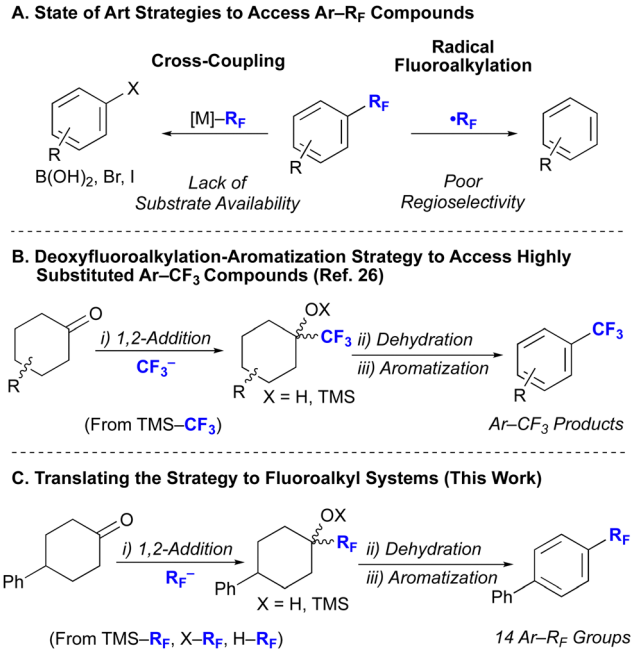


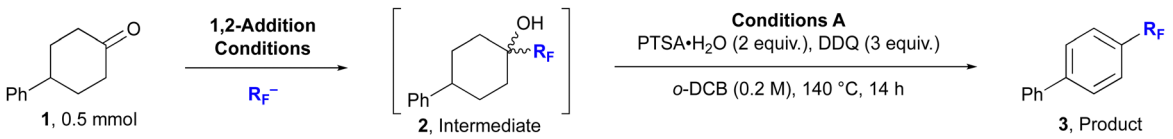
Fig. 1 Methods to access fluoroalkyl arenes. (A) Common methods to access these substructures are cross coupling and radical fluoroalkylation, which are limited due to the availability of substrate and regioselectivity issues. (B) Previous work demonstrated a complementary deoxytrifluoromethylation/aromatization of cyclohexan(en)ones to access highly substituted Ar–CF_3 compounds.[26] (C) Extension of the deoxyfluoroalkylation–aromatization strategy of cyclohexanones can complement more common cross-coupling and radical functionalization strategies for preparing a broad spectrum of fluoroalkyl arenes.

reagents under thermal conditions in *o*-dichlorobenzene (*o*-DCB; conditions A, Table 1), or (ii) a two-step protocol with thionyl chloride ($SOCl_2$) and pyridine in tetrahydrofuran (THF) followed by a silica plug filtration to afford the vinyl–R_F intermediate, and finally aromatization with DDQ under thermal conditions in *o*-DCB (conditions B, Table 2). Initially, the suitability of the reaction conditions was assessed by running small scale reactions (0.1 mmol) under both conditions, and the best conditions were subsequently repeated on a 0.5 mmol scale.

Perfluoroalkyl arenes (Ar–C_nF_m). The deoxyfluoroalkylation–aromatization strategy efficiently translated to several perfluoroalkyl arene compounds (Ar–C_nF_m) (Table 1). For Ar–C_nF_m compounds, 1,2-addition reactions were typically performed by activating respective trimethylsilyl- or bromo/iodo-precursors and the operationally simple conditions A performed adequately for the dehydration–aromatization sequence. The introduction of $-C_2F_5$ and $-C_3F_7$ groups employed trimethylsilane reagents ($TMSC_2F_5$ and $TMSC_3F_7$) with 10% CsF in *o*-DCB for the 1,2-addition reaction, and subjection of the intermediates to conditions A delivered desired products **3a–3b** in 78% and 53% yields, respectively. For these reactions, the respective TMS derivatives were used because these reagents are liquid at room temperature and easy to handle under ambient conditions relative to the iodide-derived counterparts that are gases at room temperature. Additionally, the stoichiometric silyl byproducts formed during the 1,2-addition step were compatible with the subsequent dehydration and aromatization steps. In contrast, the 1,2-addition products of other high order perfluoroarenes, Ar–C_4F_9 (**3c**),[27] Ar–C_5F_{11} (**3d**), Ar–C_6F_{13} (**3e**), Ar–$C(CF_3)_2$–F (**3f**), and Ar–$CF_2CF_2CH{=}CH_2$ (**3g**) were accessed through Li–halogen exchange with respective iodide-containing reagents {(I–C_4F_9, I–C_5F_{11}, and I–C_6F_{13},[28] I–$C(CF_3)_2$–F)} or bromide-containing reagents (Br–$CF_2CF_2CH{=}CH_2$),[29] respectively, and subsequent subjection of the reaction mixtures to conditions A delivered the desired products (**3c–3g**) in good to moderate yield. For these reactions, the iodides/bromides were preferred over the corresponding organosilane reagents for three reasons. First, they exist as stable and easily handled liquids at room temperature. Second, they are significantly cheaper (up to 140 times) than the silane-based derivatives. Third, in some cases, the corresponding organo-silane reagents are not available within commercial catalogues.

To access product **3f**, we developed new conditions. Prior attempts to react ketones with $-C(CF_3)_2$–F exploited the corresponding Sn reagent (R–Sn–$C(CF_3)_2$–F),[30] which was prepared from the corresponding iodo-reagent. To reduce the number of synthetic steps and avoid the use of Sn-based reagents, we performed 1,2-addition with commercially available iodo-reagent using a

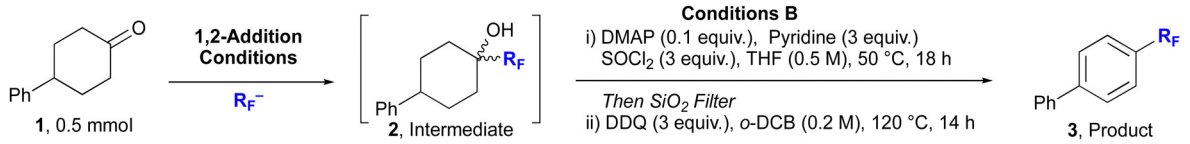
Table 1 Deoxyfluoroalkylation–aromatization to access perfluoroalkyl arenes (Ar–C_nF_m)



Entry	Product	R_F	1,2-Addition conditions	Int. yield (^{19}F NMR) (%)	Prod. yield (isolated) (%)
1	**3a**	$-C_2F_5$	TMS–C_2F_5 (1.2 equiv.), CsF (0.1 equiv.), *o*-DCB (0.5 M), rt, 15 h	99	78[a]
2	**3b**	$-C_3F_7$	TMS–C_3F_7 (1.2 equiv.), CsF (0.1 equiv.), *o*-DCB (0.5 M), rt, 15 h	99	53[a]
3	**3c**	$-C_4F_9$	I–C_4F_9 (2.2 equiv.), MeLi (2 equiv.), LiBr (2 equiv.), Et_2O (0.1 M), −78 °C, 2 h	93	47
4	**3d**	$-C_5F_{11}$	I–C_5F_{11} (2.2 equiv.), MeLi (2 equiv.), LiBr (2 equiv.), Et_2O (0.1 M), −78 °C, 2 h	99	73
5	**3e**	$-C_6F_{13}$	I–C_6F_{13} (2.2 equiv.), MeLi (2 equiv.), LiBr (2 equiv.), Et_2O (0.1 M), −78 °C, 2 h	99	83
6	**3f**	$-C(CF_3)_2F$	I–$C(CF_3)_2F$ (2.5 equiv.), MeLi (3 equiv.), Et_2O (0.2 M), −78 °C, 2 h	70	45[b]
7	**3g**	$-CF_2CF_2CH{=}CH_2$	Br–$CF_2CF_2CH{=}CH_2$ (2.2 equiv.), MeLi (2 equiv.), Et_2O (0.1 M), −78 °C, 2 h	73	46

[a] 24 h. [b] 36 h.

Table 2 Deoxyfluoroalkylation–aromatization to access difluoromethylene-containing arenes and perfluorophenyl arenes



Entry	Product	R_F	1,2-Addition conditions	Int. yield (^{19}F NMR) (%)	Prod. yield (isolated) (%)
1	**3h**	$-CF_2H$	TMS–CF_2H (2 equiv.), 20 mol% CsF, HMPA (5 equiv.), THF (0.5 M), 60 °C, 48 h	65	45
2	**3i**	$-CF_2P(O)(OEt)_2$	H–$CF_2P(O)(OEt)_2$ (1 equiv.), LDA (1.2 equiv.), THF (0.25 M), −78 °C, 4 h	99	36
3	**3j**	$-CF_2CO_2Et$	Br–CF_2CO_2Et (2 equiv.), Zn (2 equiv.), THF (0.5 M), rt, 24 h	99	62
4	**3k**	$-CF_2C(O)$–Morph	Br–$CF_2C(O)$–Morph (2.5 equiv.), MeLi (3 equiv.), Et_2O (0.1 M), −78 °C, 2 h	63	43[a]
5	**3l**	$-CF_2C(O)Ph$	[(2,2-Difluoro-1-phenylvinyl)oxy]trimethylsilane (3 equiv.), $TiCl_4$ (2 equiv.), DCM (0.5 M), 0 °C, 2 h	96	84
6	**3m**	$-CF_2SO_2Ph$	H–CF_2SO_2Ph[b], LiHMDS (2 equiv.), HMPA (15 equiv.), THF (0.5 M), −78 °C, 2 h	99	62[c]
7	**3n**	$-C_6F_5$	F_5C_6–Mg–Br (1 equiv.), Et_2O (0.12 M), reflux, 4 h	99	47

[a] 80 °C. [b] Limiting reagent (0.5 mmol), 4-Ph-cyclohexanone (2 equiv.). [c] Instead of using a silica plug filter, the vinyl intermediate after the dehydration step was isolated.

halogen–lithium exchange reaction with MeLi to generate the active nucleophile. In this reaction, we did not observe β-fluoride elimination of the intermediate organolithium species. Of note, attempts to generate and use the comparable Grignard or Reformatsky reagents failed for this substrate.

Difluoromethylene-containing arenes (Ar–CF_2R) and perfluorophenyl arenes. The deoxyfluoroalkylation–aromatization strategy effectively translated to several difluoromethylene-containing arenes (Ar–CF_2R) and perfluorophenyl arenes. Generally, conditions B (cat. DMAP, $SOCl_2$, pyridine, THF, 50 °C; SiO_2 plug; DDQ, *o*-DCB, 120 °C) performed better for dehydration–aromatization than conditions A (PTSA·H_2O, DDQ, *o*-DCB, 140 °C) for these compounds. To access a difluoromethyl arene (Ar–CF_2H, **3h**), TMS–CF_2H was used as a precursor for $-CF_2H$. Using catalytic CsF and hexamethylphosphoramide (HMPA) at 60 °C, the reaction delivered the desired 1,2-addition intermediate,[31] and the crude reaction mixture was subjected to conditions B to deliver desired compound **3h** in 45% yield. The difluoromethyldiethylphosphonate [H–$CF_2P(O)(OEt)_2$] was deprotonated with LDA to generate the corresponding anion [$^-CF_2P(O)(OEt)_2$], which participated in the subsequent 1,2-addition reaction.[32] Finally, subjection of the intermediate to conditions B delivered product **3i** in 36% yield. The α,α-ethyl difluoroacetate anion ($^-CF_2CO_2Et$) was accessed from bromodifluoroethylacetate (Br–CF_2CO_2Et) using Zn^0 to form a Reformatsky reagent *in situ*, which underwent the 1,2-addition reaction in quantitative yield.[33] The crude reaction mixture was subjected to conditions B to deliver the desired compound **3j** in 62% yield. To generate a substrate bearing a $-CF_2C(O)$(morpholine) moiety, the anion was generated from the corresponding bromide *via* a halogen–lithium exchange reaction, and subsequent reaction with 4-phenylcyclohexanone (**1**) delivered the 1,2-addition intermediate. Subsequent dehydration and aromatization delivered the desired Ar–$CF_2C(O)$morpholine product (**3k**) in 43% yield. In prior work, 1,2-addition reactions of $-CF_2C(O)$(morpholine) initiated from the corresponding silane reagent [TMS–$CF_2C(O)$(morpholine], which was prepared from the chloro-precursor.[34] To reduce the number of steps and avoid the unnecessary use of Si-based reagents, we developed a direct 1,2-addition reaction with the corresponding halogen-containing reagent. Specifically, Br–$CF_2C(O)$(morpholine) was lithiated using MeLi, and the resulting $CF_2C(O)$(morpholine) anion smoothly reacted with 4-Ph-cyclohexanone (**1**) to deliver the 1,2-addition intermediate. In contrast, attempts to use Grignard and Reformatsky modes of addition were not successful. To access α,α-difluorinated ketone derivatives, the Mukaiyama aldol reaction of 2,2-difluoro silyl enol ethers with 4-Ph-cyclohexanone (**1**) in the presence of $TiCl_4$ delivered the 1,2-addition product,[35] which was then subjected to conditions B to deliver the desired Ar–$CF_2C(O)Ph$ product (**3l**) in 84% yield. The difluoro(phenyl)methyl)sulfonyl anion ($^-CF_2SO_2Ph$) was accessed by base-mediated deprotonation of the corresponding difluoromethylsulfonyl benzene (H–CF_2SO_2Ph) with HMPA as an additive,[36] which underwent a 1,2-addition reaction. The resulting reaction mixture was then subjected to conditions B to deliver the desired compound **3m** in 62% yield. The pentafluorophenyl anion [$^-$Ph(5-F)] was used *in situ* as a Grignard reagent (C_6F_5–Mg–Br), which underwent a 1,2-addition reaction,[37] prior to subjecting the intermediate to conditions B to deliver the desired product **3n** in 47% yield.

The deoxyfluoroalkylation–aromatization strategy provides access to valuable fluoroalkyl arene compounds in moderate to excellent yields. This conceptually distinct strategy exploits cyclohexanone substrates that differ from other common preparations of fluoroalkyl arenes, such as transition metal-catalyzed coupling reactions and radical addition reactions. Using a range of activation strategies, many fluoroalkyl precursors generated fluoroalkyl anions, which underwent a 1,2-addition reaction, followed by a dehydration–aromatization sequence to deliver different fluoroalkyl arene products. Considering the range of cyclohexanones that could serve as substrates for such a transformation, as demonstrated in previous work,[26] this proof-of-concept study with alternate fluoroalkyl groups has many potential opportunities to be creatively employed to deliver highly substituted fluoroalkyl arenes that are beyond the scope of currently available technologies.

R. A. A. conceived the project. P. B. developed methodology for the project. P. B., S. K., and K. G. contributed to the investigation. Funding, project administration, and supervision were done by R. A. A., P. B. and R. A. A. wrote the original draft, and review and editing were done by all authors.

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Data availability

The data supporting this article have been included as a part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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