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Defluorodearomatization: A Photocatalytic Birch-Like Reduction That Enables C−C Bond Formation and Provides Access to Unnatural Cannabinoids

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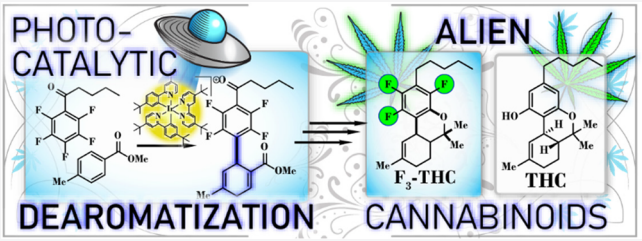
ABSTRACT: Within the framework of discovery chemistry, polyfluorination remains a synthetic challenge despite its ability to provide useful characteristics, such as a reduction in the number of hydrogen bond donors and metabolic stability. Coupling a reversal of this methodology with photocatalysis has been demonstrated to allow the rapid synthesis of previously difficult or impossible targets by starting with fluorines everywhere and selectively removing or functionalizing them. Herein, we demonstrate a novel method to synthesize 1,4-cyclohexadienes through a dearomative photocatalytic C−C coupling reaction. This allows for access to materials that are orthogonal to the selectivity of the Birch reaction and are more functional-group-tolerant. The reaction also allows the efficient synthesis of polyfluorinated cannabinoids. While the yields are modest, the access to the new chemical space provided by the reaction is unprecedented by any means. The trifluorinated analog of THC, 1-deoxy-1,2,4-trifluoro-THC, is synthesized, demonstrating the importance of discovery chemistry and the ability to explore otherwise unknown structure−activity relationships.

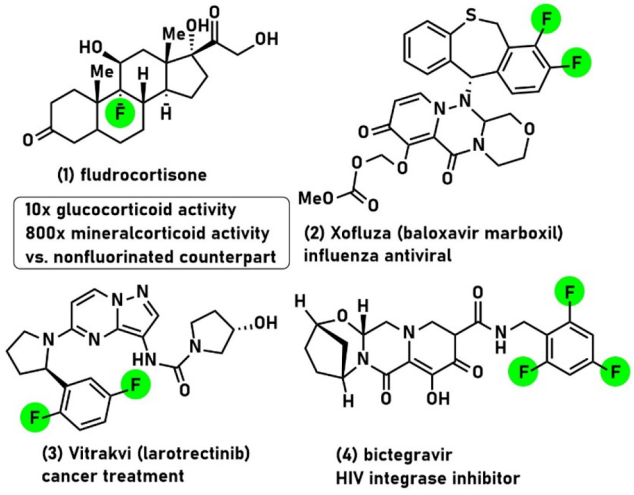


INTRODUCTION

Fluorine has a greater ability than any other element to dramatically alter, and often enhance, the properties of a molecule without dramatically altering its shape or function. Perhaps due to the fact that there are few natural products that contain fluorine,[1−5] which are usually toxic derivatives of fluoroacetate,[6] fluorination was historically overlooked as a legitimate direction for investigation. In 1953,[7] however, a fluorinated analog to hydrocortisone, fludrocortisone (**1**), was introduced to the literature. It was found to have a 10-fold increase in glucocorticoid activity compared to the non-fluorinated hormone cortisol and up to 800× the mineralocorticoid activity (Table 1).[8] As time has passed, fluorination has assumed a lead role in discovery chemistry because of its ability to improve a host of properties in a multitude of applications.[9−13] To further emphasize, an appreciation for the importance of fluorination in pharmaceuticals can be gained from an examination of the drugs approved per annum by the U.S. FDA, 30% of which[14,15] typically contain a C−F bond. Of the small-molecule entities that were approved by the U.S. FDA in 2018, 17 contained a C−F bond, 12 were fluoroarenes, and 3 were polyfluorinated arenes[16] (baloxavir marboxil (**2**), larotrectinib (**3**), and bictegravir (**4**)), indicating that arene polyfluorination specifically is becoming an increasingly important synthetic objective.

Despite the importance of fluorinated molecules in the pharmacopeia, linear syntheses to include fluorine are difficult.

Table 1. Some Important Entries in the Fluoropharmacopeia



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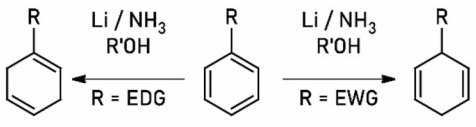
In contrast to more modern procedures, methods for sequential fluorine installation, such as the Balz–Schiemann and halex reactions,[17] exist but are difficult and are typically not functional group tolerant. Recent developments have increased the number of functional groups that can be transformed into fluorine.[17,18] While useful for monofluorination, these methods contribute little in the exploration of multifluorinated molecules because they would require a library of multisite prefunctionalized nonfluorinated starting materials to perform a comprehensive structure–activity relationship (SAR) study, and these starting materials are generally not available.

Some of us[19,20] have approached the synthesis of organofluorines from the other way around. Rather than approaching fluorination through harsh, multistep, or low-yielding linear syntheses, the desired organofluorine can be realized, starting with all of the fluorines already in place with poly- or perfluorinated core molecules and then either replacing the unwanted fluorines through hydrodefluorination (HDF)[21−25] or turning them into a desirable substituent through direct alkylation, alkenylation, arylation, and prenylation.[20,26−32] Visible-light photocatalysis with an iridium-based photocatalyst has played a critical role in this area, and the interplay between photocatalytic C–F functionalizations and other methods has the potential to allow for sophisticated but as of yet largely unrealized SARs with respect to fluorine. Furthermore, the mild nature of these reactions may lend itself to the formation of unnatural products, i.e., fluorinated natural products,[17] which could create new opportunities to explore the effect of fluorination on the function of natural products—a mostly unexplored domain.

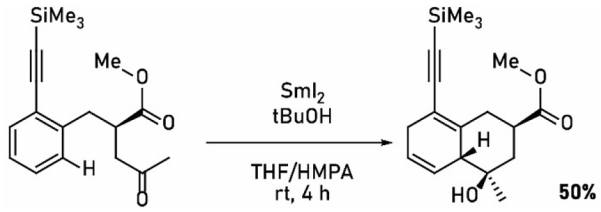
Previously, we showed that it was possible to couple a perfluoroarene directly with an arene partner via C–F and C–H functionalization. During this investigation,[28] a careful assessment of some of the minor products in the crude reaction NMR spectra revealed vinylic ^{1}H signals, and GC-MS analyses showed the [M + 2] peak with respect to the expected product, a highly unexpected result. We expected that a cyclohexadienyl radical was a likely intermediate in the mechanism for the fluoroaryl arylation reaction and that the majority of the materials would proceed through a mechanism in which they rearomatized, formally losing a H atom in the process. Under certain conditions, the reduction of that intermediate had in fact gained an H atom, resulting in what amounts to a formal hydrogenation of the intended products.

After careful isolation, we generated simulated NMR spectra of all possible perturbations of the diene geometry to compare them to the experimental spectra using the method of Bally and Rablen.[33] Of these, several contenders were similar to the experimental spectrum of **8**, although the 1,4-diene depicted in Scheme 1b appeared to most accurately match the experimental spectra (see the Supporting Information for details). Seeking more concrete data, we grew a crystal and submitted it for single-crystal X-ray diffraction analysis, which confirmed its structure (Table 3, structure **8**). This product is

Scheme 1a. Birch Reduction

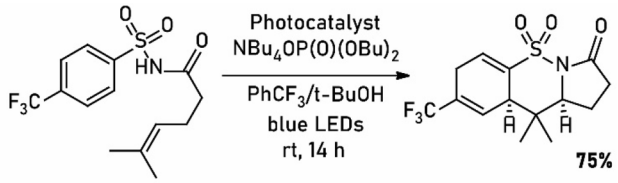


Scheme 1b. Reissig 1999

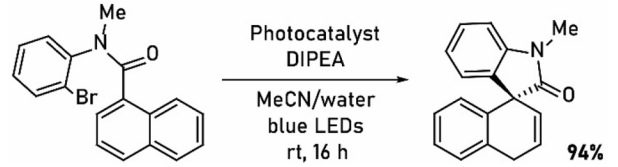


structurally related to the product of a Birch-type[34] dissolving metal reduction (Scheme 1a). However, it simultaneously formed a new C–C bond in addition to the reduction. Another key difference is the regioselectivity of the diene, which differs from those formed under Birch conditions for substrates possessing an electron-withdrawing group (Scheme 1a).[34,35] The conditions used for the Birch reaction (alkali metals in condensed liquid ammonia) are harsh and severely limit the scope of the reaction, while the reactions presented here proceed in much milder conditions and could be expected to be significantly more functional group tolerant. Work by Reissig demonstrated the ability of a ketyl radical to undergo dearomative cyclization using a stoichiometric amount of Sm(II).[36] It is important to note that during the exploration of this methodology, a few photocatalytic dearomative methods have surfaced in the literature (Scheme 1cc–1e);[37−39]

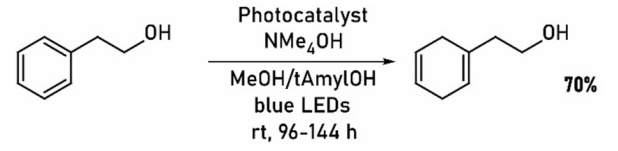
Scheme 1c. Stephenson 2020



Scheme 1d. Jui 2020



Scheme 1e. Miyake 2020



however, the reaction discussed within (Scheme 1f) is unique in that it forms a C–C bond but does not require the pieces to be tethered together, it is not a spirocyclization, and it abstracts hydrogen (formally) from water.[40] The intermolecular nature of the reaction may facilitate SAR studies in ways that intramolecular reactions cannot. We reasoned that, because of the structural complexity and functional richness of these dienes, it would be a valuable asset to the chemical community and thus set out to discover optimized conditions (Table 2) that would favor the formation of the reduced 1,4-diene.

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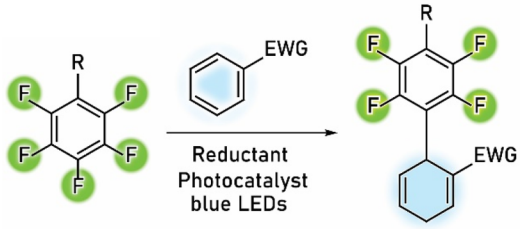
Scheme 1f. This Work



RESULTS AND DISCUSSION

Searching for optimal reaction conditions revealed that the mass balance for the products of the reaction, apart from several major products, consisted of a complex mixture of oligomers. Upon screening the photocatalysts (Table 2, entries 1−9), it was discovered that bis-4-(*tert*-butyl)-2-(4-(*tert*-butyl)phenyl)pyridine-4,4′-di-*tert*-butyl-2,2′-bipyridyl iridium-(III) hexafluorophosphate (Ir(dtbbpy)(dtbppy)2PF_6) (**PC3**), a somewhat oxidizing[41,42] and sterically bulky photocatalyst that has thus far been relatively underrepresented in the literature, was optimal, having a triplet-state emissive energy of 49.4 kcal/mol[43] and energies of $E^0(Ir^{II}/Ir^{III}*)$ = −1.04 V and $E^0(Ir^{II}/Ir^{III})$= +1.13 V[44]. While **PC5** had a similar outcome in terms of the intended product, the reaction produced many minor side products and was therefore rejected to the simplify purification.

Recently, Chaterjee and Koenig[45] disclosed a dearomatization reaction that was proposed to take place by triplet energy transfer, followed by SET. However, because the molecular radius of the photocatalyst has been shown to be critical for the energy transfer to occur,[27] the presence of large *tert*-butyl groups on this photocatalyst makes the probability of the necessary orbital overlap of the photocatalyst and the substrate unlikely.[46] Moreover, given the relatively low triplet-state energy of (Ir(dtbbpy)(dtbppy)$_2PF_6$) (49.4 kcal/mol),[27,47] the energy transfer is unlikely to be operative.

It was discovered that the presence of water significantly enhances the reaction outcome (Table 2, entries 10−13). Further, the addition of water causes the reaction mixture to remain a pale yellow color, while in the absence of water it darkens significantly. It could be that the presence of water further stabilizes a charged intermediate or transition state, or water could serve to stabilize and solvate the fragmenting fluoride, a potentially very exothermic process (see a discussion of the mechanism below). It could also serve a more abstruse role, such as preventing the formation of light absorbing compounds that could lead to photostarvation (Figure 1).[48] The screening for the identity of the terminal reductants revealed that tributylamine and diisopropylethylamine (Table 2, entries 14−16 and the Supporting Information) were nearly identical, while all the other reductants attempted gave poor yields of or no product. We chose to utilize DIPEA due to its comparatively higher vapor pressure and water solubility, which we anticipated would facilitate product isolation. A precipitous decline in the yield of the intended diene was observed on either side of the optimized stoichiometry (1.0−1.2 equiv) with respect to the amount of the terminal reductant (Table 2, entries 17−22). Hydrocarbon arene coupling partner (Ar−H) equivalents were found to be optimal at 3.0 equiv (Table 2, entries 23−25). The photocatalyst loading (Table 2, entries 26−28) was found to be optimal for an NMR tube at 0.25 mol %, but the product distribution was not affected at lower loadings as the reaction simply required more time to reach completion. Upon scaling the reaction up, the increased path length proved to slow the reaction rate, although the catalyst loading could be decreased to 0.01 mol % without decreasing the yield. It was further found that the reaction depends heavily on the reaction solvent, with poor or no reactivity in all solvents we tried except acetonitrile (see the Supporting Information for full optimization details). The reaction temperature (−2 to 50 °C) was found to have little impact on the yield (see the Supporting Information for full optimization details), allowing subsequent reactions to be run at convenient temperatures. The optimization experiments provided insight into the influence of the various parameters; however, the yields remained meager. Additionally, under no conditions found could the minor side products, which were significant and ill-defined, be completely diminished. However, given the commercial availability of all the reagents, the operational simplicity of the reaction, and the rapid enhancement of the structural complexity of the reaction, we investigated the scope.

The reaction operates in a number of different fluoroarenes and coupling partners (Table 3). Reactions that varied the Ar−H bond with benzoate esters (structures **5**, **6**, **9**, **11**, and **13**−**20**), ketones (**8**), benzonitriles (**10**), and amides (**7** and **12**) progressed nicely, though in lower yields. In addition, the separation of the material from the reaction mixture proved difficult, especially for those reactions in which the Ar−H bond was not appreciably volatile, and thus could not be separated via distillation, such as the benzamides. The variation of the fluoroarene revealed that a wide variety of fluoroarenes operated similarly, although the variation of the Ar−H bond from 4-methyl (**6**) to 4-*tert*-butyl (**5**) benzoates resulted in somewhat better yields or easier separations. Interestingly, the reaction with a bromopentafluorobenzene resulted in the typical 1,4-diene product, which was connected at the position formerly occupied by the bromine (**19**). This is interesting because it serves as a mechanistic probe, suggesting the involvement of an aryl radical (see the discussion below). The reaction with 3-chloro-2,4,5,6-tetrafluoropyridine also undergoes a chemoselective fragmentation of the chloride, superseding the regioselectivity of the 4-position to yield the dihydro product (**20**) and revealing an interesting property of the products. The bicyclic motif is rotationally locked into a conformation, producing atropisomers that do not interconvert at room temperature.[49] While likely true for all substrates, it is not evident with symmetrical fluoroarenes. In this case, C−C bond formation gives rise to both axial and point chirality, with a slight preference for one diastereomer (2.4:1). These diastereomers can be partially separated by recrystallization, with the minor diastereomer becoming enriched (1:1.9; see the characterization of **20** in the Supporting Information). Under these conditions, the reaction operates with all the fluoroarenes shown here, and reactions attempted with a simple perfluorobenzene did not react at all, indicating that the fluoroaryl reduction potential (−2.11 V in DMF vs SCE)[25,50] is outside that reachable by the photocatalyst. Additionally, when 4-iodobenzonitrile, which is devoid of fluorine, was subjected to the reaction conditions with 4-methyl acetophenone, only trace amounts of the coupled products (both diene and biaryl) were detected by GCMS; instead, hydrodeiodination was the major product. This suggests that the fluorine substituents, compared to the defluoroarene, facilitate C−C bond formation. While yields are generally modest, this

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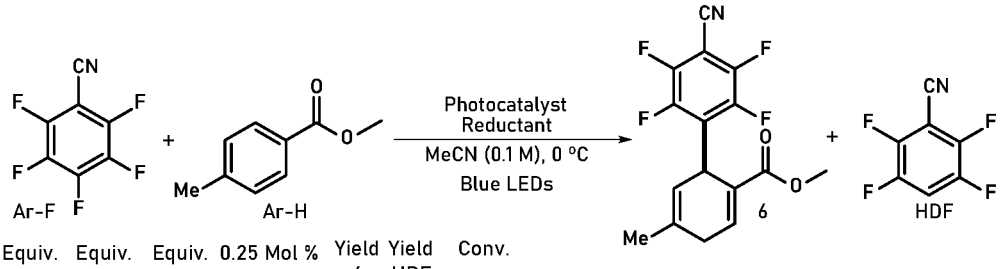
Table 2. Optimization of the Reaction Conditions[b]

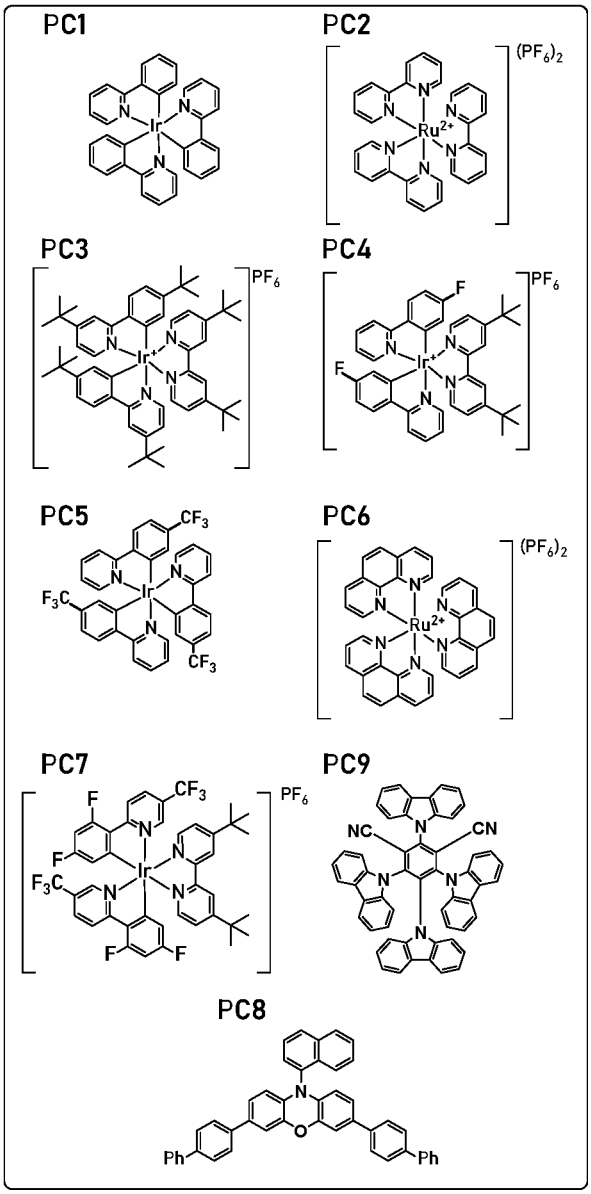


	Entry	Equiv. Ar-H	Equiv. DIPEA	Equiv. Water	0.25 Mol % PC	Yield 6	Yield HDF	Conv.
Photocatalyst Screen	1	2.6	1.5	0	PC1	4	6	20
	2	2.6	1.5	0	PC2	1	2	7
	3	2.6	1.5	0	PC3	16	52	100
	4	2.6	1.5	0	PC4	15	32	73
	5	2.6	1.5	0	PC5	16	27	90
	6	2.6	1.5	0	PC6	9	20	51
	7	2.6	1.5	0	PC7	7	27	50
	8	2.6	1.5	0	PC8	3	7	25
	9	2.6	1.5	0	PC9	-	-	-

	Entry	Equiv. Ar-H	Equiv. DIPEA	Equiv. Water	Mol % PC3	Yield 6	Yield HDF	Conv.
Water Optimization	10	3.0	1.1	0.0	0.25	8.6	24.8	48.7
	11	3.0	1.1	5	0.25	21.3	54.8	100
	12	3.0	1.1	15	0.25	22.0	48.5	100
	13	3.0	1.1	20	0.25	19.1	36.6	100

	Entry	Equiv. Ar-H	1.1 Equiv Reductant	Equiv. Water	Mol % PC3	Yield 6	Yield HDF	Conv.
Reductant Optimization	14[a]	2.6	DIPEA	15	0.25	30.3	37.2	
	15[a]	2.6	TMP	15	0.25	1.3	1.7	30.3
	16[a]	2.6	TEA	15	0.25	3.7	8.6	97.6

	Entry	Equiv. Ar-H	Equiv. DIPEA	Equiv. Water	Mol % PC3	Yield 6	Yield HDF	Conv.
DIPEA Optimization	17	2.6	0.0	10	0.25	0.0	0.0	0.0
	18	2.6	0.5	10	0.25	13.8	28	57.0
	19	2.6	1.0	10	0.25	21.0	50.7	100
	20	2.6	1.2	10	0.25	18.8	48.3	100
	21	2.6	1.5	10	0.25	15.5	39.3	100
	22	2.6	3.0	10	0.25	8.5	29.5	100
Ar-H Optimization	23	1.0	1.2	10	0.25	10.5	46.5	100
	24	3.0	1.2	10	0.25	18.0	42.0	100
	25	5.0	1.2	10	0.25	18.3	36.3	100
PC Loading	26	3.0	1.1	10	0.50	14.5	26.5	100
	27	3.0	1.1	10	0.25	17.5	34.5	100
	28	3.0	1.1	10	0.10	9.5	20	75.6



[a]Reactions were performed at rt. [b]Conversions or yields determined against the internal standard. Conducted in a 1 ml solvent NMR tube.

reaction provides a rapid increase in complexity from commercially available starting materials and scales well. Compound **6** was run on a 10 mmol scale and produced 553 mg of fluorinated diene. A 12.0 mmol scale batch reaction produced 947 mg of diene **14** according to general procedure B, which was sufficient for downstream synthetic manipulations. Reactions could be scaled using either high intensity LEDs and tubes with the addition of a stirbar or a flow reactor setup (see the Supporting Information for more details).

While phenols are largely incompatible with these conditions, Boc-protected methyl paraben was investigated and found to be a competent coupling partner. Upon cleavage with TFA, this reaction provides a keto-cyclohex-enyl methyl carboxylate. The two-step process formally provides access to the product of Michael addition with the keto-tautomer of

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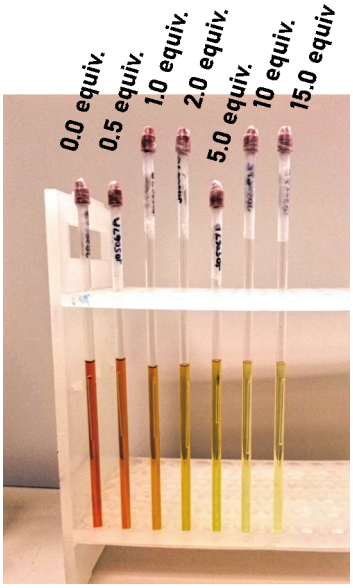

Figure 1. Darkening of the reaction as a function of the equivalents of water added.

methyl paraben (Scheme 2, right). With five sites of reactive functional groups, it is both functional-group dense and provides access to a complex molecule that can facilitate further synthetic manipulations.

Mechanism. While the selectivity of the reaction involves C−F fragmentation selectivity, C−C bond formation regioselectivity, C−H bond formation regioselectivity, and in certain case modest atropselectivity, it is remarkably predictable, forming only a single dearomatized isomer. The halogen selectivity follows trends we have previously observed in photocatalytic C−F functionalization. The 4-position of any monosubstituted perfluoroarene fragments preferentially[51] and, when present, heavier halogens preferentially undergo fragmentation (structure **19** and **20**, Table 3).[21,26,28,32] The regioselectivity of C−C bond formation between the fluoroaryl fragment and the hydrocarbon aryl coupling partner appears to be dictated by the LUMO of the Ar−H partner. The reaction is selective for the carbon *ortho* to an electron-withdrawing group and works best for substrates in which the predicted LUMO is larger at the *ortho*-position and significantly smaller elsewhere (see the Supporting Information for details). Arenes lacking electron-withdrawing groups fail to give any cyclohexadiene product, suggesting that the electron-withdrawing functional group may play other critical roles. At this time, the driving forces that lead to the observed diene regioisomer are unclear.

As mentioned above, water played a critical role in the reaction. The darkening of the reaction mixture could be avoided by adding water (Figure 1). This accompanied much-welcomed improvements in the product distribution (Table 2) and a reduction of the number of minor side products formed. This might be explained by the formation of cyanine dyes that arise from the oligomerization of DIPEA, as they are known to form under similar conditions and participate in photocatalytic reactions. The inclusion of water may either prevent their formation or hydrolyze them if they do form.[52,53]

We had presumed that the amine indirectly (as the radical cation) served as both the terminal reductant and the source of a H atom in the formation of the diene. However, we found that when normal water was replaced with heavy water (15 equiv D_2O, Scheme 3a) the reaction resulted in 69% deuterium incorporation into the diastereotopic methylene signal. Resubjecting the isolated product (**22** or **23**) to the reaction conditions with the inclusion of D_2O rather than H_2O showed that the postreaction exchange was not operative (slow HDF was observed). Furthermore, the deuterium incorporation occurred with a ca. 3:1 (75%) selectivity on the side opposite the perfluoroaryl ring. These findings obviate the possibility of the reaction proceeding solely through a hydrogen atom transfer (HAT) process because the bond dissociation energy of water at 117.9 kcal/mol[54] is far from the weakest bond (the BDE for cyclohexadiene is ca. 77 kcal/mol,[55] that for neutral DIPEA is ca. 90 kcal/mol, and that for DIPEA as the amine radical cation is ca. 42 kcal/mol),[54,56] placing water well outside the realm of reasonable H atom sources. It is more likely that the reaction proceeds through either an anionic reaction mechanism similar to the traditional Birch reaction or through a proton-coupled electron transfer (PCET) event in which the cyclohexadienyl radical is reduced to the carbanion and protonated. Because the deuteration is incomplete, however, it is possible that the reaction proceeds through both an anionic pathway and an HAT event.[57] Attempts to identify more acidic or nonaqueous additives instead of water (isopropanol, ethanol, and trifluoroethanol) that would favor the formation of the intended product proved deleterious to the reaction.

Upon further investigation, a kinetic isotope effect (KIE) was observed in parallel experiments where either H_2O or D_2O were included in the reaction mixture, with a k_H/k_D of 1.4 (Scheme 3b, eq 1) that is consistent with a secondary KIE or a solvent KIE.[58] This indicates that the rate-determining step (RDS) is not the protonation of an anionic intermediate by water nor a PCET event, steps for which a larger KIE could be expected.[59] One potential explanation could be that there is a pre-rate-determining equilibrium and the protonation of the carbanionic intermediate is near the rate-determining step. Alternatively, it could also be explained by the fragmentation of a fluoride as the RDS. The observed KIE would result from the solvation of the fragmenting fluoride,[60] a generally exothermic step by ca. 104.4 kcal/mol that could be expected to affect the kinetics of this step.[61,62] By comparison, the solvations of chloride and bromide are generally less exothermic (74.5 and 68.3 kcal/mol respectively) and in general undergo faster mesolytic fragmentation.[62] Reactions with either bromopentafluorobenzene or 3-chloro-tetrafluoropyridine (Scheme 3b, eqs 2 and 3, respectively) lead to a 1,4-diene product by fragmenting a nonfluorine halogen. Initial rate studies with these substrates indicate a KIE of 1.1, which is much less than those of analogous substrates in which a C−F bond is functionalized. This suggests that the RDS is the mesolytic fragmentation of the radical anion for the substrates from which fluoride is fragmented.

Taking the above experiments and observations, we present our working mechanistic understanding (Scheme 4). After that absorption of a photon, an initial singlet photocatalyst rapidly undergoes intersystem crossing to yield the triplet excited-state photocatalyst.[63,64] Based on redox potentials, the reaction is expected to proceed through a reductive quenching cycle in which the triplet photocatalyst ($E^0(Ir^{II}/Ir^{III*}) = -1.04$ V[44]) is reduced by an amine (E_{ox} ca. 0.5 V vs SCE[65]). The reduced photocatalyst then undergoes SET to the fluoroarene (**A**) to form the radical anion (**B**) and return the photocatalyst to the

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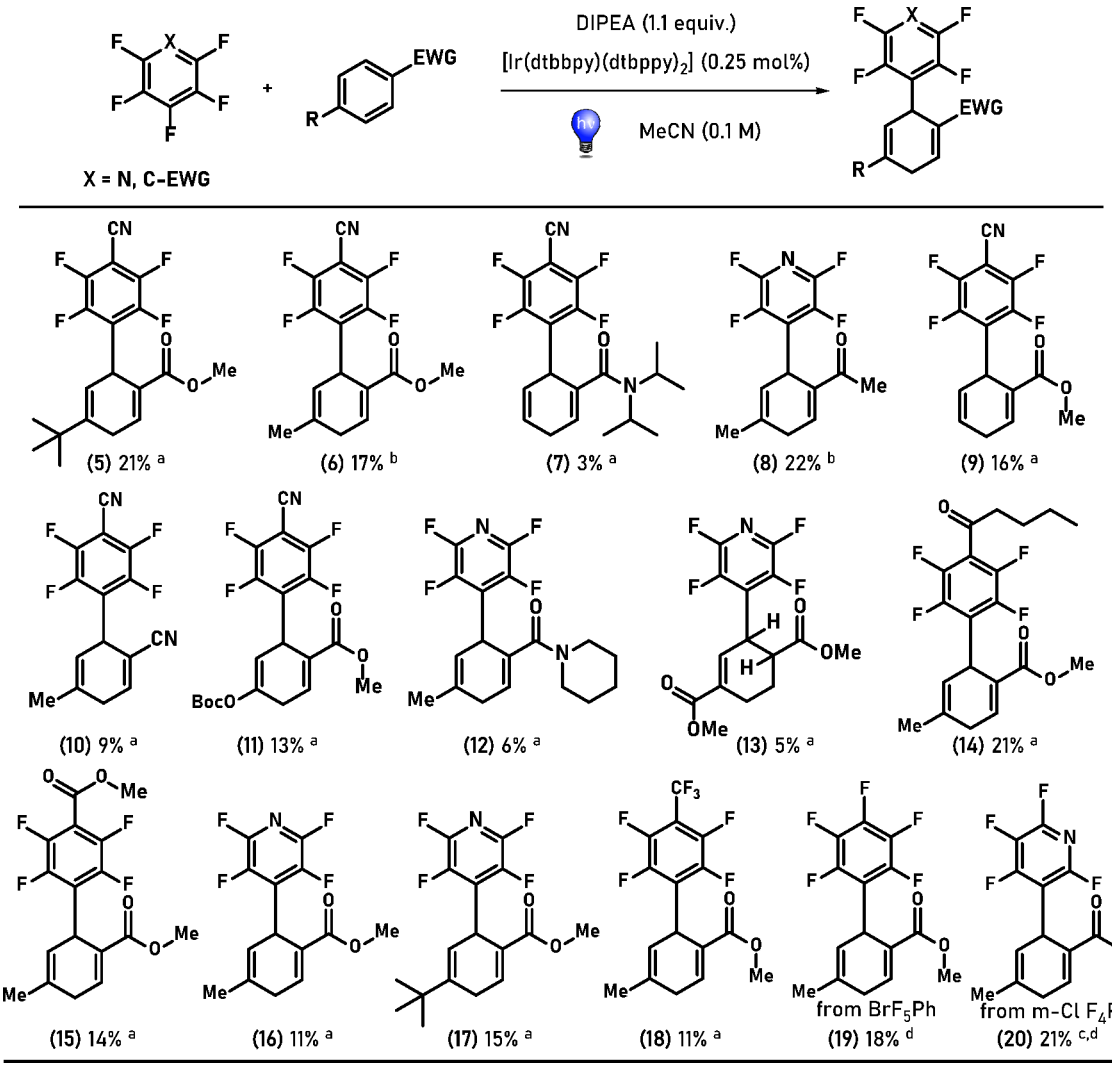
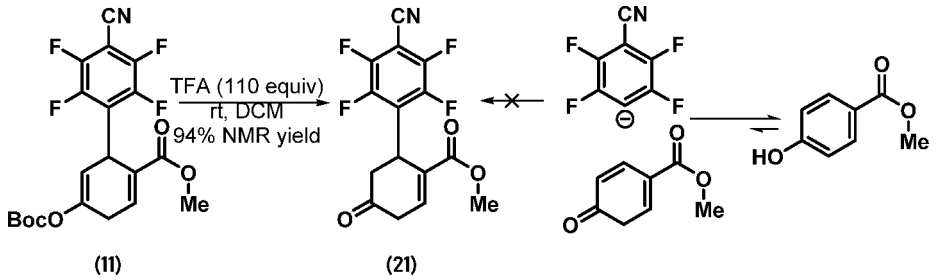
Table 3. Scope[e]



[a]Batch reaction conditions. [b]Flow reaction conditions. [c]Produces atropisomers. [d]NMR yield. [e]Isolated yields.

Scheme 2. Cleavage of the Boc Protecting Group



ground state. In the RDS, this radical anion, aided by water, fragments mesolytically to give the fluoroaryl radical (**C**) and a fluoride anion.[21,26,28] Based on BDEs, the fluoroaryl radical is expected to easily abstract a H atom from either DIPEA or its corresponding radical cation to give the major byproduct, the hydrodefluorinated product (**D**).

One might expect that the fluoroaryl radical anion (**B**, Scheme 4) with its abundance of electron density could potentially act nucleophilically,[66,67] attacking the LUMO of the Ar−H bond to produce an intermediate distonic radical anion. While there are reports of nucleophilic attacks by related radical anions,[67] it seems unlikely in this reaction. This is due to the observation that both chlorinated and brominated fluoroarenes lead to the same 1,4-diene product, the observation of a rate enhancement upon an increase in the amount of H_2O, and the observation that the KIE is significantly retarded in the presence of a fragmenting bromide or chloride, all of which are consistent with the fragmentation of the halogen being rate-determining. In other words, the rate of halogen fragmentation increases as the size of the halogen increases and the corresponding radical anions are less reliant on solvation (compared to fluoride) to facilitate fragmentation.

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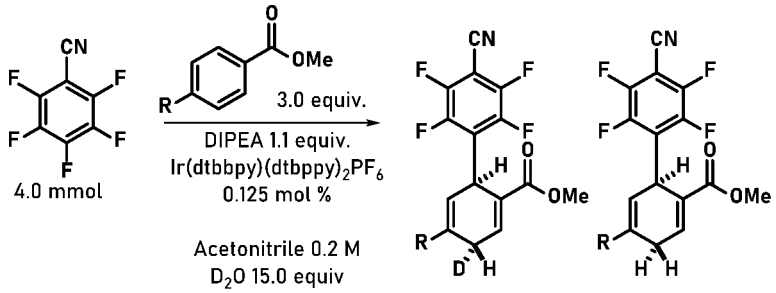
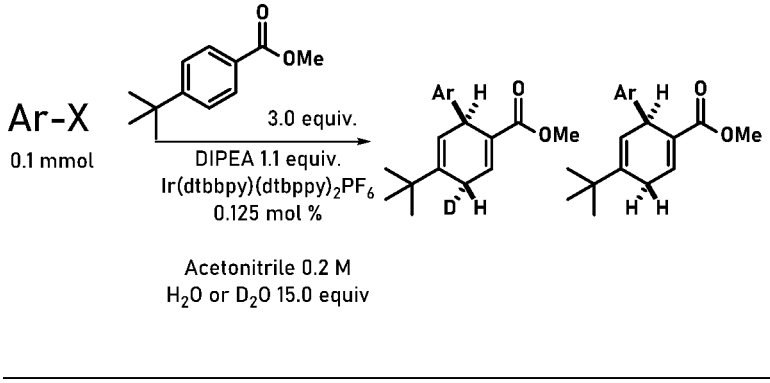
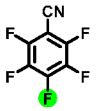
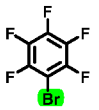
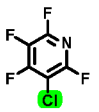
Scheme 3a. Deuteration



Structure	R=	Incorporation
(6.4.22)	Me	66% deuteration dr = 3.6 : 1
(6.4.23)	tBu	71% deuteration dr = 3 : 1

Scheme 3b. KIE



Ar-X	KIE
	1.4
	1.1
	1.1

Consequently, the k_H/k_D value diminishes as the rate of fragmentation increases, barring a mechanistic change between these substrates. This rate could be expected to be much more rapid upon the formation of an intermediate distonic radical anion. A solvent KIE, if observed at all under such conditions, would be the same for all substrates regardless of the identity of the fragmenting halogen.

Therefore, as with previous photocatalytic reactions we have reported, we are proposing that the reaction occurs through the mesolytic fragmentation of the radical anion (**B**, Scheme 4) to form the fluoroaryl radical (**C**), which then attacks the LUMO of the Ar−H bond and leads directly to (**E**). The partial incorporation of protium may be best explained by a mechanistic bifurcation from intermediate **E**. Therefore, we propose that the delocalized doubly allylic radical (**E**) is itself either reduced by the photocatalyst to give an anionic intermediate[68] (**G**), which provides the observed 1,4-diene (**H**) upon protonation, or oxidized to give the other observed major byproduct, the rearomatized biaryl product (**F**). It is also possible that the formation of the biaryl product and the intended dienyl product originate from the disproportionation reaction of the radical **E** in which the cyclohexadienyl radical abstracts a H atom from another cyclohexadienyl radical **E** to form both the observed reduced product (BDE ca. 77 kcal/mol for the unsubstituted substrate)[55] and the oxidized biaryl. Although this pathway fails to account for the incorporation of the deuterium from water, the deuteration is incomplete. The amount of the biaryl side product is always less than the amount of the 1,4-diene, which supports a mechanistic bifurcation although it is hardly conclusive.

Application. Returning to our original goal of enabling the synthesis of unnatural products, we were pleased to see that this motif maps very nicely onto the structural skeleton of classical cannabinoids (Scheme 5a), the most prominent, and also most notorious, of which is *trans*-Δ^9-tetrahydrocannabinol (THC),[69] the molecule responsible for not only most of the psychoactive effects of cannabis but also many of its medicinal properties. Despite the extensive and ongoing research on classical cannabinoids, F_3-THC has, to the best of our knowledge, not been reported before. Related compounds with mono-[70] or difluorination[71] are known in the literature[72,73] and have been shown to have bioefficacy (Scheme 5b). This method allows access to a completely unknown series of trifluoro analogs with substitution at either the Ar−F or Ar−H bond for diversification through a straightforward series of reactions and, importantly, will allow us to investigate the role of the hydroxyl group on THC.

For the synthesis of F_3-THC, we chose a diene (**14**, Scheme 5a) as the most suitable starting material because reactions toward a more direct route with the simple pentyl alkyl pentafluoroarene produced none of the intended intermediate materials, presumably because the reduction potential is too high due to an electron-donating pentyl group. Following the photo-Birch reaction, we began an investigation of methods for the deoxygenation of the aromatic ketone. Following a clean reduction of the ketone with $NaCNBH_3$, we obtained compound **24** (Scheme 6) in a high yield. We found the Barton−McCombie[74] approach attractive and pursued the elegant photochemical approach developed by Reiser et al.,[75] which provided the intended deoxygenated product in three straightforward steps[75,76] with a total yield of 76%.

Following the successful formation of the desired intermediate diene (**26**), the reduction of the Michael system was addressed. This proved to be remarkably difficult. This was surprising given the expected electronic and steric differences between the alkenes, and yet when using a number of the more

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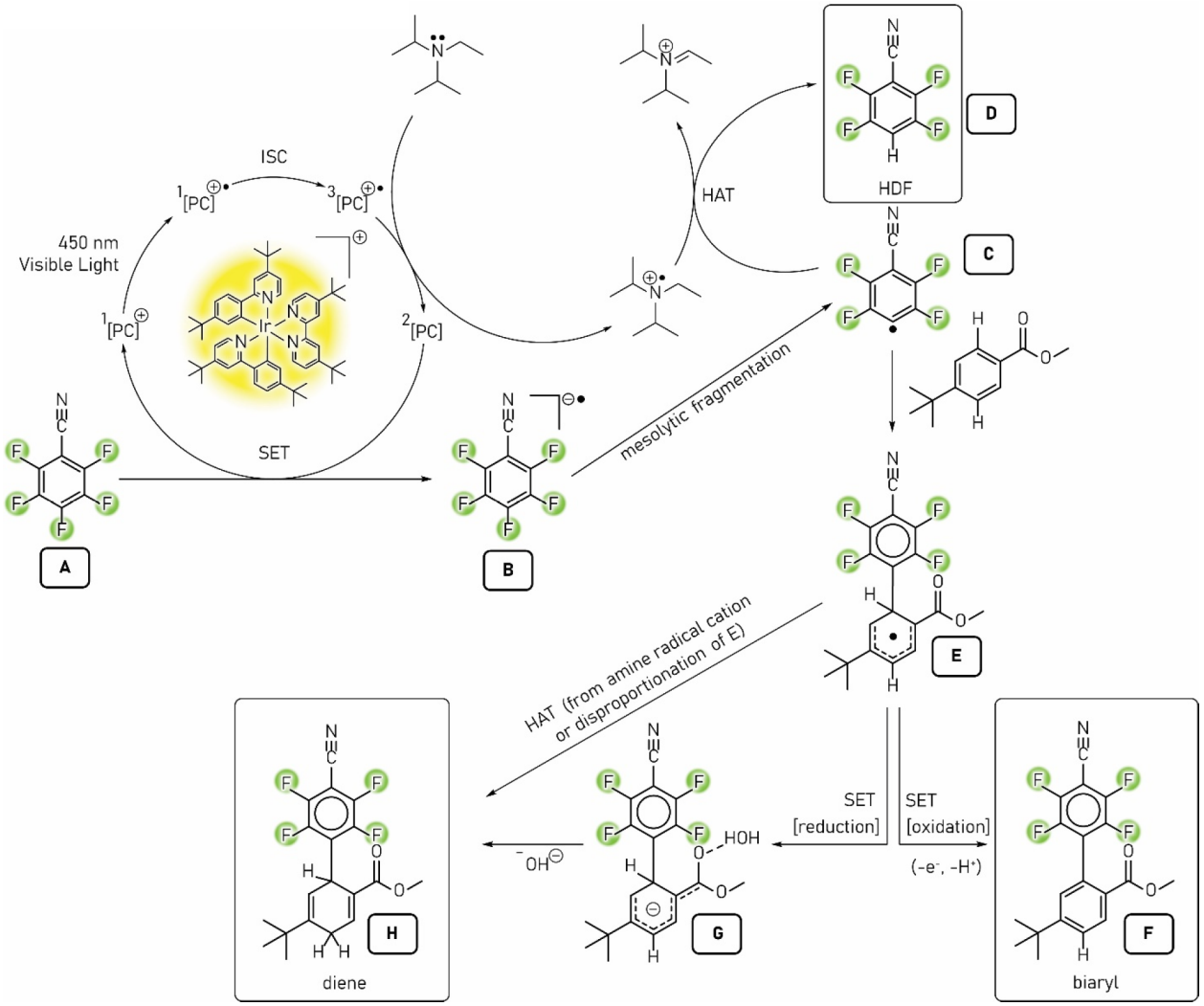
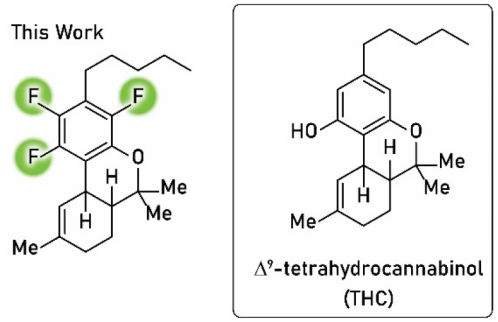
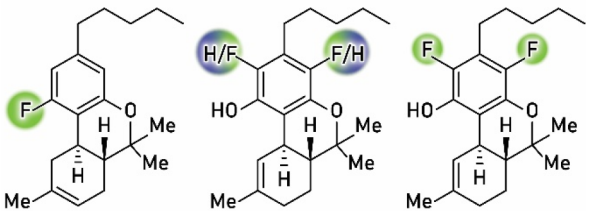
Scheme 4. Mechanistic Discussion



Scheme 5a. THC Fluoroanalog Target



Scheme 5b. Known Cannabinoid Fluoroanalogs



common methods we observed an unselective reaction, unintended side products, or a poor conversion. The most reliable method was found to be a derivative of the method by Chandrasekhar et al.,[77] i.e., hydrogenation via polymethylhydrosiloxane (PHMS) with the strong Lewis acid tris(pentafluorophenyl)borane (Scheme 7), which ultimately gave the hydrogenated product in modest yields and in a diastereomeric ratio of around 5:1 (varying between 4:1 and 6:1) in favor of the *cis*-product (**27**) over the *trans*-product (**28**). The desired epimer **28** could be achieved using a stoichiometric amount of KHMDS in THF to yield a 1:44 diastereomeric ratio in favor of *trans*-**28**. The *trans*-diastereomer was desirable in part as natural (*trans*) THC has a higher affinity for cannabinoid receptors than its *cis*-counterpart. It could be reasonably expected that the fluorinated analogs would perform similarly.

Having determined a route to the *trans*-intermediate cyclohexene (**28**), we then investigated the formation of the bridging ring (Scheme 8). We initially hoped to be able to form the third ring through the tandem nucleophilic addition of the methyl groups, followed by the subsequent S_NAr displacement of the fluoride. Unfortunately, this did not prove fruitful with either a methyl Grignard or lithiate reagent. Of note, while the *cis*- and *trans*-cyclohexenyl methyl esters (**27**

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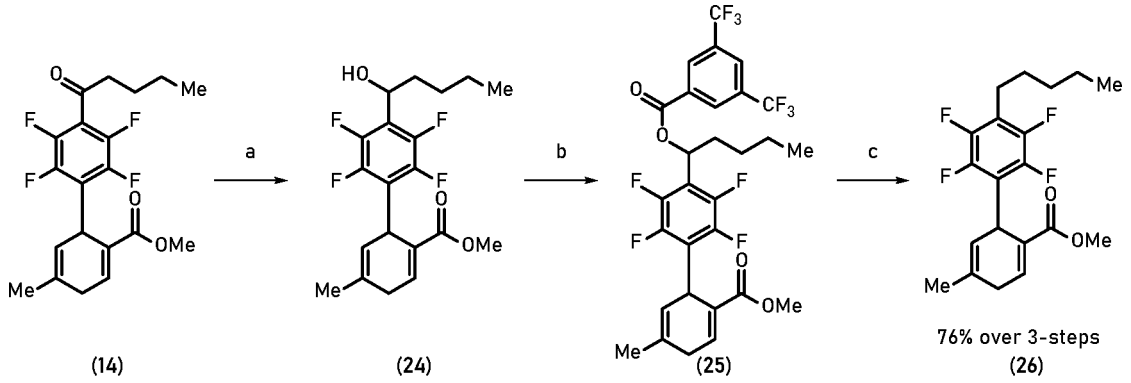
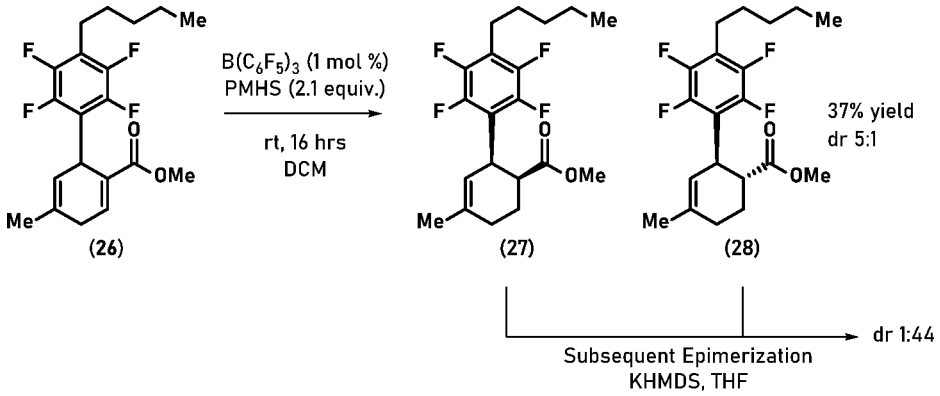
Scheme 6. Deoxygenation[a]

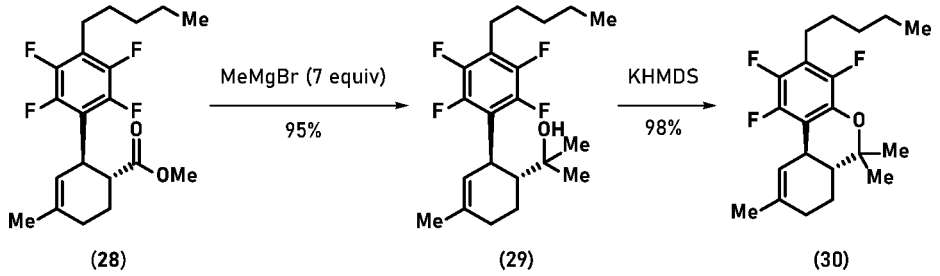


[a]Reagents and conditions are as follows: (a) ZnI_2 (1−5 equiv), $NaBH_3CN$ (7.5 equiv), DCE, 80 °C, 97%; (b) bis(trifluoromethyl)benzoyl chloride (1.1 equiv), 80 °C, 89%; and (c) DIPEA (2.0 equiv), $[Ir(dtbbpy)(dtbppy)_2]PF_6$ (1.5 mol %), 45 °C, 455 nm irradiation, 86%.

Scheme 7. Reduction of the Michael System



Scheme 8. Intramolecular Cyclization



and **28**) were challenging to separate, conversion to the corresponding *cis*- and *trans*- alcohols (**29**) showed different R_f values, and the compounds could be more easily separated chromatographically. However, treating alcohol (**29**) with KHMDS caused cyclization, similar to the work by Westphal, Trauner, Carreira, Frank, and co-workers,[71] and provided the intended cannabinoid product (**30**) with a 93% yield over two steps (Scheme 8). Ultimately, the reaction starts with two commodity chemicals and takes place in eight succinct steps with 6% overall yield. Furthermore, several points of diversification exist that could be used for further exploration of the motif. Several fluorinated cannabinoids are undergoing bioassay analysis now. The results will be reported in due course.

CONCLUSION

We have demonstrated a new reaction that provides a new and expedient route to 1,4-dienes that, despite being produced in modest yields, represent a rapid enhancement in chemical complexity, which may prove useful in discovery chemistry. Further, we have shown that the reaction likely proceeds through an anionic intermediate, which opens the door for potential further diversification through a Birch-like alkylation. These dienes map readily onto the carbon framework of classical cannabinoids, which we have shown can be synthesized in short order and would otherwise have been prohibitively difficult to reach. In addition, the synthetic steps offer a wealth of synthetic possibilities for diversification. Further, we expect that the synthesis laid out herein can provide access to fluorinated analogs of existing CB1/CB2 agonists, such as classical THC, related cannabinoids, or perrottetinenes. In addition, one of the major byproducts, the

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rearomatized biaryl species, could lead to additional analogs of the natural cannabinoid cannabinol (CBN). Coupled with existing defluorination techniques and the possibilities present for downstream diversification, the possibilities for a more complete SAR with respect to fluorination are possible. The reactivity we have shown was previously unknown and is orthogonal to other dearomative reactions.

EXPERIMENTAL PROCEDURES

General Comments. All reactions were conducted in dried and deoxygenated solvents. Solvents for column chromatography were used without further purification. Commercially available starting materials were used as received and included all Ar−F compounds except the pentafluorophenyl butyl ketone. Photocatalysts PC1,[78] PC4,[79] PC5,[79] PC7,[79] PC8,[80] and PC9[81] were synthesized according to literature procedures, and structures were confirmed by ^{1}H NMR spectroscopy. PC2, PC3, and PC6 were purchased and used as received. Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments.

Melting Points. Melting points were determined on a Stuart SMP10 melting point apparatus and are reported uncorrected.

NMR Analysis. NMR spectra were recorded using a Bruker Avance 400 spectrometer (400 MHz for ^{1}H, 101 MHz for ^{13}C, and 376 MHz for ^{19}F) or a Bruker Neo 600 spectrometer with a BBO BBF-H-D-05 SmartProbe (599 MHz for ^{1}H, 564 MHz for ^{19}F, and 151 MHz for ^{13}C) as noted. Chemical shifts are reported in parts per million (ppm) on the δ scale using the residual solvent signal as an internal standard. As abbreviations for the multiplicity were used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, pt = pseudo triplet, and app = apparent.

The analysis of reaction mixtures was performed in undeuterated solvents with either a DMSO-d_6 or C_6D_6 capillary as reference. Spectra were analyzed using Topspin 4.0.6 or MestReNova 14.0.1-23559 software.

Thin-Layer Chromatography. Thin-layer chromatography was done on with silica gel-precoated aluminum sheets (Machery-Nagel, silica gel 60 G/UV254, 0.2 mm), and UV light (254 nm) and a potassium permanganate stain were used for visualization.

High-Resolution Mass Spectrometry. HRMS was performed on a ThermoFisher LTQ OrbitrapXL or an Agilent Q-TOF 6540 UHD.

X-ray Analysis. X-ray analysis was performed by the crystallography laboratory of the University of Regensburg. Structure solving was done by Florian Meurer.

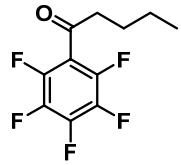
General Procedure A (Batch) For the Formation of the 1,4-Diene. In a darkened lab space, a new 25 mL test tube fitted with a stirbar was charged the fluoroarene (2.0 mmol) and a stock solution consisting of the Ar−H (3.0 equiv), DIPEA (1.1 equiv), Ir(dtbbpy)-(dtbppy)$_2$PF$_6$ (0.125 mol %), water (15 equiv), a C_6F_6 internal standard (1/6 equiv, testing showed no difference between reactions in which the standard was included and those in which it was not), and acetonitrile (0.1 M). The test tube was fitted with a rubber septum. This solution was chilled to 0 °C and then sparged with argon for 10 min at 0 °C. The solution was attached to low and constant positive argon pressure, added to an irradiation bath at 460 nm, and held at 0 °C until NMR analysis indicated the complete consumption of SM. The reaction was then concentrated and extracted at least thrice with boiling hexanes or until no remaining color was apparent in the hexanes extracts. The pooled hexanes extracts were then concentrated, and the resultant mixture was heated in a 10 mL round bottomed flask at 90 °C under high vacuum for 1−2 h. The resultant mixture was then dry-loaded onto silica and subjected to flash chromatography on a silica column with a hexanes/ethyl acetate mobile phase. The fractions containing the product were pooled and concentrated in a 20 mL scintillation vial. To the resultant oil was added a minimal amount of methanol from which pure crystals formed upon repeated freezing of the solution in liquid nitrogen, followed by vigorous shaking as the solution warmed.

General Procedure B (Batch) For the Formation of the 1,4-Diene. Perfluoroarene (12 mmol), an aromatic trapping agent (31.2 mmol, 2.6 equiv), and [Ir(dtbbpy)(dtbppy)$_2$]PF$_6$ (2 mg, 0.014 mol %) were dissolved in 120 mL of acetonitrile inside a Tauchschacht reactor (for more details, see the Supporting Information). DIPEA (14.4 mmol, 2.52 mL, 1.2 equiv) was added, and the solution was irradiated at 455 nm. After three days, the solvent was removed under reduced pressure. The residue was dissolved in 100 mL of boiling hexanes and filtered to remove insoluble components. The solvent was removed under reduced pressure, and most of the Ar−H coupling partner was distilled off with Kugelrohr distillation (for methyl toluate and methyl acetophenone; 95 °C, 1 mbar, 80−90% recovered). The residue was purified analogously to that in general procedure A.

General Procedure C (Flow) For the Formation of the 1,4-Diene. In a darkened labspace, the same as above, a 250 mL PFA round-bottom flask test tube fitted with a stirbar was charged the fluoroarene and a stock solution consisting of the Ar−H (3.0 equiv), DIPEA (1.1 equiv), Ir(dtbbpy)(dtbppy)$_2$PF$_6$ (0.125 mol %), water (15 equiv), and acetonitrile (0.1 M). The flask was fitted with a rubber septum. The solution was attached to low and constant positive argon pressure and circulated through PFA tubing via a peristaltic pump at 70 rpm. the solution was irradiated and held at room temperature until NMR spectroscopy indicated the of complete consumption of SM through an analysis of the aliquot. The products were isolated analogously to that in general procedure A.

General Procedure D (NMR Scale). Same as general procedure A except in a clean and dry NMR tube. A sealed melting point capillary containing a deuterated solvent was included in the NMR tube. The tube was then chilled to 0 °C and degassed by sparging with argon through an 18 gauge stainless steel needle for 10 min. The NMR tube was fitted with a septum and sealed with parafilm.

Synthesis of 1-(Perfluorophenyl)pentan-1-one. Literature-known compound. A 1 M solution of bromopentafluorobenzene (6.17



g, 25 mmol) was prepared and slowly added to activated magnesium turnings (729 mg, 30 mmol, 1.2 equiv). First, enough of the solution was added to cover the Mg. A grain of iodine was added, and the solution was heated until the color of the iodine disappeared. The remaining solution was added dropwise while stirring to keep the reaction mixture refluxing slightly. After all the bromopentafluorobenzene was added, the mixture was stirred until it had cooled to room temperature. A solution of pentanal (2.37 g, 27.5 mmol, 1.1 equiv based on bromopentafluorobenzene) in 20 mL of THF was added to the Grignard solution. The reaction mixture was stirred overnight at rt, quenched with a saturated NH_4Cl solution, extracted with ethyl acetate, and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The crude alcohol was used for the Jones oxidation without further purification.

The crude secondary alcohol was dissolved in approximately 50× its volume of acetone. The exact amount of solvent did not have any observable effect on the yield. A 2 M solution of CrO_3 in a 5:1 mixture (volume) of water/sulfuric acid was added in small portions while stirring until the complete consumption of starting material occurred. The reaction progress was monitored via TLC. After the completion of the reaction, isopropanol was added to decompose the remaining Cr(VI). Small amounts of water and ethyl acetate were added to the mixture, and the mixture extracted with ethyl acetate, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude product was purified by vacuum distillation (100 °C, 1 mbar) to give the product as a slightly yellow liquid. Isolated yield: 3.10 g, 11.9 mmol, 49% based on bromopentafluorobenzene. The spectra matched the literature values.[82]

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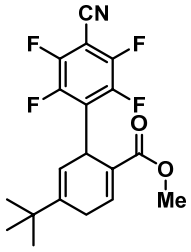
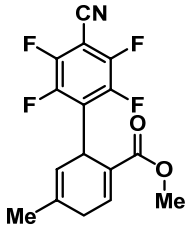
^{19}F NMR ($CDCl_3$ 377 MHz): δ −141.42 to −141.67 (m, 2 F), −150.06 to −150.35 (m, 1 F), −160.06 to −160.37 (m, 2 F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.88 (t, 2H, J = 7.48 Hz), 1.76−1.65 (m, 2 H), 1.46−1.34 (m, 2 H), 0.95 (t, 3H, J = 7.3 Hz). ^{13}C{^{1}H} NMR (CD_3CN, 101 MHz): δ 194.2, 144.0 (dm, J = 252.86 Hz), 142.5 (dm, J = 258.11 Hz), 137.6 (dm, J = 255.97 Hz), 115.6−115.0 (m), 44.80, 25.55, 22.01, 13.50.

*(**5**) Methyl 5-(tert-Butyl)-4′-cyano-2′,3′,5′,6′-tetrafluoro-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate.* General procedure A was



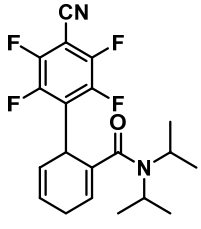
followed. Colorless crystalline solid, mp 108−110 °C. ^{19}F NMR (CD_3CN, 376 MHz,): δ −136.63 (td, 2F, J = 16.0, 7.1 Hz), −143.09 (td, 2F, J = 16.0, 7.1 Hz). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.28 (t, 1H, J = 3.9 Hz), 5.60−5.36 (m, 1H), 4.89 (q, 1H, J = 6.1 Hz), 3.62 (s, 3H), 3.17−3.00 (m, 2H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 165.6, 147.1 (ddt, J = 257.6, 17.2, 4.0 Hz), 145.3 (d, J = 248.2 Hz), 144.3, 140.6, 129.6 (t, J = 14.7 Hz), 125.8, 114.2, 107.9 (t, J = 3.8 Hz), 91.8 (tt, J = 17.6, 3.1 Hz), 51.3, 34.7, 33.1 (t, J = 2.1 Hz), 28.0, 26.4. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{19}H_{16}F_4NO_2^-$ 366.1123, found 366.1137. NMR yield: 32.9%. Isolated yield: 151.0 mg, 20.5%.

*(**6**) Methyl 4′-cyano-2′,3′,5′,6′-tetrafluoro-5-methyl-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate.* General procedure C was followed.



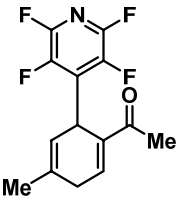
Colorless crystalline solid, mp 91−95 °C. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −133.47 (td, 2F, J = 16.6, 7.4 Hz), −141.19 (td, 2F, J = 15.9, 6.8 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, 1H, J = 3.8 Hz), 5.39−5.22 (m, 1H), 4.83 (q, 1H, J = 5.6 Hz), 3.67 (s, 3H), 2.98 (dd, 1H, J = 23.8, 7.9 Hz), 2.85 (dt, 1H, J = 23.9, 5.5 Hz), 1.76 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 166.0, 147.1 (ddt, J = 261.5, 16.6, 3.7 Hz), 145.2 (app-dm, J = 250.4 Hz), 140.3, 133.2, 129.5 (t, J = 14.3 Hz), 126.4, 117.5, 107.9 (t, J = 3.8 Hz), 92.3, 52.0, 33.2 (t, J = 2.1 Hz), 32.1, 22.7. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{16}H_{10}F_4NO_2^-$ 324.0653, found 324.0665. Isolated yield: 552.9 mg, 17.0%.

*(**7**) 4′-Cyano-2′,3′,5′,6′-tetrafluoro-N,N-diisopropyl-1,4-dihydro-[1,1′-biphenyl]-2-carboxamide.* General procedure A was followed,



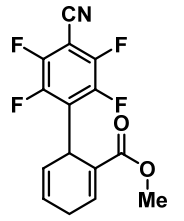
except Ar−H was not removed by heating under high vacuum but rather separated by column chromatography using a 40 g silica column. The material was eluted with large amount of benzamide Ar−H. A second 24 g silica column was run on these combined fractions, which provided a peak that contained the intended product and the biaryl product. The material was found to crystallize only from pentane. Colorless crystalline solid, mp 165−167 °C. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −135.27 to −135.57 (m, 2F), −142.00 to −142.19 (m, 2F). ^{1}H NMR (CD_3CN, 400 MHz): δ 6.03−5.91 (m, 2H), 5.67 (ddt, 1H, J = 10.0, 3.9, 2.1 Hz), 4.90−4.80 (m, 1H), 3.75 (s, 3H), 3.04−2.74 (m, 2H), 1.21 (d, 6H, J = 6.7 Hz), 1.01 (s, 6H). ^{13}C{^{1}H} NMR (CD_3CN, 101 MHz): δ 169.4, 147.6 (ddt, 4.0 Hz, J = 258.7, 16.9), 145.9 (app. dm, J = 248.4 Hz), 131.7, 130.7, 129.6, 128.7 (t, J = 15.0 Hz), 126.6, 125.1, 123.0, 108.3 (t, J = 3.8 Hz), 93.1 (tt, J = 17.6, 3.0 Hz), 33.6 (p, J = 1.5 Hz), 26.1, 20.5, 20.2. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{20}H_{19}F_4N_2O^-$ 379.1439, found 379.1458. NMR yield: 25.0%. Isolated yield: 19.7 mg, 2.6%.

*(**8**) 1-(4-Methyl-6-(perfluoropyridin-4-yl)cyclohexa-1,4-dien-1-yl)ethan-1-one.* Synthesized according to general procedure C from



pentafluoropyridine and *p*-methyl acetophenone. Purification via column chromatography (5% EA in PE) yielded a mostly clean product, which was contaminated with the rearomatized product as a viscous yellow liquid that solidified within three days. Recrystallization from either *n*-hexane or MeOH yielded the clean product. Colorless crystalline solid, mp 57−58 °C. The structure of this compound could be definitively determined by single crystal X-ray diffractometry. TLC: R_f = 0.35 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 377 MHz): δ = −92.86 to −93.10 (m, 2F), −146.26 to −146.51 (m, 2F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19−7.14 (m, 1H), 5.37−5.29 (m, 1H), 4.86−4.77 (m, 1H), 3.14−2.99 (m, 1H), 2.99−2.85 (m, 1H), 2.29 (s, 3H), 1.76 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 197.1, 144.8−144.4 (m), 142.3−141.9 (m), 141.9−141.5 (m), 141.1, 139.4−138.9 (m), 136.7−136.2 (m), 135.7, 132.6, 117.6, 32.3, 32.2, 25.0, 22.4. HRMS (+APCI): Calcd for [$C_{14}H_{11}F_4O$ + NH_4^+]$^+$ 303.1115, found: 303.1133. Isolated yield: 765 mg, 22%.

*(**9**) Methyl 4′-Cyano-2′,3′,5′,6′-tetrafluoro-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate.* General procedure A was followed using a 4 g



silica column. Colorless crystalline solid, mp 147−149 °C. ^{19}F NMR (CD_3CN 376 MHz): δ −136.45 (td, J = 16.0, 7.0 Hz), −143.01 (app. td, J = 16.1, 7.0 Hz). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.25 (t, 1H, J = 4.0 Hz), 6.18−5.86 (m, 1H), 5.76−5.52 (m, 1H), 5.03−4.73 (m, 1H), 3.63 (s, 3H), 3.17−2.90 (m, 2H). ^{13}C{^{1}H} NMR (CD_3CN, 101 MHz): δ 166.6, 148.2 (ddt, J = 257.8, 17.1, 3.9 Hz), 146.2 (d, J = 247.6 Hz), 140.9 (t, J = 1.4 Hz), 130.1 (t, J = 14.7 Hz), 127.4, 126.3, 123.6, 108.9 (t, J = 3.8 Hz), 93.1 (tt, J = 17.5, 2.6 Hz), 52.4, 32.9 (p, J = 2.1 Hz), 27.8. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{15}H_8F_4NO_2^-$ 310.0497, found 310.0509. NMR yield: 25.0%. Isolated yield: 98.5 mg, 15.8%.

*(**10**) 2′,3′,5′,6′-Tetrafluoro-5-methyl-1,4-dihydro-[1,1′-biphenyl]-2,4′-dicarbonitrile.* General procedure A was followed, except that the material was repeatedly recrystallized from either hexanes or methanol. Colorless crystalline solid, mp 117−120 °C. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −131.79 (td, 2F, J = 16.8, 7.3 Hz), −140.34 (td, 2F, J = 16.6, 6.5 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.87 (td, 6H, J = 3.7, 1.6 Hz), 5.44−5.19 (m, 6H), 4.85−4.49 (m, 6H), 3.13−

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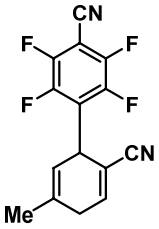
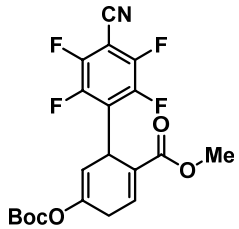


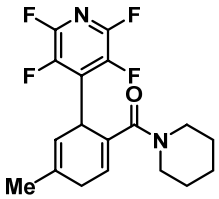
2.73 (m, 12H), 1.78 (s, 20H), 1.25 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 151 MHz): δ 147.4 (ddt, J = 259.1, 16.8, 3.9 Hz), 145.2 (ddt, J = 250.0, 11.7, 5.2 Hz), 145.0, 133.2, 131.8, 126.1 (t, J = 14.4 Hz), 115.4, 108.7, 107.7 (t, J = 3.9 Hz), 93.6 (tt, J = 17.4, 2.6 Hz), 34.2, 30.9, 21.7. HRMS (ESI/ion trap) m/z: $[M - H^+]^-$ Calcd for $C_{15}H_7F_4N_2^-$ 291.0551, found 291.0552. NMR yield: 16.4%. Isolated yield: 30.0 mg, 9.1%.

(11) Methyl 5-((tert-Butoxycarbonyl)oxy)-4′-cyano-2′,3′,5′,6′-tetrafluoro-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate. General pro-



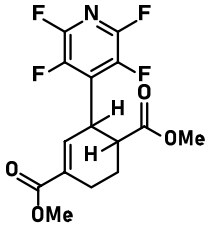
cedure A was followed but with only 1 equiv of water. The Ar−H was not removed by heating under high vacuum but rather separated by column chromatography using a 40 g silica column. Colorless crystalline solid, mp 104−105 °C. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −132.84 (td, 2F, J = 16.6, 7.3 Hz), −140.61 (td, 2F, J = 16.5, 15.8, 6.7 Hz). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.13 (ddd, 1H, J = 4.4, 3.0, 1.0 Hz), 5.43 (dd, J = 4.3, 2.0 Hz, 1H), 4.98 (q, J = 6.1 Hz, 1H), 3.61 (s, 3H), 3.23 (ddt, 1H, J = 23.4, 7.5, 2.7 Hz), 3.06 (ddd, 1H, J = 23.4, 6.4, 4.6 Hz), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 165.7, 151.0, 147.5, 147.5 (ddt, J = 262.2, 16.6, 3.1 Hz), 145.6 (d, J = 250.0 Hz), 139.0, 128.3 (t, J = 14.0 Hz), 126.6, 110.3, 108.0 (t, J = 3.6 Hz), 84.3, 52.6, 33.5, 31.4, 29.2, 28.1. HRMS (ESI/ion trap) m/z: $[M - H]^-$ Calcd for $C_{20}H_{16}F_4NO_5^-$ 426.0970, found 426.0995. Isolated yield: 118.6 mg, 13.8%.

(12) (4-Methyl-6-(perfluoropyridin-4-yl)cyclohexa-1,4-dien-1-yl)-(piperidin-1-yl)methanone. General procedure B was followed, at a



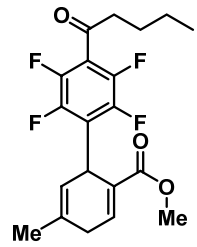
12 mmol scale, with 2.6 equiv of Ar−H and 10 equiv of water. The Ar−H was not removed by heating under high vacuum but rather separated by column chromatography. The product was recrystallized from *n*-hexane. Colorless crystalline solid. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −92.00 to −92.38 (m, 2F), −145.53 to −145.89 (m, 2F). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.08 (ddd, 1H, J = 4.2, 2.9, 1.7 Hz), 5.32 (td, 1H, J = 3.1, 1.6 Hz), 4.93 (q, 1H, J = 6.4 Hz), 3.65−3.22 (m, 3H), 2.89 (dd, 1H, J = 23.3, 6.8 Hz), 2.75 (ddd, 1H, J = 22.9, 7.3, 4.0 Hz), 1.75 (s, 3H), 1.59 (p, 2H, J = 5.8 Hz), 1.53−1.18 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 168.6, 145.0−141.9 (m), 140.6 (dd, J = 260.6, 20.8 Hz), 135.4 (t, J = 13.3 Hz), 133.5, 129.0, 128.3, 117.0, 34.4, 31.6, 30.9, 26.2, 24.5, 22.7, 14.1. HRMS (+ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}F_4N_2O^+$ 355.1428, found 355.1423. Isolated yield: 220.0 mg, 6.2%. The reaction was repeated at a later stage with the organic photocatalyst 4CzIPN (**PC9**). Crude NMR spectra sowed similar results. The isolated yield was 9.9% due to a slower gradient during column chromatography (0 → 5% EtOAc in hexanes) and a better separation.

(13) Dimethyl 3-(Perfluoropyridin-4-yl)cyclohex-1-ene-1,4-dicarboxylate. General procedure B was followed. The Ar−H was not



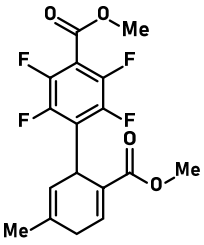
removed by heating under high vacuum but rather separated by column chromatography, mp 93−94 °C. ^{19}F NMR ($CDCl_3$, 376 MHz): δ −90.76 to −91.23 (m, 2F), −142.62 to −143.66 (m, 2F). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.84−6.45 (m, 1H), 4.35 (d, 1H, J = 10.5 Hz), 3.74 (s, 3H), 3.63 (s, 3H), 2.95 (ddd, 1H, J = 12.5, 10.4, 2.8 Hz), 2.77−2.56 (m, 1H), 2.54−2.22 (m, 2H), 1.99−1.65 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz) δ 173.5, 166.6, 143.7 (dddd, J = 246.0, 16.5, 13.0, 3.1 Hz), 140.7 (d, J = 259.5), 134.8, 134.7 (tt, J = 14.3, 2.4 Hz), 132.1, 52.4, 52.1, 43.2 (t, J = 2.2 Hz), 35.8 (t, J = 2.0 Hz), 26.0, 23.9. HRMS (ESI/ion trap) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}F_4NO_4^+$ 348.0853, found 348.0856. Isolated yield, 200 mg, 575.93 umol, 4.8%.

Example of the Large-Scale Synthetic Method. *(14) Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentanoyl-1,4-dihydro-[1,1′-bi-*



phenyl]-2-carboxylate. General procedure B was followed from 1-(perfluorophenyl)pentan-1-one and methyl *p*-toluate. Purification via column chromatography (5% EA in PE) yielded the product, which was contaminated with variable amounts of the rearomatized product as a viscous yellow liquid. Recrystallization from MeOH yielded the product as colorless needles, mp 66.8 °C. TLC: R_f = 0.50 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −143.85 to −14.17 (m, 4F). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24−7.17 (m, 1H), 5.42−5.21 (m, 1H), 4.78 (q, 1H, J = 6.2, 5.8 Hz), 3.65 (s, 3H), 3.11−2.70 (m, 4H), 1.73 (t, 3H, J = 1.4 Hz), 1.67 (p, J = 7.4 Hz, 2H), 1.36 (h, J = 7.4 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 195.8, 166.1, 145.2 (ddt, J = 253.8, 16.3, 5.4 Hz), 143.5 (dddd, J = 254.4, 17.6, 6.5, 5.0 Hz), 139.7, 132.2, 127.0, 124.6 (t, J = 14.0 Hz), 118.3, 118.1 (t, J = 17.8 Hz), 51.8, 44.8, 32.6 (p, J = 1.9 Hz), 32.0, 25.7, 22.6, 22.2, 13.8. HRMS (EI) m/z: $[M]^+$ exact mass Calcd. for $C_{20}H_{20}F_4O_3$ 384.1349, found 384.1337. Isolated yield: 947 mg, 2.46 mmol, 21%.

(15) Dimethyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-1,4-dihydro-[1,1′-biphenyl]-2,4′-dicarboxylate. General procedure A was followed.



https://doi.org/10.1021/acs.joc.1c00169
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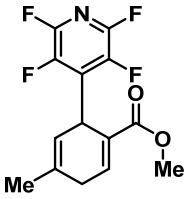
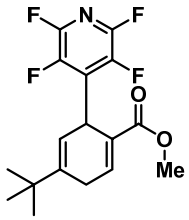
The product eluted at 5% EtOAc in hexanes after 38 CV in a 24 g column as a colorless crystalline solid, mp 91−95 °C. ^{19}F NMR ($CDCl_3$, 564 MHz): δ −139.20 (dd, J = 22.2, 12.6 Hz, 2F (biaryl impurity)), −139.46 (dd, J = 22.6, 13.0 Hz, 2F (biaryl impurity)), −140.33 to −140.90 (m, 2F), −142.99 to −143.96 (m, 2F). ^{1}H NMR ($CDCl_3$, 599 MHz) δ 7.25−7.16 (m, 1H), 5.39−5.25 (m, 1H), 4.81 (q, 1H, J = 5.5, 5.0 Hz), 3.95 (s, 3H), 3.66 (s, 2H), 2.97 (ddt, 1H, J = 24.8, 6.5, 2.4 Hz), 2.83 (dt, 1H, J = 23.8, 5.5 Hz), 1.74 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 166.2, 160.6, 145.3 (ddt, J = 249.6, 14.3, 4.7 Hz), 144.7 (ddt, J = 256.7, 15.9, 4.4 Hz), 139.8, 132.4, 126.9, 125.7 (t, J = 14.7 Hz), 118.2, 110.5 (t, J = 15.8 Hz), 53.3, 51.9, 32.7, 32.1, 22.6. HRMS (ESI/ion trap) m/z: [M + Na$^+$]$^+$ Calcd for $C_{17}H_{13}F_4O_4Na$ 381.0726, found 381.0707. Isolated yield: 99.6 mg, 13.8%.

(16) Methyl 4-Methyl-6-(perfluoropyridin-4-yl)cyclohexa-1,4-diene-1-carboxylate. General procedure A was followed. Separation



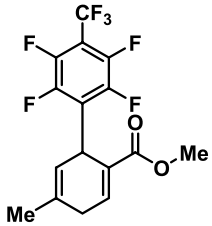
occurred via a 4 g chromatography column. Colorless crystalline solid, mp 93−96 °C. ^{19}F NMR (CD_3CN, 564 MHz) δ −94.96 to −95.25 (m, 2F), −146.97 to −147.15 (m, 2F). ^{1}H NMR (CD_3CN, 599 MHz): δ 7.38−7.13 (m, 1H), 5.45−5.34 (m, 1H), 4.93−4.82 (m, 1H), 3.63 (s, 3H), 3.02 (app. dd, 1H, J = 24.3, 7.2, Hz), 2.92 (dddt, 1H, J = 24.1, 6.5, 4.5, 0.9 Hz), 1.79−1.76 (m, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 166.6, 144.3 (apparent d, J = 241.7 Hz), 141.8 (apparent d, J = 256.9 Hz), 137.5 (tt, J = 13.3, 2.2 Hz), 134.3, 127.1, 117.7, 52.3, 34.1 (t, J = 1.9 Hz), 32.4, 30.9, 22.6. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{14}H_{10}F_4NO_2^-$ 300.0653, found 300.0658. NMR yield: 13.2%. Isolated yield: 69.1 mg, 11.4%.

(17) Methyl 4-(tert-Butyl)-6-(perfluoropyridin-4-yl)cyclohexa-1,4-diene-1-carboxylate. General procedure A was followed. Colorless



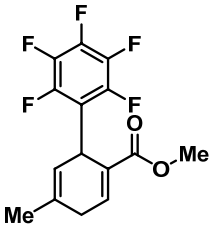
crystalline solid, mp 59−60 °C. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −91.85 to −92.17 (m, 2F), −145.34 to −145.88 (m, 2F). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (td, 1H, J = 3.9, 1.1 Hz), 5.40 (dt, 1H, J = 4.3, 1.5 Hz), 4.89 (q, 1H, J = 5.9 Hz), 3.67 (s, 3H), 3.05 (ddd, J = 6.7, 4.0, 1.5 Hz, 2H), 1.07 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 165.9, 144.9, 143.6 (d, J = 248.4 Hz), 141.1, 140.8 (d, J = 273.3 Hz), 136.3 (t, J = 13.1 Hz), 125.8, 114.1, 52.0, 35.2, 33.5 (t, J = 1.8 Hz), 28.8, 26.9 (t, J = 1.6 Hz). HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{17}H_{16}F_4NO_2^-$ 342.1123, found 342.1143. NMR yield: 16.7%. Isolated yield: 99.5 mg, 14.5%.

(18) Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-(trifluoromethyl)-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate. General procedure A was



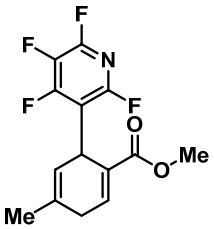
followed, except the product was recrystallized from isopropanol. Colorless crystalline solid, mp 104−105 °C. ^{19}F NMR (CD_3CN, 564 MHz): δ −57.07 (t, 3F, J = 21.3 Hz), −144.10 to −144.22 (m, 2F), −144.22 to −144.46 (m, 2F). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.24−7.17 (m, 1H), 5.41−5.34 (m, 1H), 4.83 (q, 1H, J = 5.5 Hz), 3.6 (s, 3H), 2.99 (ddt, 1H, J = 24.2, 6.6, 2.5 Hz), 2.88 (ddd, 1H, J = 24.1, 6.5, 4.6 Hz), 1.74 (s, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 166.6, 146.5 (d, J = 246.3 Hz), 145.0 (d, J = 235.4 Hz), 140.7, 133.8, 128.2 (t, J = 14.7 Hz), 127.4, 122.2 (q, J = 273.3 Hz), 108.5−107.4 (m), 52.2, 33.6 (t, J = 2.1 Hz), 32.4, 22.5. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{16}H_{10}F_7O_2^-$ 367.0575, found 367.0587. NMR yield: 29.3%. Isolated yield: 84.0 mg, 11.4%.

(19) Methyl 2′,3′,4′,5′,6′-Pentafluoro-5-methyl-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate. General procedure A was followed



from bromopentafluorobenzene. Colorless oily semisolid. Partial isolation was achieved via silica gel chromatography using a 4 g column with hexanes/ethyl acetate. ^{19}F NMR (CD_3CN, 376 MHz): δ −146.20 (dd, 2F, J = 21.2, 7.8 Hz), −160.17 (td, 1F, J = 20.2, 1.1 Hz), −165.56 to −165.83 (m, 2F). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.22−7.12 (m, 1H), 5.41−5.34 (m, 1H), 4.74 (q, 1H, J = 6.1 Hz), 3.03−2.90 (m, 1H), 2.92−2.79 (m, 1H), 1.73 (s, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 165.8, 145.4 (d, J = 245.3 Hz), 139.8 (d, J = 247.4 Hz), 139.3, 137.5 (d, J = 247.5 Hz), 132.2, 129.2, 127.0, 118.2, 51.2, 31.9, 31.4, 21.5. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{15}H_{10}F_5O_2^-$ 317.0606, found 317.0628. NMR yield: 18.1% (corresponding to 115 mg).

(20) Methyl 4-Methyl-6-(perfluoropyridin-3-yl)cyclohexa-1,4-diene-1-carboxylate. General procedure A was followed with 3-



chlorotetrafluoropyridine. Partial resolution of the atropisomers was achieved through repeated recrystallizations. HRMS (ESI/ion trap) m/z: [M − H$^+$]$^-$ Calcd for $C_{14}H_{10}F_4NO_2^-$ 300.0653, found 300.0668. NMR yield: 21.3% (corresponding to 128 mg), 2.4:1 dr.

Atropisomer 1 (Major). ^{19}F NMR (CD_3CN, 376 MHz): δ −73.99, −89.41 (ddd, J = 22.2, 18.8, 14.6 Hz, 1F), −118.89 (q, J = 17.2 Hz, 1F), −168.50 (ddd, J = 24.0, 21.8, 18.4 Hz, 1F). ^{1}H NMR (CD_3CN, 400 MHz): δ 6.77 (m, 1H), 5.75 (m, 1H), 4.47 (q, 1H, J = 6.5 Hz), 3.73 (s, 3H), 3.00 (ddp, 2H, J = 7.6, 3.9, 2.0 Hz), 1.67−1.56 (m, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 167.6, 159.7 (d, J = 261.0 Hz), 154.1 (d, J = 242.3 Hz), 149.1 (d, J = 240.2 Hz), 134.4 (d, J = 256.4 Hz),134.5, 130.4, 129.1, 122.4, 112.2, 52.3, 37.1, 26.8, 20.8.

Atropisomer 2 (Minor). ^{19}F NMR (CD_3CN, 376 MHz): δ −74.63 (dt, J = 21.0, 14.3 Hz), −90.73 (ddd, J = 21.9, 18.2, 14.8 Hz, 1F), −119.82 (tdd, 1F, J = 18.2, 14.8, 1.2 Hz), −169.33 (ddd, 1F, J = 23.9, 22.0, 18.4 Hz). ^{1}H NMR (CD_3CN, 400 MHz): δ 7.22 (m, 1H), 5.40 (m, 1H), 4.74−4.60 (m, 1H), 3.62 (s, 3H), 3.07−2.94 (m, 1H), 2.94−2.79 (m, 1H), 1.77 (s, 3H). ^{13}C{^{1}H} NMR (CD_3CN, 151 MHz): δ 166.7, 159.3 (d, J = 262.2 Hz), 153.8 (d, J = 237.5 Hz), 148.4 (d, J = 244.8 Hz), 134.0 (d, J = 267.7 Hz), 133.5, 127.5, 112.0, 118.6, 52.2, 140.5, 32.6, 32.3, 22.5.

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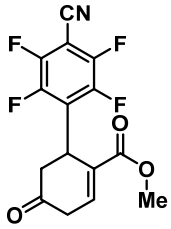
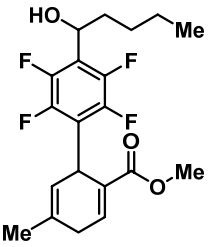


(21) Methyl 4′-Cyano-2′,3′,5′,6′-tetrafluoro-5-oxo-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate. Methyl 5-((*tert*-butoxycarbonyl)oxy)-4′-cyano-2′,3′,5′,6′-tetrafluoro-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate (**11**) (5.0 mg, 0.0117 mmol) was dissolved in DCM (0.02 M) in an NMR tube. to the NMR tube was added 10 equiv of trifluoroacetic acid (TFA), and the mixture was sonicated for 2 h. An additional 50 equiv of TFA was added, and the mixture sonicated 2 h. An additional 50 equiv of TFA was added, and the mixture sonicated for 2 h, after which TLC indicated the complete consumption of (**11**). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −131.70 to −132.11 (m, 2F), −138.94 to −139.44 (m, 2F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (dd, 1H, J = 4.4, 3.4 Hz), 4.88 (d, 1H, J = 8.5 Hz), 3.72 (s, 3H), 3.24 (s, 2H), 2.96 (dd, 1H, J = 15.7, 8.6 Hz), 2.63 (dd, 1H, J = 15.6, 3.1 Hz). HRMS (ESI/ion trap) m/z: [M − H+]- Calcd for $C_{15}H_8F_4NO_3^-$ 326.0446, found 326.0453. NMR yield: 94% (corresponding to 3.6 mg).

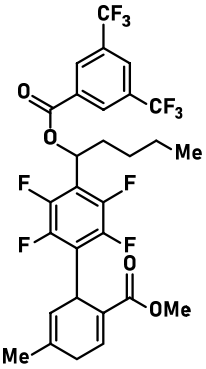
(24) Methyl 2′,3′,5′,6′-Tetrafluoro-4′-(1-hydroxypentyl)-5-methyl-1,4-dihydro-[1,1′- biphenyl]-2-carboxylate. The reaction was



derived from the literature procedure[76] for the deoxygenation of aromatic ketones. Compound **14** (77 mg, 200 μmol) was dissolved in 1 mL of DCE. Anhydrous ZnI_2 (96 mg, 300 μmol, 1.5 equiv) and $NaBH_3CN$ (94 mg, 7.5 equiv) were added to the mixture, and the dispersion was heated to 80 °C in an oil bath for 6 h. After cooling to room temperature, 2 mL of 2 M HCl was added dropwise until the excess $NaBH_3CN$ was decomposed. The solution was extracted with DCM, the organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. Purification via column chromatography (10% EA in PE) yielded the product as a slightly yellow viscous liquid, which solidified from $CHCl_3$ as a white waxy solid.

TLC. R_f = 0.30 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −145.70 (dd, 2F, J = 21.51, 12.24 Hz), −146.51 (dd, 2F, J = 21.50, 12.24 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J = 2.81 Hz, 1 H), 5.27 (s, 1 H), 5.00−4.89 (m, 1 H), 4.75−4.67 (m, 1 H), 3.58 (s, 3 H), 2.98−2.67 (m, 2 H), 2.20−2.07 (m, 1 H), 1.96−1.86 (m, 1 H), 1.80−1.70 (m, 1 H), 1.67 (s, 3 H), 1.44−1.11 (m, 5 H), 0.83 (t, 3 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 166.3, 145.1 (d, J = 245.8 Hz), 144.4 (d, J = 245.0 Hz), 139.4, 131.6, 127.3, 120.9 (t, J = 14.7 Hz), 120.3 (t, J = 15.2 Hz), 118.8, 66.7, 51.7, 36.7, 32.3(t, J = 2.2 Hz), 32.0, 31.6, 28.0, 22.7, 22.5, 22.4, 14.1, 13.9. HRMS (EI) m/z: [M]+ exact mass Calcd for $C_{20}H_{22}F_4O_3$ 386.1500, found 386.1498. Isolated yield: 75 mg, 194 μmol, 97%.

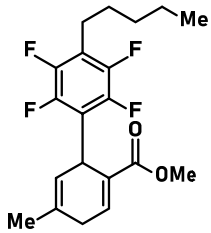
(25) Methyl 4′-(1-((3,5-Bis(trifluoromethyl)benzoyl)oxy)pentyl)-2′,3′,5′,6′-tetrafluoro-5- methyl-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate. According to a procedure derived from Reiser and co-workers,[75] compound **24** (900 mg, 2.33 mmol) was dissolved in 24 mL of DCM and cooled in an ice bath. 3,5-Bis(trifluoromethyl)-benzoyl chloride (460 μL, 1.1 equiv) was added dropwise. The solution was warmed to room temperature, and the solvent was removed under reduced pressure. The residue was extracted with hot petroleum ether, most of the solvent was removed under reduced



pressure, and the product was purified via column chromatography (0−10% EA in PE) to yield the product as a viscous colorless liquid as a mixture of diastereomers. The diastereomers are not distinguishable in the ^{19}F and ^{1}H NMR spectra, but most of the ^{13}C resonances appeared as slightly split signals.

TLC. R_f = 0.70 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −63.62 (s, 6F), −144.34 to −144.57 (m, 2F), −145.02 (dd, J = 21.3, 12.2 Hz, 2F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 2H), 8.07 (s, 1H), 7.22−7.18 (m, 1H), 6.31 (t, J = 7.43 Hz, 1H), 5.37−5.31 (m, 1H), 4.83−4.74 (m, 1H), 3.67−3.63 (2s, overlapping, 3H), 3.04−2.90 (m, 1H), 2.81 (dt, 1H, J = 23.74, 5.26 Hz), 2.33−220 (m, 1H), 2.11−2.00 (m, 1H), 1.77−1.70 (m, 3H), 1.51−1.25 (m, 4H + 2H impurities), 0.92 (t, J = 7.09 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 166.3 (d, J = 4.8 Hz), 163.3 (d, J = 3.5 Hz), 145.3 (d, J = 246.5 Hz), 144.7 (d, J = 246.9 Hz), 139.6 (d, J = 8.2 Hz), 132.5 (q, J = 34.0 Hz), 132.2 (d, J = 2.2 Hz), 130.0 (d, J = 3.9 Hz), 127.2, 127.0−126.4 (m), 123.0 (q, J = 273.1 Hz), 122.4 (td, J = 14.7, 3.0 Hz), 118.7 (d, J = 2.2 Hz), 115.9 (t, J = 14.7 Hz), 69.4, 51.8 (d, J = 2.6 Hz), 33.4, 32.5, 32.1, 27.8, 22.7, 22.6, 22.3, 13.9. Isolated yield: 1.30 g, 2.08 mmol, 89%.

(26) Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentyl-1,4-dihydro-[1,1′-biphenyl]-2-carboxylate. According to a procedure derived



from Reiser and co-workers,[75] **25** (376 mg, 600 μmol), 10 mg of [Ir(dtbbpy)(dtbppy)$_2$]PF_6, and DIPEA (210 μL, 2 equiv) were dissolved in a mixture of 15 mL of acetonitrile and 1 mL of water. The solution was degassed and irradiated for 3 h at 455 nm while heating to 45 °C in an oil bath. After cooling to room temperature, 20 mL of petroleum ether was added. The solution washed with a concentrated K_2CO_3 solution and water and dried over Na_2SO_4.. The solvent was removed under reduced pressure, and the residue was purified via column chromatography (5% EA in PE) to yield the product, which was contaminated with small amounts of the rearomatized product as a slightly yellow viscous liquid. Recrystallization from MeOH yielded the product as colorless needles, mp 54−55 °C. TLC: R_f = 0.70 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −146.66 to −147.14 (m, 4F). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21−7.16 (m, 1H), 5.40−5.31 (m, 1H), 4.82−4.71 (m, 1H), 3.65 (s, 3H), 3.03−2.91 (m, 1H), 2.80 (dpt, 1H, J = 23.7, 5.4 Hz), 2.65 (t, J = 7.7, 2H), 1.74 (s, 3H), 1.62−1.52 (m, 2H), 1.26−1.28 (m, 4H), 0.89 (t, J = 6.9 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 166.2, 146.3−145.8 (m), 143.9−143.3 (m), 139.0, 131.2, 127.5, 119.1, 119.02−118.40 (m), 51.5, 32.1, 31.9, 31.3, 28.9, 22.6, 22.4, 22.3, 13.8. HRMS (EI) m/z: [M]$^+$ exact mass Calcd for $C_{20}H_{22}F_4O_2$ 370.1556, found: 370.1545. Isolated yield: 193 mg, 521 μmol, 86%.

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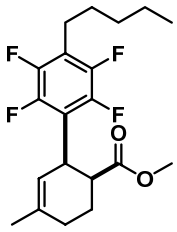
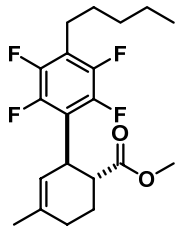


(27)



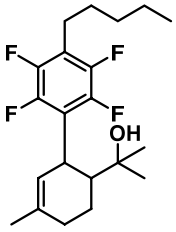
(28)

*(**27** and **28**) Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]- 2-carboxylate.* Diene (**26**) (800 μmol) and PMHS (101 mg, 1.68 mmol, 2.1 equiv) were put into a crimp vial under nitrogen. A solution of tris(pentafluorophenyl)-borane (4 mg, 8 μmol, 1 mol %) in 4 mL of DCM was added. The solution was stirred overnight at room temperature and the stirred for either another 24 h with a saturated NH_4F solution or another 2 h with TBAF·$3H_2O$ in DCM. Shorter quenching times led to the incomplete cleavage of the silyl ethers formed and diminished the yield. The solution was extracted with DCM, column chromatography (5% EA in PE) yielded the product. The products were obtained as mixtures of the *cis*- and *trans*-isomer, which were not separable by means of column chromatography. Column chromatography (5% EA in PE) yielded the product as a viscous colorless liquid. Different reactions gave the product in varying drs of 4−6 in favor of the *cis*-diastereomer. Isolated yield: 26 mg, 70 μmol, 37%.

*(**27**) cis-Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]- 2-carboxylate.* NMR data were derived from subtraction of the pure *trans*-diastereomer. TLC: R_f = 0.70 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −142.16 (dd, *J* = 21.5, 12.2 Hz, 2F), −146.63 (dd, 2F, *J* = 21.9, 12.3 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.40 (d, *J* = 3.1 Hz, 1H), 4.2 (s, 1H), 3.5 (s, 3H), 3.0−2.9 (m, 1H), 2.7 (t, 2H, *J* = 7.6 Hz), 2.25−2.14 (m, 1H), 2.14−1.99 (m, 2H), 1.94−1.83 (m, 1H), 1.73 (s, 3H), 1.62−1.52 (m, 2H), 1.38−1.27 (m, 4H), 0.89 (t, 3H, *J* = 6.7 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 174.0, 146.6−154.8 (m), 144.2−143.5 (m), 136.2, 119.4 (t, *J* = 18.9), 117.0 (t, *J* = 14.8 Hz), 51.4, 43.7, 33.3, 31.3, 28.8, 28.7, 23.5, 22.7, 22.3, 21.4, 13.9. HRMS (EI) *m*/*z*: $[M]^+$ exact mass Cacld for $C_{20}H_{24}F_4O_2$ 372.1707, found 372.1706.

*(**28**) trans-Methyl 2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]- 2-carboxylate.* TLC: R_f = 0.70 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −144.6 (dd, 2F, *J* = 21.8, 12.5 Hz), to −146.3 (dd, 2F, *J* = −22.1, 12.5 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.19 (s, 1H), 4.11 (d, 1H, *J* = 10.0 Hz), 3.58 (s, 3H), 2.94−2.86 (m, 1H), 2.67 (t, 2H, *J* = 7.6 Hz), 2.24−2.11 (m, 2H), 2.10−2.00 (m, 1H), 1.92−1.79 (m, 1H), 1.70 (s, 3H), 1.63−1.52 (m, 2H + 2H impurities), 1.36−1.28 (m, 4H + 2H impurities), 0.89 (t, 3H + 1H impurities, *J* = 6.87 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 175.0, 146.3−145.8 (m), 143.8−143.4 (m), 134.6, 120.7, 51.7, 119.4 (t, *J* = 15.7 Hz), 119.0 (t, *J* = 19.0 Hz), 44.2, 34.9, 31.3, 29.3, 28.9, 26.7, 23.2, 22.7, 22.3, 13.9. HRMS (EI) *m*/*z*: $[M]^+$ exact mass Calcd for $C_{20}H_{24}F_4O_2$ 372.1707, found 372.1700.

*(**29**) 2-(2′,3′,5′,6′-Tetrafluoro-5-methyl-4′-pentyl-1,2,3,4-tetrahydro-[1,1′-biphenyl]-2-yl)propan-2-ol.* A 3 M solution of MeMgBr in

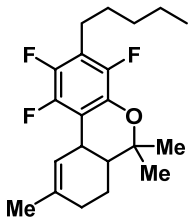


Et_2O (7 equiv) was added to a 2 M solution of ester (20 mg, 54 μmol) in dry THF while cooling in an ice bath. The solution was warmed to rt and stirred for 30 min. The reaction was quenched with a saturated NH4Cl solution and extracted with ethyl acetate. Column chromatography (20% EA in PE) yielded the tertiary alcohol. The product was obtained as a viscous colorless liquid (19 mg, 51 μmol, 95%). The *cis*- and *trans*-isomers were separable by column chromatography.

*cis-(**29**).* TLC: R_f = 0.35 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): δ −135.83 to −136.11 (m, 1F), 142.71 (dd, 1F, *J* = 22.4, 11.6 Hz), 146.10 (dd, 1 F, *J* = 22.4, 12.2 Hz), −146.40 (dd, 1F, *J* = 21.8, 11.7 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30−5.24 (m, 1H), 4.08−4.00 (m, 1H), 2.68 (t, 2H, *J* = 7.6 Hz), 2.19−2.13 (m, 1H), 2.06−1.97 (m, 1H), 1.94−1.76 (m, 2H), 1.70 (s, 3H), 1.63−1.52 (m, 2H), 1.37−1.29 (4H), 1.07 (s, 3H), 1.00 (s, 3H), 0.89 (t, 3H, *J* = 6.9 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 135.7, 120.5, 119.3−118.7 (m), 72.7, 49.5, 32.0, 31.3, 30.8, 28.9, 28.3, 27.2, 23.4, 22.7, 22.3, 20.4, 20.3, 13.9. HRMS (EI) *m*/*z*: $[M - H_2O]^+$ exact mass Calcd for $C_{21}H_{26}F_4^+$ 354.1965, found 354.1962.

*trans-(**29**).* TLC: R_f = 0.40 (hexanes/ethyl acetate 9:1). ^{19}F NMR ($CDCl_3$, 376 MHz): −144.51 to −144.94 (broad s, 2F), −146.84 (dd, 2F, *J* = 22.02, 12.18 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.05 (s, 1H), 3.82 (d, 1H, *J* = 9.3 Hz), 2.65 (t, 2H, *J* = 7.7 Hz), 2.25−2.10 (m, 2 H), 2.03−1.92 (m, 2H), 1.68 (s, 3H), 1.63−1.52 (m, 2H + 1H impurities), 1.49−1.38 (m, 1H), 1.36−1.28 (m, 4 H), 1.20 (s, 3H), 1.12 (s, 3H), 0.93 (s, 1H), 0.89 (t, 3H, *J* = 7.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 146.3−145.5 (m), 143.9−143.1 (m), 135.2, 123.4 (t, *J* = 15.20 Hz), 117.8 (t, *J* = 18.9 Hz), 122.1, 73.7, 48.0, 34.1, 31.4, 30.2, 29.0, 28.9, 23.2, 22.6, 22.3.

*(**30**) 1,2,4-Trifluoro-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromene (1-Deoxy-1,2,4-trifluoro-THC).* The pro-



cedure was derived from that of Carreira and co-workers.[71] Tertiary alcohol **29** (14 mg, *cis*/*trans* 4:1) was dissolved in dry THF. A 1 M solution of KHMDS in THF (1.5 equiv) was added. The solution was heated to 40 °C in an oil bath for 15 min. The reaction is quenched with a saturated NH_4Cl solution and extracted with ethyl acetate. Column chromatography (2% EA in PE) yielded the target compound as a viscous colorless liquid. Isolated yield: 13 mg, 37 μmol, *cis*/*trans* 4:1, 98%.

*cis-(**30**).* ^{19}F NMR ($CDCl_3$, 376 MHz): δ −142.75 to −142.90 (m, 1F), −145.54 (d, 1F, *J* = 12 Hz), −153.50 (d, 1F, *J* = 22.41 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.39−6.31 (m, 1H), 4.03−3.96 (m, 1H), 2.97 (t, *J* = 7.5 Hz, 2H), the alkyl region could not be analyzed due to overlaps from both diastereomers. Colorless viscous liquid. HRMS (EI)*m*/*z*: $[M]^+$ exact mass Calcd for $C_{21}H_{27}F_3O^+$ 352.2009, found 352.1999.

*trans-(**30**).* ^{19}F NMR ($CDCl_3$, 376 MHz): δ −145.04 to −145.17 (m, 1F), −145.40 (d, 1F, *J* = 14 Hz), −154.26 (d, 1F, *J* = 22.8 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.41 (s, 1H), 3.69 (d, *J* = 11.4 Hz, 1H), alkyl region could not be analyzed due to overlaps from both diastereomers. HRMS (EI) *m*/*z*: $[M]^+$ exact mass Calcd for $C_{21}H_{27}F_3O^+$ 352.2009, found 352.2004.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00169.

Experimental details, additional experiments, spectra, and X-ray diffraction analysis(PDF)

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Accession Codes

CCDC 2060753 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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[∇]Authors contributed equally to this publication.

Notes

The authors declare no competing financial interest.

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