Cross Dehydrogenative Coupling of Chloro- and Fluoroalkanes with Methylarenes

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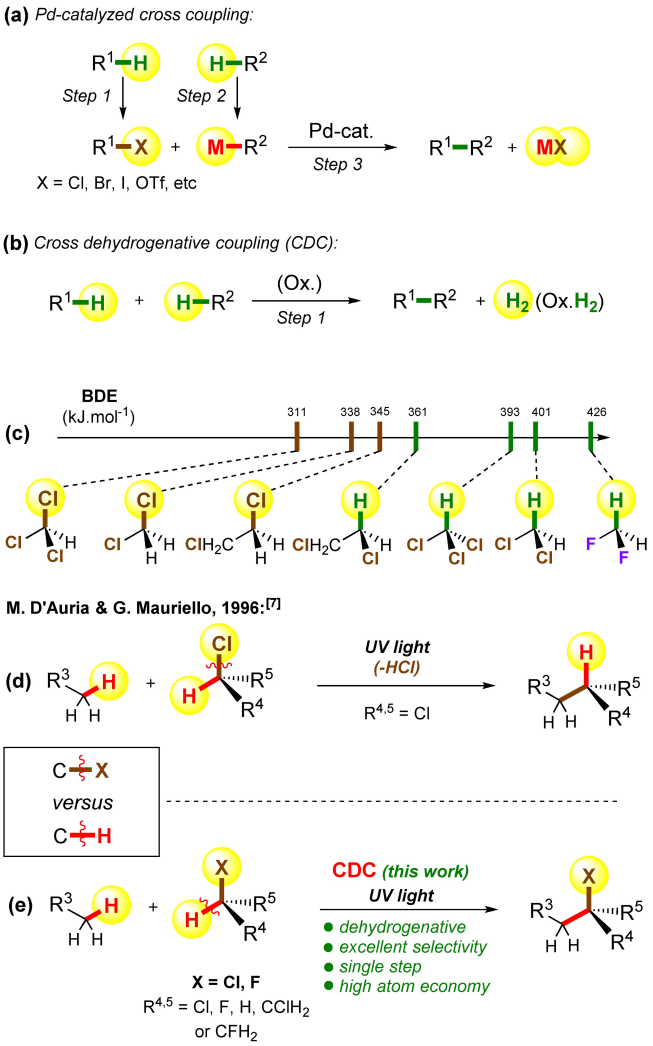
Cross dehydrogenative coupling reactions (CDCs) are considerably more step- and atom efficient compared to classical cross coupling methods. In this context, the photochemical CDCs of hydrochlorocarbons and hydrofluorocarbons with methylarenes are herein described. This unprecedented CDC reaction concept enables a new retrosynthetic cut for the selective construction of valuable chlorinated and fluorinated organic skeletons, from industrially important dichloromethane, dichloroethane, difluoromethane (HFC-32), and 1,1,1,2-tetrafluoroethane (HFC-134a).

Introduction

With the rise of Pd-catalyzed cross coupling reactions,[1] incredibly complexes organic scaffolds can now be accessed, with almost no limits with regards to structural design.[2] Thus, given enough time and resources, one can now synthetize almost any carbon skeleton. Most C–C bond forming cross coupling methods however still heavily depend on the pre-functionalization of the building blocks, usually with both strongly activated leaving groups and organometallic reagents (Scheme 1a). These are therefore neither step nor atom efficient. In contrast, the rise of cross dehydrogenative couplings methods (CDCs) enables ultimate step and atom efficient C–C bond forming processes, from two simple C–H bonds (Scheme 1b).[3] Many of these are moreover operationally very simple.

In this context, we turned our attention to industrially important alkyl chlorides and fluorides as C–H substrates for C–C bond forming CDCs, in particular dichloromethane and dichloroethane.[4] To the best of our knowledge, and in spite of their great industrial relevance, neither compounds have ever been utilized as a building block in a cross dehydrogenative coupling method so far. This may be due to their relatively high stability[5] and high C–H bond dissociation energies (BDEs) compared to the competing C–Cl bonds (Scheme 1c).[6] For example, D'Auria and Mauriello found in 1996 that irradiating methyl arenes in chloroform under UV light delivers the C–Cl activation coupling products in high yields (Scheme 1d).[7] In contrast, a challenging dehydrogenative reaction design, if possible, would deliver complex and valuable chloroalkanes in a most efficient manner.



Scheme 1. CDC reaction design.

Thus, utilizing a photo-reactor recently developed by us (see SI),[8] we envisioned the CDC coupling of simple chloro and fluoroalkanes with likewise industrially important methyl arenes

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(Scheme 1e). Such a process would provide unique C(sp^3)–C(sp^3)Cl/F_x skeletons, which would otherwise be very difficult to access through classical synthetic methods.[7,9]

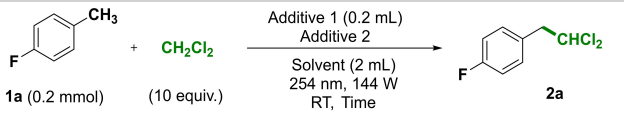
Results and Discussion

We began our investigations into the proposed CDC C(sp^3)–H dichloromethylation of methyl arenes by exposing dichloromethane and test substrate 4-fluorotoluene **1a** in the presence of chlorobenzene as a reaction initiator in sulfolane as a solvent, under 254 nm UV light in a 144 Watts photo reactor (Scheme S1 in the SI), providing initially 13% NMR yield of the anticipated CDC product **2a** (Table 1). Dichloromethane having by far the more stable C–H bond in the series of considered chloroalkane substrates (Scheme 1c), we imagined that optimizing the method with it would also unlock the other slightly more facile chloroalkanes (chloroform and 1,2-dichloroethane). We thus conducted all optimization experiments with dichloromethane. No other solvent performed any better than sulfolane (Table 1, entries 1 to 4, see SI for additional solvents).

Importantly, the absence of the chlorobenzene additive switches the reaction off (entry 5), suggesting that it might initiate the reaction upon UV irradiation. Likewise, the absence of light, or a different, less energetic wavelength, does not deliver any detectable product **2a** (entry 6). Interestingly, the reaction displays a high specificity for chlorobenzene as initiator, as neither fluoro- nor bromo- nor iodo-benzene deliver any detectable product **2a**. This is surprising considering the greater lability of C–Br and C–I bonds compared to C–Cl bonds. This might indicate a high kinetic sensitivity of the radical chain propagation process, unless a chlorine radical is specifically involved therein.[10] Therefore, the effect of substituents on the C(sp^2)–Cl initiator was also investigated. Surprisingly, no other tested chloroarene performed any better than chlorobenzene itself. The second best chloroarene was found to be 4-fluorochlorobenzene, delivering product **2a** in a reduced 5% yield (entry 10). Next, we explored the benefit of a second additive. A Lewis acid was notably considered, BF_3, with however little effect (entry 11). Simply increasing the amount of chlorobenzene proved more rewarding (entry 12). Interesting, a noticeable increase in yield of product **2a** was observed by the addition of 1 equiv. of elemental zinc (entry 15).[11] Next, pushing the reaction time from 8 to 20 h doubled the yield of product **2a** (55%, entry 16), which we judged remained an acceptable reaction time. The use of a less powerful photoreactor (254 nm, 72 W) still enabled the reaction, although with a considerably slower rate, and is thus not compatible with a less than a day reaction time. Finally, the reaction was scaled up to 0.5 mmol of substrate **1a** (Table 1, entry 17), whereby product **2a** was still obtained in a 50% yield.

With these reaction conditions in hand, we then explored the substrate scope of the reaction with dichloromethane and some other chloroalkanes such as 1,2-dichloroethane (Scheme 2). First, CDC product **2a** could not be isolated at this stage by means of classical silica column chromatography. Indeed, the modest polarity differences make product isolation from the crude mixture highly challenging. We were more successful with some different methylarenes (**2b**–**2d**, Scheme 2). 1,2-Dichloroethane also performed well (**3a**–**3j**), with isolated yields up to 75% (product **3j**). It should be noted however that many products **2** and **3** described as isolated (Scheme 2) still have moderate purities, as can been seen in their NMR spectra (see SI). The NMR spectra and elemental analysis data is provided for every isolated example within the SI. This isolation challenge is due again to the moderate polarity differences compared to the other components contained in the crude mixtures. Indeed, the functional group tolerance at the methyl arene building block is limited to diverse fluorinated, trifluoromethylated, and methylated positions. Some perfluorinated ethers were also well tolerated (**2d**, **3c**). Other important functional groups however, such as methoxy, chloro, bromo, and carbonyl groups were not tolerated, presumably due to their incompatibility with the short wave UV light. Making the functional group compatibility broader remains therefore a priority for future research efforts, in part because it would allow for more polar products, which would in turn facilitate their purification through classical column chromatography techniques. This will almost certainly require the design of more complex synthetic methods, presumably with catalytic strategies. As to scope limits regarding the halo-alkane coupling partner, neither chloroform, chloromethane, dibromomethane, chloro-dibromomethane, 1,2-dibromoethane, dichloro-bromomethane nor iodomethane were found operational as CDC building blocks. In spite of all

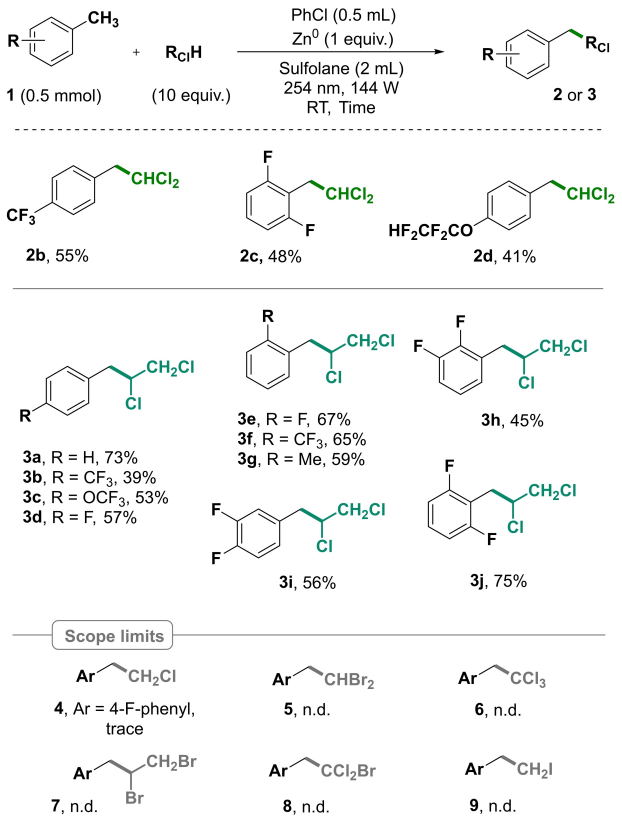
Table 1. Optimization table.[a]



1a (0.2 mmol) (10 equiv.) **2a**

Entry	Solvent	Add. 1	Add. 2	Time	**2a**, Yield [%][b]
1	CH_3CN	PhCl	–	8 h	trace
2	PhCN	PhCl	–	8 h	8
3	Cyclohexane	PhCl	–	8 h	0
4	Sulfolane	PhCl	–	8 h	13
5	Sulfolane	–	–	8 h	0
6 [c]	Sulfolane	PhCl	–	8 h	0
7	Sulfolane	PhF	–	8 h	0
8	Sulfolane	PhBr	–	8 h	0
9	Sulfolane	PhI	–	8 h	0
10	Sulfolane	*p*FC_6H_4Cl	–	8 h	5
11	Sulfolane	PhCl	$BF_3(H_2O)_2$[d]	8 h	11
12	Sulfolane	PhCl [e]	–	8 h	20
13	Sulfolane	PhCl [e]	Mg^0 [f]	8 h	21
14	Sulfolane	PhCl [e]	Zn^0 [f]	8 h	22
15	Sulfolane	PhCl [e]	Zn^0 [g]	8 h	26
16	**Sulfolane**	**PhCl** [e]	**Zn^0** [g]	**20 h**	**55**
17 [h]	**Sulfolane**	**PhCl**	**Zn^0**	**20 h**	**50**

[a] The photo-reactor comprises 8 PL-L 18 W UV lamps (144 W in total, λ = 254 nm) fixed in a 23 cm diameter steel cylinder, cooled from the top with a power ventilator (10 W, air flow: 140 m^3/h), and wrapped around with kitchen aluminum foil (see the Supporting Information). A 50 mL quartz vessel was utilized for each reaction mixture. [b] ^{19}F NMR yield, fluorobenzene as internal standard. [c] Dark, or 300 nm, or 365 nm, or 400 nm. [d] 0.2 mL. [e] 0.3 mL. [f] 0.1 mmol. [g] 0.2 mmol. [h] Substrate **1a**: 0.5 mmol scale, 10 equiv. CH_2Cl_2, 0.5 mL PhCl, 1 equiv. Zn^0, 2 mL sulfolane, 254 nm, 144 W, RT, 20 h.

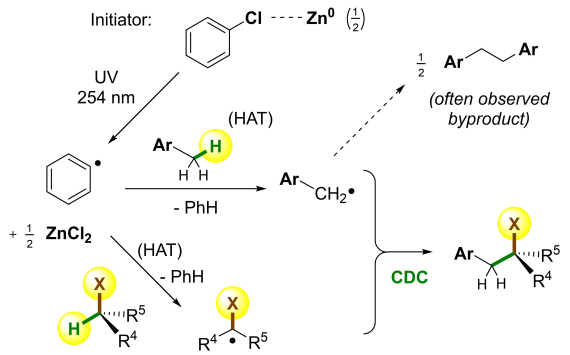


Scheme 2. Reaction scope, isolated yields. Conditions: methyl arene (0.5 mmol), chloroalkane (10 equiv.), PhCl (0.5 mL), Zn^0 (1 equiv.), sulfolane (2 mL), 254 nm, 144 W, RT, 20 h (CH_2Cl_2), 24 h (1,2-dichloroethane).

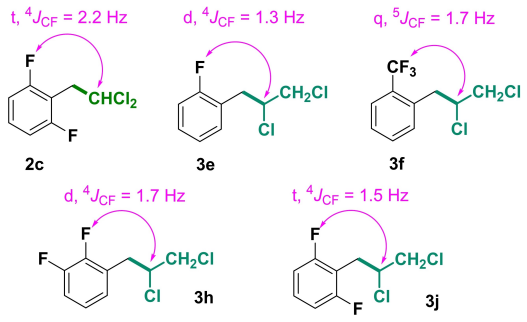
the above described limitations in terms of purity and scope, we judge the herein presented results to be of such conceptual significance in terms of direct cross dehydrogenative coupling, that their publication is justified in order to stimulate further research efforts in this area.

Because the reaction also operates in the absence of elemental Zn, albeit slower (Table 1, entries 4 & 12), a radical mechanism seems the most plausible (Scheme 3). The reaction is thus assumed to start through the UV activation of the initiator, chorobenzene, to form phenyl radicals.[12] This step might be facilitated by the Zn^0 additive, capturing chlorine radicals. The involvement of the latter chlorine radicals however, cannot be excluded in the radical chain propagation. Indeed, the replacement of the chorine position in the initiator's structure with bromine or iodine does not deliver any product, indicating a high specificity for chlorine (Table 1, entries 8 & 9).[10] In any case, the radical system would then attack the chloroalkane substrate in a Hydrogen Atom Transfer step (HAT), generating the key chloroalkane radical. The latter would then be intercepted by the trivial benzyl radical, which arose from another HAT step. The *homo* dimerization of this benzyl radical intermediate is an often observed byproduct, thus confirming this radical reaction pathway. Finally, we noticed characteristic long range ^{13}C–^{19}F spin-spin NMR couplings when a fluorinated functional group is positioned in *ortho* to the methyl arene reaction site, including with the newly attached carbon atom from dichloromethane or 1,2-dichloroethane (Scheme 4). These could therefore be utilized in future studies in order to rapidly identify the products.

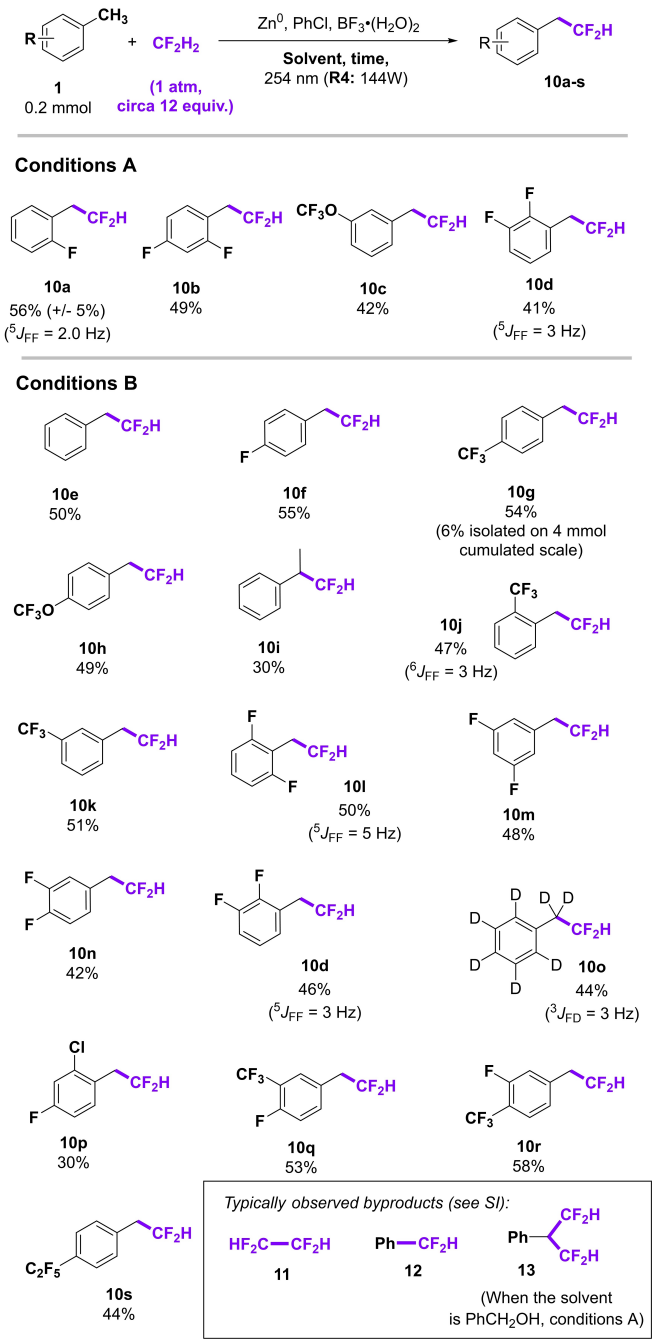
In parallel to the investigations on chloroalkanes, we also focused our attention on fluoroalkanes, in particular difluoromethane (HFC-32).[13–16] The difluoromethyl functional group possesses key steric and electronic properties that make it a chemically inert surrogate of alcohols and thiols, which are important in a large number of molecular recognition processes.[17] Moreover, the difluoromethyl group (CF_2H) shows promising biological activities, allowing it to act as a lipophilic and metabolically stable hydrogen-bond donor in drugs.[18] However, with a high bond dissociation energy (BDE) of 426 kJ/mol, and a p*K*a value as high as 35–42 (very poor C–H acidity),[19] difluoromethane possesses a very inert C–H bond. Therefore, all known methods so far to install the difluoromethyl group[20] require pre-activation steps.[21] Thus, the direct engagement of difluoromethane in a cross dehydrogenative coupling reaction would be synthetically very significant. A slight adjustment of the reaction conditions (Scheme 5), in particular the addition of BF_3 as well as a scale reduction (see SI), allowed to access the target dehydrogenative difluoromethylation coupling products in good ^{19}F NMR yields. The functional group tolerance however remains similarly limited as in the case of dichloromethane and dichloroethane (Scheme 2), namely to fluoro, chloro, fluoroalkyl, and perfluorinated ethers. The cause of this scope limitation is likewise functional group incompatibility with the strong UV light. Moreover, none of the



Scheme 3. Proposed reaction mechanism.



Scheme 4. Notable long range ^{13}C–^{19}F spin-spin NMR couplings (see the Supporting Information).



Scheme 5. Direct dehydrogenative difluoromethylation, ^{19}F NMR yields, fluorobenzene as an internal standard. (**A**) Optimized conditions: reactions were conducted on a 0.2 mmol scale with 12 equivalents of CF_2CH_2 (atmospheric pressure), 0.2 mL of PhCl, 0.1 mmol Zinc powder and 0.2 mL of $BF_3 \cdot 2H_2O$ in 4 mL benzyl alcohol. Reaction conducted at rt for 16 h. The photo-reactor comprises 8 PL-L 18 W UV lamps (144 W in total, $\lambda = 254$ nm) fixed in a 23 cm diameter steel cylinder, cooled from the top with a power ventilator (10 W, air flow: 140 m^3/h), and wrapped around with kitchen aluminum foil. A 50 mL quartz vessel was utilized for each reaction mixture. (**B**) Same as (**A**) but for the solvent (3 mL sulfolane) and reaction time (8 h).

difluoromethlylation coupling products could be satisfactorily isolated in spite of our best efforts, due again to poor polarity differences with the rest of the reaction mixtures. These contain however mechanistically interesting byproducts, which are easily identified through ^{19}F NMR spectroscopy.

The most notable byproduct is 1,1,2,2-Tetrafluoroethane (**11**), arising from the *homo* dimerization of the difluoromethyl radical, which thus demonstrates its intermediacy. This also suggests that our method could be further developed in order to oxidatively oligomerize difluoromethane into potentially valuable perfluorinated building blocks or polymers. Other notable byproducts include the phenyl radical initiator's interception with the difluoromethyl radical (**12**), or the solvent's interception with it when benzyl alcohol is utilized in method **A** (byproduct **13**). These observations reinforce the strong radical character of the reaction. The best difluoromethylation isolation result was obtained upon uniting several crude batches of product **10g** (cumulated scale: 2 mmol), affording an isolated yield of overall 6%. The technical challenges associated to product isolation constitute a limitation of the presented method, in spite of its otherwise high conceptual significance due to the inherent stability of difluoromethane.

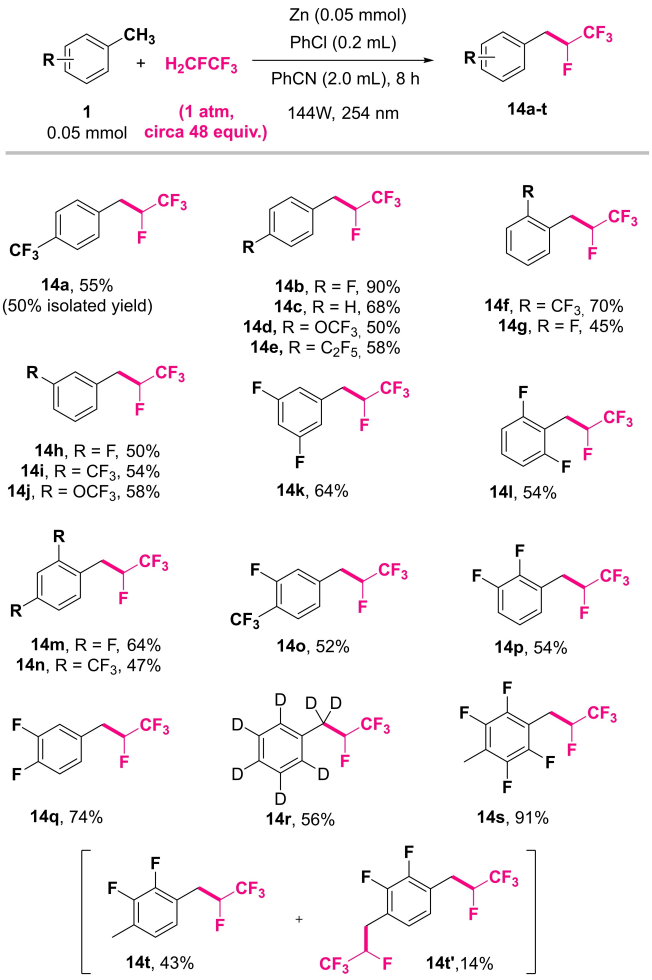
Next, we turned our attention to 1,1,1,2-tetrafluoroethane (HFC-134a). HFC-134a is one of the most produced refrigerants.[13] Nevertheless, very few methods are available for the introduction of the tetrafluoroethyl building blocks into organic or organometallic targets,[22] and certainly none in a dehydrogenative fashion. Further reaction condition adjustments were nevertheless necessary, such as reducing strongly the scale of the reaction to only 0.05 mmol, and switching the solvent to benzonitrile (see SI). There too, most yields could only be evaluated with ^{19}F NMR (Scheme 6). Fortunately, one example could be isolated: product **14a** (50%), allowing for its unambiguous characterization (Scheme 7). Moreover, this confirmed the relevance of the ^{19}F NMR yield determination method, in spite of the very low scale (55% ^{19}F NMR yield versus 55% isolated).

Conclusion

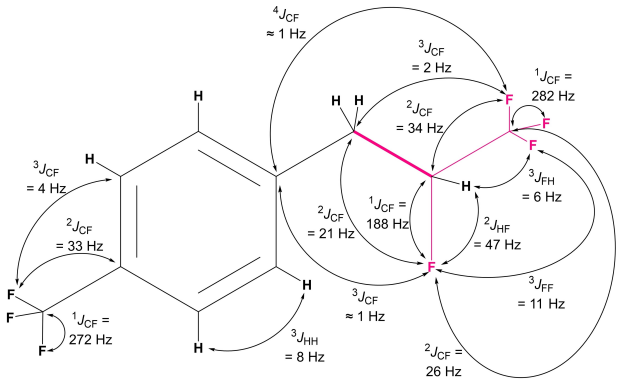
In conclusion, we have reported here the unprecedented cross dehydrogenative coupling of methylarenes with some of the most relevant and stable chloroalkanes as well as fluoroalkanes: dichloromethane, 1,2-dichloroethane, difluoromethane, and 1,1,1,2-tetrafluoroethane. Most of the obtained scaffolds, herein accessed through a single step from simple building blocks, would be very difficult to construct otherwise with classical synthetic approaches. The herein presented methods are therefore expected to considerably enhance the C–C bond formation toolbox, and to pave the way for the direct inclusion of these industrially important building blocks in synthetic chemistry.

Experimental Section

General note concerning product isolation and purity: The modest polarity differences within the crude reaction mixtures make product isolation challenging. As a result, many examples could only be quantified through ^{19}F NMR spectroscopic yields using an internal standard. For those that are described as isolated (wherein most impurities could be removed), please see the



Scheme 6. Direct dehydrogenative tetrafluoroethylation. ^{19}F NMR yields, fluorobenzene as an internal standard. Entry **14a**: (isolated yield). Reaction conditions: **1** (0.05 mmol), CFH_2CF_3 (~48 equiv.), Zn powder (0.05 mmol), PhCl (0.2 mL), benzonitrile (2.0 mL), UVC lamps 144 W, λ = 254 nm, rt, 8 h.



Scheme 7. Selected NMR landmarks of product **14a**.

Supporting Information for purity (^1H, ^{13}C, ^{19}F NMR, and elemental analysis results). Experimental details can also be found in the Supporting Information.

Notes

The authors submitted a patent for this work.

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Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: C–C bond formation · chloroalkanes · cross coupling · cross dehydrogenative coupling · fluoroalkanes · radicals · coupling

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