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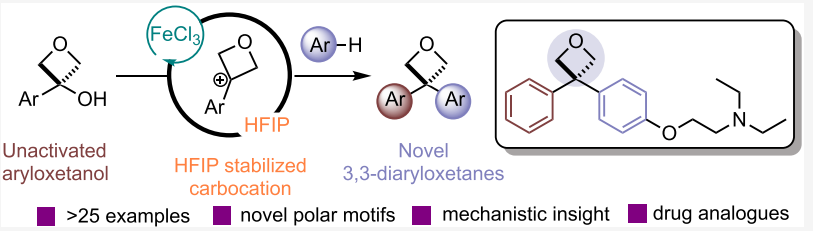
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Iron-Catalyzed Friedel–Crafts Reactions of Unactivated 3-Aryl-Oxetanols Exploiting HFIP Stabilization of Carbocations

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ABSTRACT: Robust methods to access 3,3-disubstituted oxetanes are desired due to the attractive physicochemical properties offered by the polar 4-membered rings and their potential use as replacement groups for carbonyl or *gem*-dimethyl functionality in medicinal chemistry. The generation of benzylic oxetane carbocations from oxetanols offers considerable potential, particularly in the generation of diaryloxetanes, a structural type that is seldom reported. To date, however, Friedel–Crafts reactions have been limited to oxetanols bearing an electron-rich aromatic group due to the carbocation destabilizing nature of the oxetane. Here, an alternative Fe-catalyzed Friedel–Crafts reaction is described, employing HFIP as a solvent, enabling oxetanyl carbocation formation directly from oxetanols bearing phenyl and other electron-poor arenes. HFIP with its strong hydrogen bond donor (HBD) ability and enhanced Brønsted acidity cooperatively promotes the generation of the carbocations in the presence of the Lewis acid. The oxetane-HFIP adduct was detected, likely formed reversibly as a stabilizing off-cycle intermediate. The developed methodology enabled the concise synthesis of oxetane analogues of Fenofibrate and Tesmilifene, replacing diarylmethane and benzophenone motifs, respectively. Additional mechanistic studies into the fate of these carbocation intermediates provide insights into the reaction mechanism.

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INTRODUCTION

Oxetanes have emerged as valuable design elements for medicinal chemistry due to their small, polar nature and their ability to influence the physiochemical properties of drug compounds.[1] These features have led to several oxetane-containing compounds entering clinical trials,[2] and the first fully synthetic oxetane-containing drug received FDA approval very recently.[3] Particularly relevant are 3,3-disubstituted oxetanes, which can mimic carbonyl functionality and which avoid the introduction of additional stereocenters (Figure 1 for 3,3-disubstituted oxetane clinical candidates). This interest in incorporating the oxetane motif has led to the development of several valuable methods for the preparation of oxetane derivatives.[4−6]

Diaryloxetanes have been surprisingly understudied, yet present interesting structural comparisons to diarylmethanes and benzophenones. There are to date only two synthetic approaches to these substructures. Baran recently reported a multistep sequence involving a Ni-electrocatalytic cross-coupling to form 3 examples of heteroaryl substituted variants (Figure 2A).[7] In 2016, we demonstrated the first synthesis of 3,3-diaryloxetanes through a Friedel–Crafts approach with selective oxetanol activation, as the first example of benzylic oxetanyl-carbocations.[5a] This method used catalytic lithium triflimide, but necessitated electron-rich aromatic derivatives to provide resonance stabilization, as well as phenol nucleophiles.[5a] Reactions with phenols were observed to proceed through the *O*-linked phenol ether, an off-cycle intermediate that provided a stabilizing carbocation reservoir, and which would convert to the Friedel–Crafts product by regeneration of the carbocation.[8]

Subsequent advances in oxetane carbocation derivatives have exploited alternative leaving groups (Figure 2B).[4b,c] Zhang's trichloroacetimidate approach is notable in that less electron-rich aromatic groups were used to stabilize the carbocation intermediate, being successful for phenyl groups, for example.[4b] While requiring an additional activation step,

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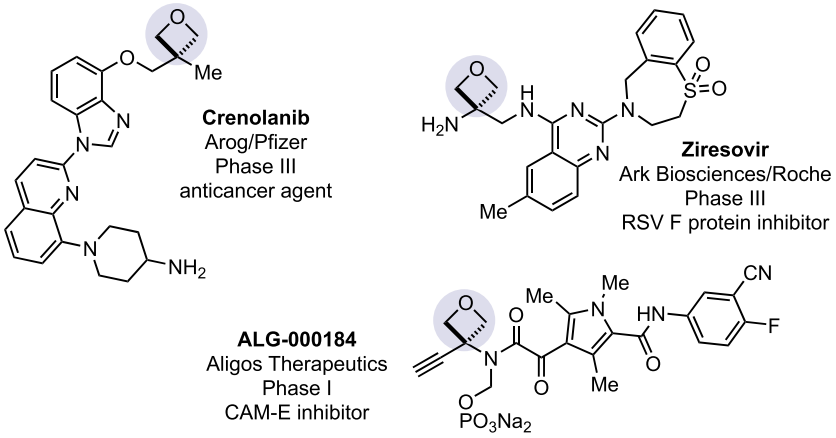


Figure 1. Clinical candidate compounds that contain 3,3-disubstituted oxetanes.

the use of the trichloroacetimidate allowed selective activation by preferential coordination of a copper Lewis acid to this leaving group over the oxetane or nucleophile. Friedel–Crafts reactivity was not observed, however, and phenols gave ether products, which were presumably not prone to further activation under the conditions. Direct activation of oxetanols bearing less electron-rich arenes remains unrealized and would provide a valuable addition to the preparation of these compound classes.

HFIP exhibits unique solvent properties due to its ability to aggregate as dimers or trimers, which simultaneously enhance both its hydrogen bond donor (HBD) ability and increase its Brønsted acidity (pK_a = 9.3).[9] These strong HBD properties and dielectric constant (ε = 15.7) have been shown to accelerate a variety of chemical reactions.[9,10] In 2012, Nájera reported the first instance of alcohol activation using TFE and HFIP, in a metal-free substitution of allylic alcohols with amines and carbamates.[11] Subsequently, Hall and Moran independently developed Friedel–Crafts conditions for the preparation of diarylmethanes from highly electronically deactivated benzylic alcohols, catalyzed by boronic acid and TfOH respectively and enabled by HFIP (Figure 2C).[12] Leboeuf reported the use of calcium triflimide as a catalyst in HFIP for hydroarylation of styrenes.[13] The utility of HFIP has since been further demonstrated in the Friedel–Crafts arylation of other challenging substrates, highlighting the potential of polyfluorinated solvents to enable novel reactivities.[14]

Encouraged by the potential of HFIP to stabilize carbocation intermediates, we hypothesized that it could be employed to facilitate Friedel–Crafts reactions with less electron-rich 3-aryl-3-oxetanols and to extend the range of successful arene nucleophiles. Consequently, we would expand the accessible chemical space of diaryloxetanes. However, oxetanes have been shown to polymerize or ring-open under acidic conditions.[13] The success of this strategy would be reliant on the stability of the oxetane, especially given the strong hydrogen bonding of HFIP with ethers and the increased acidity of the solvent O–H group in the presence of a Lewis acid.[15]

Here we report the development of an iron chloride-catalyzed Friedel–Crafts reaction of aryloxetanols. The use of HFIP as solvent was crucial to enable the productive reaction with nonelectron-rich arene substituents and nonphenolic arene nucleophiles, while minimizing unproductive oxetane ring-opening processes (Figure 2D). We demonstrate the utility of this new methodology by synthesizing oxetane-containing drug analogues of tesmilifene and fenofibrate. Moreover, we examined side products and intermediates to explain the overall reactivity profile of the oxetane derivatives under the reaction conditions.

RESULTS AND DISCUSSION

Initially we investigated the Friedel–Crafts reaction of unactivated 3-phenyloxetan-3-ol (**1**) with 2,6-dimethylphenol, chosen to prevent dihydrobenzofuran formation.[16] Early attempts using HFIP solvent did indeed give the desired product in low yields, and led to very low overall recovery of oxetane. Considerable optimization of conditions was necessary to prevent degradation of the oxetane ring. Various Brønsted and Lewis acids were tested to modulate acidity and improve mass recovery employing 4 equiv of nucleophile. Brønsted acids such as TFA, TfOH, and Tf_2NH were investigated at 80 °C (Table 1, entries 1–3), but none promoted the reaction efficiently, leading to recovered starting material or degradation. A combination of $Ca(NTf_2)_2$/nBu$_4$NPF$_6$ in HFIP gave 17% yield (Table 1, entry 4).[5a,13,17] The use of lithium triflimide increased the yield of oxetane **2** to 38%, albeit with similar loss of material (entry 5). The combination of LiCl and HFIP, reported by Zhu in the Friedel–Crafts alkylation of phenol with ethyl glyoxylate, was unreactive,[14] and $F_5C_6B(OH)_2$[18] gave recovered starting material (See SI, Table S1 for further details of catalyst screening).

The use of $FeCl_3$ markedly improved the transformation, affording oxetane **2** in 53% yield with 25% of starting material recovered (Table 1, entry 6), and was selected as the optimal catalyst owing to its efficiency, low cost, and earth abundance. Additional iron catalysts (Table 1, entries 6–9) including $Fe(acac)_3$ and $FeCl_2$ were unreactive, while $Fe(OTf)_2$ gave only low conversion. Catalyst loading, concentration, and temperature strongly influenced the reaction outcome. Lowering the concentration (0.1 M) increased the yield to 73% (Table 1, entry 10). Reducing the temperature or increasing catalyst loading suppressed reactivity (See SI for details). The equivalents of nucleophile were crucial, where unlike typical Friedel–Crafts processes, excess phenol was detrimental to the reaction outcome. Reducing nucleophile equivalents to 1.7 provided the optimal conditions, yielding diaryloxetane **2** in 94% yield (Table 1, entry 11). The reaction was not sensitive to air and moisture, and HFIP was essential as a solvent,

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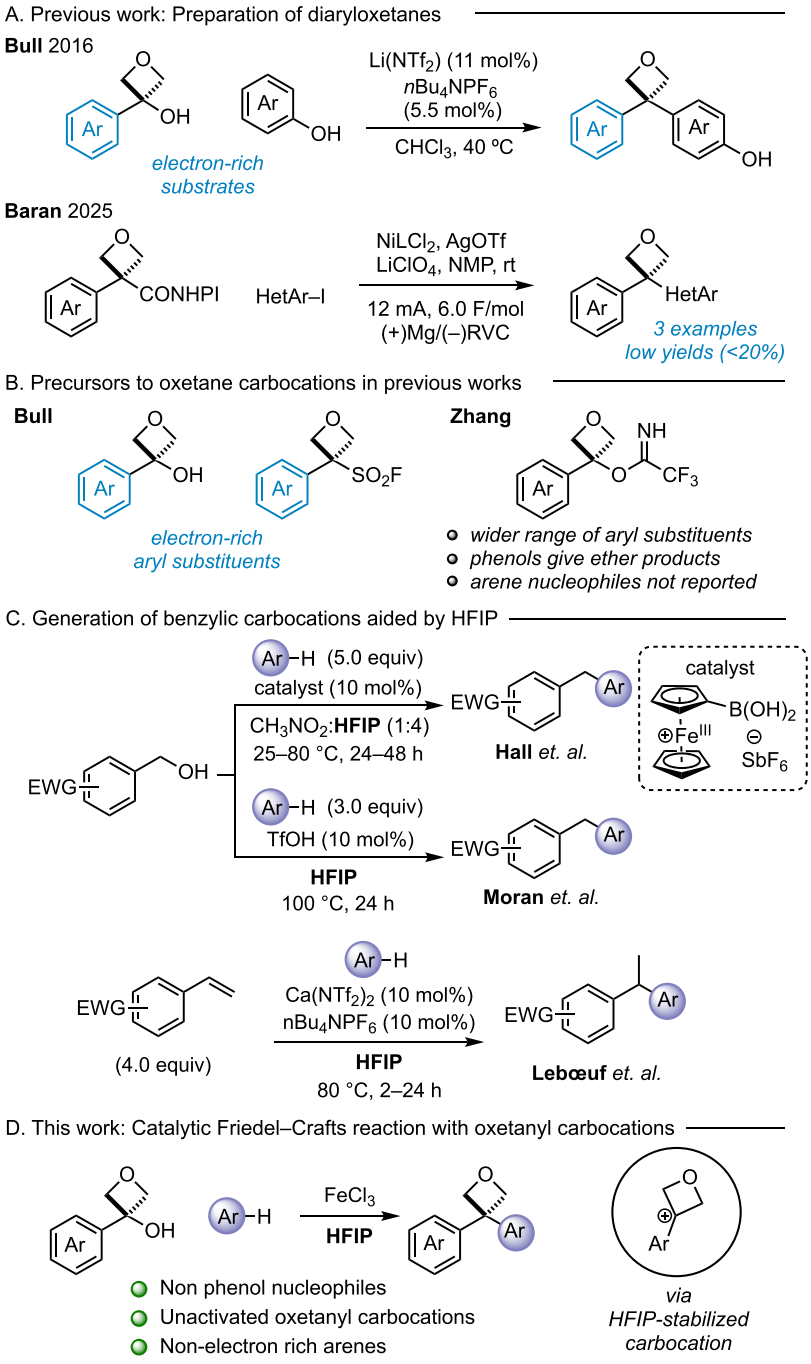


Figure 2. (A) Previous approaches to diaryloxetanes. (B) Previous oxetane carbocation precursors and limitations. (C) Previous Friedel–Crafts reactions and hydroarylation with deactivated benzylic alcohols and styrenes, enabled by HFIP. (D) This work: the HFIP promoted Friedel–Crafts alkylation of nonelectron-rich 3-aryloxetan-3-ols and nonphenolic arene nucleophiles.

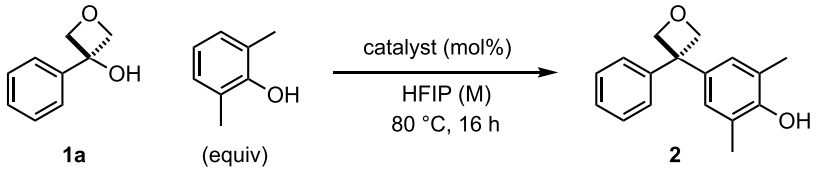
outperforming trifluoroethanol (TFE) and mixed solvent systems using HFIP in various proportions (See SI for further details).[19]

Extending the nucleophile classes revealed differing reactivity when using *p*-xylene and anisole as nucleophiles (Table 2). Both nucleophiles were successful in the Friedel–Crafts addition to oxetanol **1a**, affording diaryloxetanes **3** and **4**, but aldehyde side products **3b** and **4b** were also isolated. Increasing equivalents of *p*-xylene nucleophile up to 5 improved the yield of oxetane **3** to 55% (Table 2, entries 1–2). However, using *p*-xylene in large excess (as cosolvent, ~ 32 equiv) adversely affected the reaction, reducing the yield to 40%, presumably due to reducing the HFIP stabilization. Aldehyde formation increased markedly when a larger quantity of anisole was employed as nucleophile (Table 2, entries 3,4) and a lower excess was preferable.

With two sets of conditions in hand, for the more and less reactive nucleophiles, the scope of the reaction was evaluated by varying both the nucleophile and oxetanol components (Scheme 1). Using phenyl oxetanol **1a**, *p*-xylene gave diaryloxetane **3** in 58% yield, while mesitylene and durene afforded oxetanes **5** and **6** in 73 and 71% yield, respectively. *p*-Cymene gave diaryloxetane **7** in 42% yield, with the reaction occurring regioselectively at the position adjacent to the

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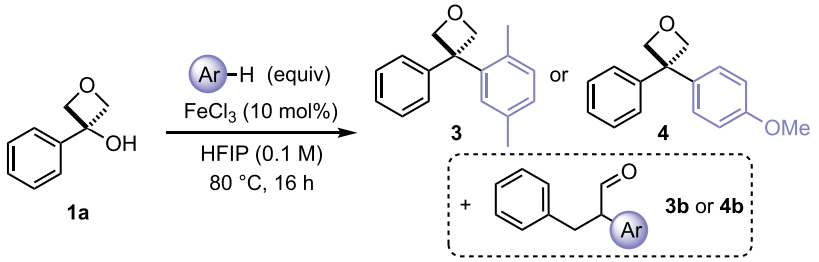
Table 1. Initial Catalyst Screen, Effect of the Catalyst Loading, Concentration, Temperature, and Nucleophile Equivalents on the Friedel–Crafts Alkylation of 2,6-Dimethylphenol with 1a



entry	catalyst	cat. loading (mol %)	nuc. equiv	conc (M)	RSM 1a (%)[a]	yield of 2 (%)[a]
1	Tf_2NH	10	4	0.2	0	1
2	TFA	10	4	0.2	91	5
3	TfOH	10	4	0.2	0	21
4	$Ca(NTf_2)_2/nBu_4NPF_6$	10	4	0.2	0	17
5[b]	$Li(NTf_2)_2/nBu_4NPF_6$	11	4	0.2	0	38
6	$FeCl_3$	10	4	0.2	25	53
7	$Fe(acac)_3$	10	4	0.2	100	0
8	$FeCl_2$	10	4	0.2	98	0
9	$Fe(OTf)_2$	10	4	0.2	0	20
10	$FeCl_3$	10	4	0.1	0	73
11[c]	$FeCl_3$	10	1.7	0.1	0	94
12	no cat.	0	4	0.2	100	0

[a]Yields were calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [b]$Li(NTf_2)$ (11 mol %) and nBu_4NPF_6 (5.5 mol %) were used. [c]If the reaction is performed at 60 °C, 52% yield is obtained.

Table 2. Effect of Nucleophile Equivalents Using Anisole and *p*-Xylene



entry	nucleophile	equivalents	yield (%)[a] 3 or 4	yield (%)[a] aldehydes 3b or 4b
1	*p*-xylene	1.7	44	13
2	*p*-xylene	5.0	55	9
3	anisole	1.7	35	11
4	anisole	3.0	38	33

[a]Yields calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard.

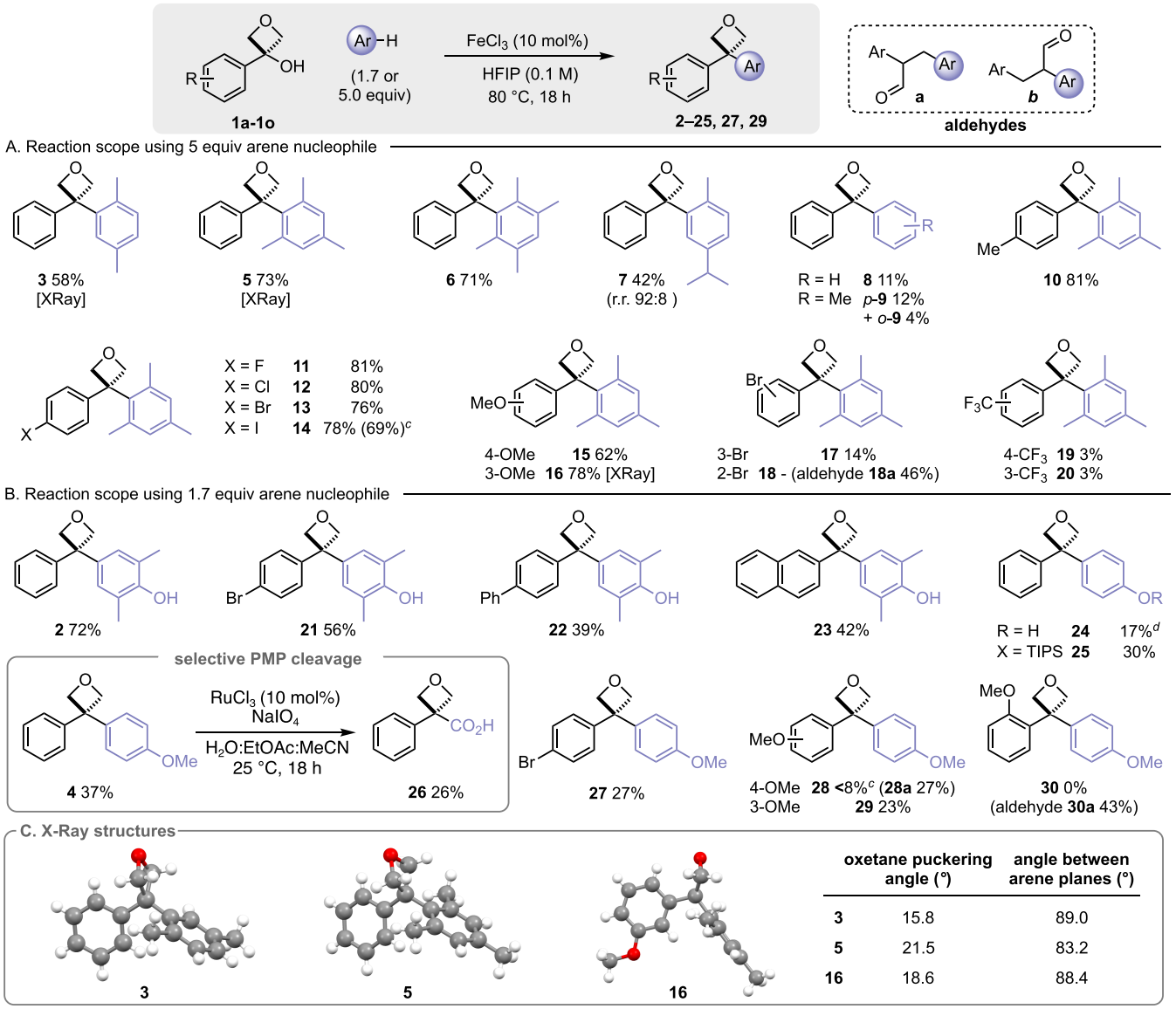
methyl group to minimize steric hindrance (rr 92:8). Benzene and toluene gave 3,3-diaryloxetanes **8** and **9** in low yields. Attempts to incorporate *N*-methylindole or furan were unsuccessful. Notably, two different classes of aldehyde side products were observed in low quantities (see the SI for further discussion).[20]

On varying the oxetanol, the tolyl substituent gave comparable yields with mesitylene (81% **10**). Halide substituents all reacted successfully, providing halogenated diaryloxetanes **11**–**14** in 76–81% yields. These halide-containing oxetane products offer valuable synthetic handles and such products were not accessible using previous methodologies. The reaction scaled efficiently to 4.0 mmol, producing 1 g of iodophenyl oxetane **14** (69% yield). Substrates with a methoxy group at the *meta*- and *para*-positions were both successfully reacted with mesitylene (**15**, **16**). By comparison, while 4-methoxyphenyloxetanol was successful in our previous reports with phenol nucleophiles, it was unreactive with mesitylene, and 3-methoxyphenyl was previously unreactive to Friedel–Crafts reactions in general, highlighting the increased reactivity of the HFIP system. The 3-bromophenyl substrate formed diaryloxetane **17** in low yield (17%). However, the 2-bromo derivative did not form the desired product, forming aldehyde products in 46% yield. Notably, the *o*-tolyl oxetanol led to the formation of aldehyde product exclusively, with no formation of the target oxetane (see Supporting Information). Deactivating trifluoromethylphenyl derivatives were essentially unreactive (**19**, **20**), and the oxetanol substrate was recovered.[21,22]

Reacting oxetanol **1a** with 2,6-dimethylphenol (1.7 equiv) on a 0.5 mmol scale afforded the corresponding 3,3-diaryloxetane **2** in 72% isolated yield (Scheme 1B). *p*-Bromophenyl afforded oxetane **21** in 56% yield. Biphenyl and naphthyl substituents were also tolerated, giving oxetanes **22** and **23** in 39 and 42% yields. By contrast, phenol itself gave a complex mixture with only 17% of oxetane **24** (^{1}H NMR yield), alongside dihydrobenzofuran and unidentified side products, with no recovered starting material. TIPS-protected phenol (using 5 equiv of nucleophile) gave **25** in 30% isolated yield. Using anisole as the nucleophile yielded oxetane **4** in

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Scheme 1. Catalytic Synthesis of Diaryloxetanes: Substrate Scope Varying Nucleophile and Oxetanol[a]



A. Using 5 equiv of nonoxygenated nucleophile. B. Using 1.7 equiv of oxygenated nucleophiles. C. Single crystal X-ray structures and analysis. [b]The reaction was performed on a 4.0 mmol scale. [c]A ketone side product was also observed. See the SI for further details. [d]Yields were calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [a]Reactions were performed on a 0.50 mmol scale unless stated otherwise. Isolated yields were reported unless stated.

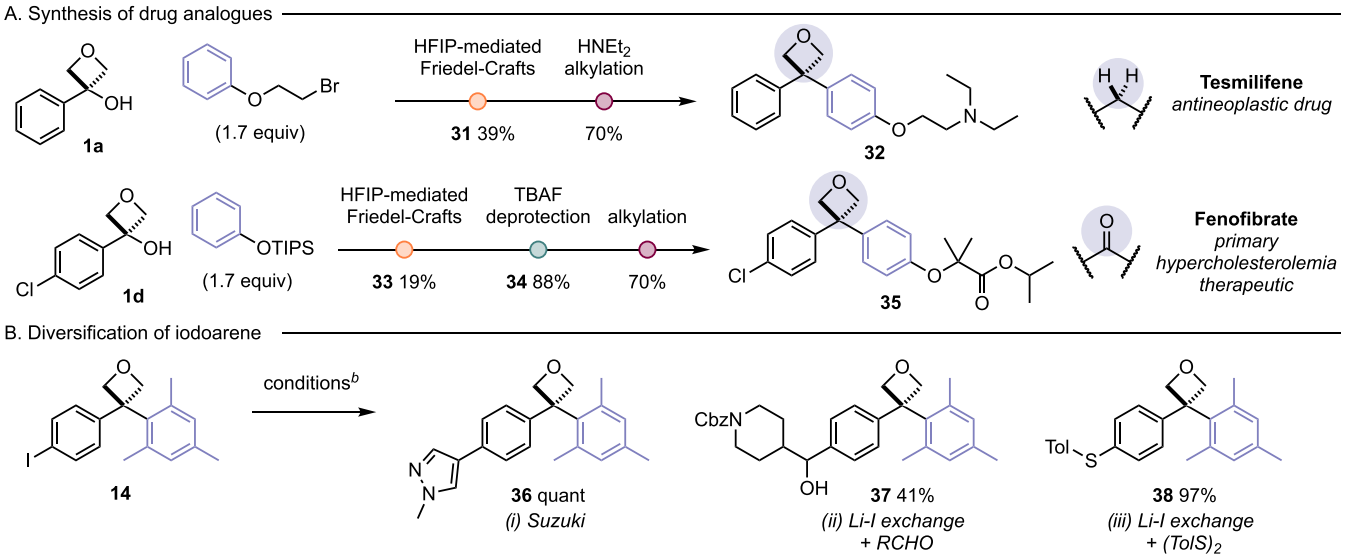
37% yield, isolated exclusively as the *para*-substituted isomer. The 4-methoxyphenyl group could be selectively cleaved to yield the corresponding oxetane carboxylic acid **26**.[23] With anisole nucleophile, 4-bromophenyl oxetanol gave **27** in 27% yield with full conversion of starting material. 4- and 3-methoxyphenyloxetanols gave low product yields and significant aldehyde formation **28a** (27%) and **30a** (43%; see SI for further discussion). *o*-Methoxyphenyloxetanol also led to the exclusive formation of aldehyde products.

Several of the diaryloxetanes were further characterized by single crystal X-ray diffraction (SCXRD, Scheme 1C). Analysis of **3**, **5**, and **16** revealed that each compound adopts a near-perpendicular orientation of the arene planes (83.2−89.0°) and pronounced oxetane ring puckering (15.8−21.5°). This dihedral twist feature is reminiscent of conformations typically observed in sterically hindered biaryl systems.

To demonstrate the utility of the method to provide rapid routes to potentially valuable oxetane compounds, two oxetane analogues of drug compounds were targeted (Scheme 2A). Tesmilifene is an antineoplastic agent bearing a diarylmethane.[24] Such diarylmethanes can be metabolically vulnerable, and oxetanes may provide a valuable role in blocking sites of oxidative metabolism.[1] The HFIP-mediated Friedel−Crafts conditions were applied to the reaction of oxetanol **1a** with commercial *β*−bromophenetole (2-bromoethyl phenyl ether). This nucleophile was compatible with the reaction conditions in the presence of the primary bromide, giving 3,3-diaryloxetane **31** in 39% yield.[25] Nucleophilic substitution of bromide **31** with $HNEt_2$ provided oxetano-tesmilifene **32**. Fenofibrate is used for the treatment of hypercholesterolemia, and contains a benzophenone structure that may be mimicked by the oxetane as an isostere.[26] Attempts to react oxetanol **1d**

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Scheme 2. (A) Synthesis of Oxetane-Containing Fenofibrate and Tesmilifene Analogues. (B) Diversification of Iodoarene 14[a]



[a]Isolated Yields. [b]Reaction conditions: (i) 1-methylpyrazole-4-boronic acid pinacol ester, $Pd(dppf)Cl_2$, K_2CO_3, dioxane/H_2O (2:1), 100 °C, 16 h, quant.; (ii) *n*-BuLi, benzyl 4-formylpiperidine-1-carboxylate, THF, − 78 °C, 1 h, 41%; (ii) *n*-BuLi, *p*-tolyl disulfide, THF, − 78 °C, 1 h, 97%.

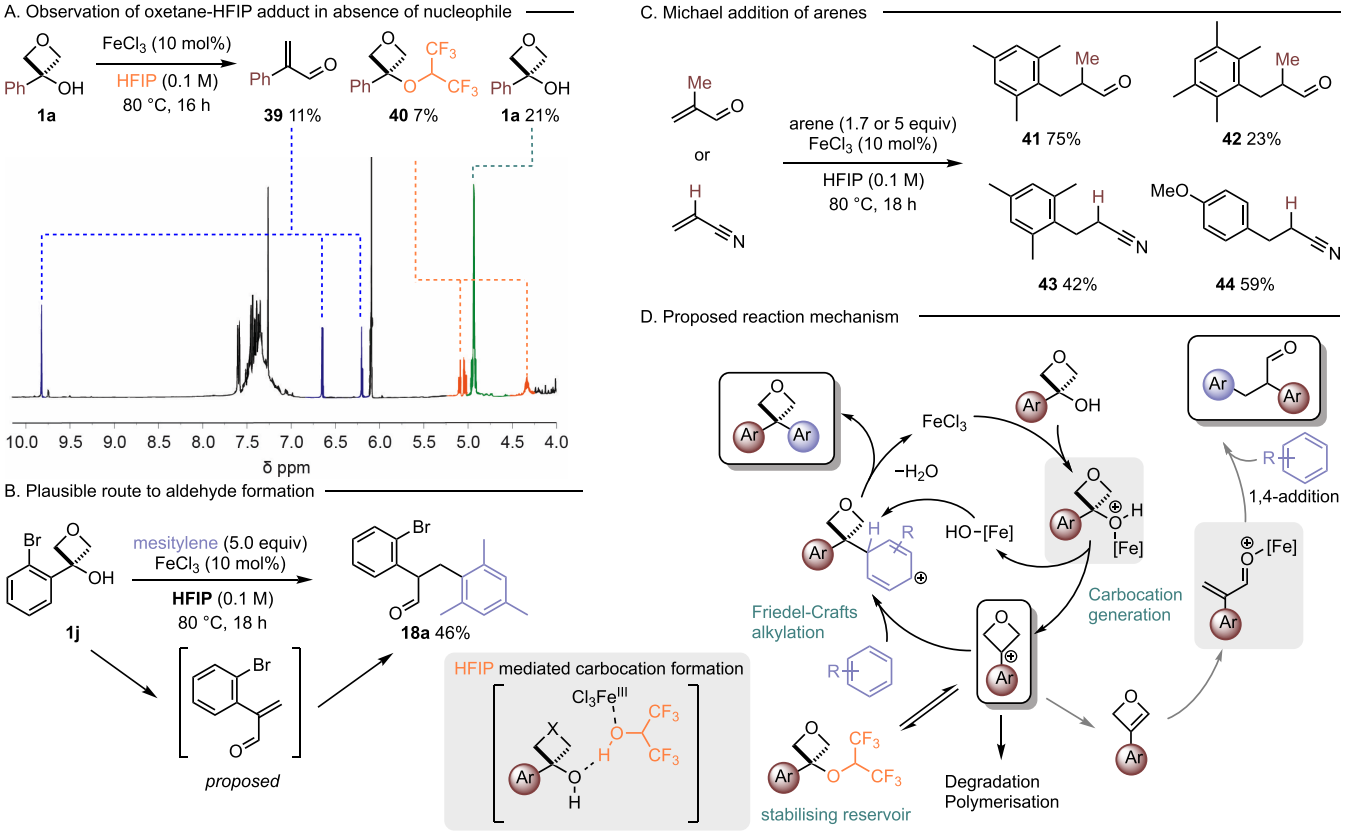


Figure 3. (A). Product distribution for the reaction of oxetanol **1a** in the absence of nucleophile was determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. (B) Proposed route to degradation to form a major aldehyde product. (C) Alternative Michael-acceptor reactions using the optimized HFIP Friedel−Crafts conditions. (D) Catalytic cycle for the HFIP-mediated Friedel−Crafts reaction of aromatics with oxetanols and formation of aldehyde side products.

with phenol itself were unsuccessful, but the TIPS ether of phenol successfully gave oxetane **33**, which was readily deprotected with TBAF to give phenol **34**. Nucleophilic substitution with isopropyl 2-bromo-2-methylpropanoate gave oxetano-fenofibrate **35**.

In addition, a range of diversification reactions was readily applied with iodoarene **14** (Scheme 2B). A palladium-catalyzed Suzuki-Miyaura cross-coupling reaction proceeded to give pyrazole **36** in quantitative yield. The organolithium reagents derived from iodoarene **14** and *n*-BuLi readily reacted

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with a piperidine carboxaldehyde and a disulfide to give the corresponding alcohol **37** and thioether **38** products in 41 and 97% yield, respectively.

Next, studies were undertaken to better understand the reaction mechanism. Oxetanol **1a** was subjected to the optimized reaction conditions in the absence of nucleophile and was examined using ^{1}H NMR spectroscopy. After 16 h, 21% of oxetanol **1a** was recovered along with 18% of the other two products, which could not be isolated due to their instability. One of these products was identified as ether **40**, presenting two doublets for oxetane peaks (in orange, Figure 3A) at δ_H = 5.10 ppm integrating for four protons and one heptet at δ_H = 4.3 ppm corresponding to a CH adjacent to the CF_3 groups. Ether **40** results from the addition of HFIP to the oxetanyl carbocation intermediate. We postulate that this type of intermediate may provide a general reason for the observed HFIP carbocation-stabilizing effect, providing a stabilizing carbocation reservoir that can rerelease the carbocation under the reaction conditions. i.e., suggesting the HFIP performs a similar stabilizing role to that seen with phenols in our previous work.[8]

The second product had one aldehyde peak δ_H = 9.8 ppm and two alkene signals at δ_H = 6.7 and 6.3 ppm (in blue, Figure 3A), each integrating for one proton, which is consistent with the known compound atropaldehyde (**39**, 2-phenylacrylaldehyde).[27] The formation of this product was proposed to occur through deprotonation of the carbocation intermediate, forming an unstable oxetene species which rearranges into α,β−unsaturated aldehyde **39** (Figure 3A). We proposed that the Friedel−Crafts alkylation of the arene nucleophiles with the α,β−unsaturated aldehyde was likely to be the source of the observed aldehyde **a** side products observed in most cases through the successful reaction scope (See SI for isolation and characterization of the aldehyde products). These aldehyde products were particularly prevalent in the presence of *ortho*-substituted aryloxetanols, suggesting that the steric bulk of the *ortho*-substituents destabilize the carbocations or promote the rearrangement.[4c] For example, *ortho*-bromophenyl oxetanol **1j** cleanly gave aldehyde **18a** in 46% isolated yield (Figure 3B).[20]

Atropaldehyde **39** proved unstable and could not be isolated; however, application of the reaction conditions to commercially available methacrolein afforded aldehyde **41** in 75% yield, consistent with aldehyde formation via 1,4-addition of aromatics (Figure 3C). Such Friedel−Crafts alkylation of arenes have previously been promoted by Lewis[28] and Brønsted acid[29] catalysts including $Fe(OTf)_3$,[30] often with electron-rich arene nucleophiles.[31] Other strategies,[32,33] including synergistic $FeCl_3$/TfOH catalysis in HFIP for nonbenzylic tertiary alcohols,[12c] remain largely restricted to heteroarenes or electron-rich aromatics.

The application of $FeCl_3$ with HFIP conditions enabled direct Friedel−Crafts alkylation of nonactivated aromatics with α,β-unsaturated aldehydes to yield 3-arylpropanal derivatives (**41**, **42**, Figure 3C). Acrylonitrile also functioned as a Michael acceptor under these conditions, reacting with mesitylene and anisole to give products **43** (42%) and **44** (59%).

A proposed mechanism for the iron-catalyzed Friedel−Crafts reaction of unactivated 3-aryl-oxetanols is outlined in Figure 3D. A $[FeCl_3{\cdot}(HFIP)_n]^+$ complex, akin to that proposed by Moran and Lebœuf,[13] may activate either the oxetanol or α,β-unsaturated aldehyde. Coordination of $FeCl_3$ or activated HFIP (boxed structure) to the oxetanol hydroxyl group promotes ionization to an oxetanyl carbocation, which alkylates the arene to give the 3,3-diaryloxetane. Reaction of the carbocation with HFIP directly generates an oxetane ether that can reversibly regenerate the carbocation, effectively serving as a cation reservoir, which aids stability and productive lifetime of the carbocation. Alternatively, α-deprotonation can occur if a Lewis base is present in the reaction, including competitively with Lewis basic nucleophiles (i.e., anisole, phenol), to form an unsaturated oxetene species, rationalizing the reduced yields observed with these substrates and the detrimental effect of higher nucleophile loadings in these cases. Owing to their ring strain, unsaturated oxetenes can readily rearrange to acrolein derivatives. Subsequent Fe-catalyzed activation of the aldehyde enables 1,4-addition of the arene, followed by rearomatization and tautomerization, as one route to yield ring-opened aldehyde products.

CONCLUSION

We have developed an $FeCl_3$-catalyzed Friedel−Crafts alkylation in HFIP that enables the efficient synthesis of 3,3-diaryloxetanes bearing electron-neutral and electron-poor arenes, overcoming previous limitations. The combination of Fe catalysis and HFIP cooperatively stabilizes the oxetanyl carbocation intermediate, allowing activation of oxetanols substituted with arenes bearing electron-donating, neutral, and electron-withdrawing substituents in both *para* and *meta* positions. A much wider range of arene nucleophiles was tolerated than previously reported for oxetane functionalization, including nonoxygenated arenes and masked phenols. The developed methodology enables concise synthetic access to two novel oxetane-containing drug analogues inaccessible by previous approaches, establishing the potential for $FeCl_3$/HFIP catalysis for challenging oxetane functionalization reactions.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article, in its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.6c00762.

Structures of aldehyde products, additional reaction optimization, mechanistic proposals for side product formation, detailed experimental procedures, characterization data, X-ray crystallography data, copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

Deposition Numbers 2542557−2542559 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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■ REFERENCES

(1) (a) Rojas, J. J.; Bull, J. A. Oxetane in Drug Discovery Campaigns. *J. Med. Chem.* **2023**, *66*, 12697−12709. (b) Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetane: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116*, 12150−12233. (c) Wuitschik, G.; Carreira, E. M.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetane in Drug Discovery: Structural and Synthetic Insights. *J. Med. Chem.* **2010**, *53*, 3227−3246. (d) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257−8322.

(2) (a) Symes, O. L.; Ishikura, H.; Bull, J. A. Oxetanes and Thietanes. In *Burger's Medicinal Chemistry and Drug Discovery*; Wiley, 2025; pp 1−43. (b) Ishikura, H.; Bull, J. A. Synthetic Oxetanes in Drug Discovery: Where are we in 2025? *Expert Opinion on Drug Discovery* **2025**, *20*, 1621−1638.

(3) U.S. Food and Drug Administration. *FDA Approves Drug to Treat Adults with Persistent or Chronic Immune Thrombocytopenia. FDA.gov.*, https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-adults-persistent-or-chronic-immune-thrombocytopenia (accessed Sept 10, 2025).

(4) For recent examples: (a) Spránitz, P.; Sőregi, P.; Hegedüs, K.; Igriczi, B.; Szakács, G.; Jemnitz, K.; Szabó, P.; Galushchak, Y.; Mykhailiuk, P. K.; Soós, T. Strain-Release-Driven Modular Synthesis of Oxetane-Based Amide Bioisosteres: Concise, Robust and Scalable Approach. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202410554. (b) Tian, D.; Chen, D.; Wang, X.; Zhang, H.-J. Modular Access to Functionalized Oxetanes as Benzoyl Bioisosteres. *J. Am. Chem. Soc.* **2024**, *146*, 18011−18018. (c) Rojas, J. J.; Croft, R. A.; Sterling, A. J.; Briggs, E. L.; Antermite, D.; Schmitt, D. C.; Blagojevic, L.; Haycock, P.; White, A. J. P.; Duarte, F.; Choi, C.; Mousseau, J. J.; Bull, J. A. Amino-Oxetanes as Amide Isosteres by an Alternative Defluorosulfonylative Coupling of Sulfonyl Fluorides. *Nat. Chem.* **2022**, *14*, 160−169. (d) Symes, O. L.; Ishikura, H.; Begg, C. S.; Rojas, J. J.; Speller, H. A.; Cherk, A. M.; Fang, M.; Leung, D.; Croft, R. A.; Higham, J. I.; Huang, K.; Barnard, A.; Haycock, P.; White, A. J. P.; Choi, C.; Bull, J. A. Harnessing Oxetane and Azetidine Sulfonyl Fluorides for Opportunities in Drug Discovery. *J. Am. Chem. Soc.* **2024**, *146*, 35377−35389. (e) Dinh, L. P.; Starbuck, H. F.; Hamby, T. B.; LaLama, M. J.; He, C. Q.; Kalyani, D.; Sevov, C. S. Persistent Organonickel Complexes as General Platforms for Csp^2−Csp^3 Coupling Reactions. *Nat. Chem.* **2024**, *16*, 1515−1522. (f) Laudadio, G.; Neigenfind, P.; Péter, Á.; Rubel, C. Z.; Emmanuel, M. A.; Oderinde, M. S.; Ewing, T. E.; Palkowitz, M. D.; Sloane, J. L.; Gillman, K. W.; Ridge, D.; Mandler, M. D.; Bolduc, P. N.; Nicastri, M. C.; Zhang, B.; Clementson, S.; Petersen, N. N.; Martín-Gago, P.; Mykhailiuk, P.; Engle, K. M.; Baran, P. S. Nickel-Electrocatalytic Decarboxylative Arylation to Access Quaternary Centers. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202314617.

(5) (a) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. Structurally Divergent Lithium-Catalyzed Friedel−Crafts Reactions on Oxetan-3-ols: Synthesis of 3,3-Diaryloxetanes and 2,3-Dihydrobenzofurans. *Chem. Eur. J.* **2016**, *22*, 16271−16276. (b) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. Lithium-Catalyzed Thiol Alkylation with Tertiary and Secondary Alcohols: Synthesis of 3-Sulfanyl-Oxetane as Bioisosteres. *Chem. - Eur. J.* **2018**, *24*, 818−821. (c) Croft, R. A.; Dubois, M. A. J.; Boddy, A. J.; Denis, C.; Lazaridou, A.; Voisin-Chiret, A. S.; Bureau, R.; Choi, C.; Mousseau, J. J.; Bull, J. A. Catalytic Friedel−Crafts Reactions on Saturated Heterocycles and Small Rings for sp^3−sp^2 Coupling of Medicinally Relevant Fragments. *Eur. J. Org. Chem.* **2019**, *2019*, 5385−5395. (d) Dubois, M. A. J.; Croft, R. A.; Ding, Y.; Choi, C.; Owen, D. R.; Bull, J. A.; Mousseau, J. J. Investigating 3,3-Diaryloxetanes as Potential Bioisosteres through Matched Molecular Pair Analysis. *RSC Med. Chem.* **2021**, *12*, 2045−2052. (e) Ishikura, H.; Begg, C. S.; Rojas, J. J.; Blagojevic, L.; Smith, G. J.; Luk, J.; Croft, R. A.; Romain, C.; Choi, C.; Bull, J. A. Do Amino-Oxetanes Resemble Amides? A Matched Molecular Pairs Property and Structural Comparison. *J. Med. Chem.* **2026**, *69*, 3941−3956.

(6) (a) McLaughlin, M.; Yazaki, R.; Fessard, T. C.; Carreira, E. M. Oxetanyl Peptides: Novel Peptidomimetic Modules for Medicinal Chemistry. *Org. Lett.* **2014**, *16*, 4070−4073. (b) Powell, N. H.; Clarkson, Gj.; Notman, R.; Raubo, P.; Martin, N. G.; Shipman, M. Synthesis and structure of oxetane containing tripeptide motifs. *Chem. Commun.* **2014**, *50*, 8797−8800. (c) Phelan, J. P.; Patel, E. J.; Ellman, J. A. Catalytic Enantioselective Addition of Thioacids to Trisubstituted Nitroalkenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 11329−11332. (d) Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. Iron-Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140*, 11317−11324.

(7) Massaro, L.; Neigenfind, P.; Feng, A.; Kuehn, G.; Attard, F. C.; DeSanti, A.; Collins, M. R.; Bravo, M.; Twumasi, R. K.; Chen, D.; Bolduc, P. N.; Nicastri, M.; Emmanuel, M. A.; Oderinde, M. S.; Palkowitz, M. D.; Zheng, X.; Hunter, A. C.; Harper, K. C.; Tyrol, C. C.; Mykhailiuk, P. K.; Kawamata, Y.; Baran, P. S. Triply Convergent Ni-Electrocatalytic Assembly of 1,1-Diaryl Cyclobutanes, Azetidines, and Oxetanes. *Nat. Chem.* **2026**, *18*, 326.

(8) Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. Oxetane ethers are formed reversibly in the lithium-catalyzed Friedel−Crafts alkylation of phenols with oxetanols: Synthesis of dihydrobenzofurans, diaryloxetanes, and oxetane ethers. *Tetrahedron* **2018**, *74*, 5427−5435.

(9) (a) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a highly versatile solvent. *Nat. Rev. Chem.* **2017**, *1*, No. 0088. (b) Vuluga, D.; Legros, J.; Crousse, B.; Slawin, A. M. Z.; Laurence, C.; Nicolet, P.; Bonnet-Delpon, D. Influence of the structure of polyfluorinated alcohols on Brønsted acidity/hydrogen-bond donor ability and consequences on the promoter effect. *J. Org. Chem.* **2011**, *76*, 1126−1133. (c) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. Unveiling the "booster effect" of fluorinated alcohol solvents: aggregation-induced conformational changes and cooperatively enhanced H-bonding. *J. Am. Chem. Soc.* **2006**, *128*, 8421−8426. (d) Lebœuf, D. The Rise and

Future of Hexafluoroisopropanol as a Solvent. *Trends Chem.* **2025**, *7*, 205−207. (e) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, I. V. V. M.; Aubé, J. HFIP in organic synthesis. *Chem. Rev.* **2022**, *122*, 12544−12747.

(10) Berkessel, A.; Adrio, J. A. Kinetic Studies of Olefin Epoxidation with Hydrogen Peroxide in 1,1,1,3,3,3-Hexafluoro-2-propanol Reveal a Crucial Catalytic Role for Solvent Clusters. *Adv. Synth. Catal.* **2004**, *346*, 275−280.

(11) Trillo, P.; Baeza, A.; Nájera, C. Fluorinated alcohols as promoters for the metal-free direct substitution reaction of allylic alcohols with nitrogenated, silylated, and carbon nucleophiles. *J. Org. Chem.* **2012**, *77*, 7344−7354.

(12) (a) Mo, X.; Yakiwchuk, J.; Dansereau, J.; McCubbin, Adam.; Hall, J. D. G. Unsymmetrical Diarylmethanes by Ferroceniumboronic Acid Catalyzed Direct Friedel−Crafts Reactions with Deactivated Benzylic Alcohols: Enhanced Reactivity due to Ion-Pairing Effects. *J. Am. Chem. Soc.* **2015**, *137*, 9694−9703. (b) Vuković, V. D.; Richmond, E.; Wolf, E.; Moran, J. Catalytic Friedel−Crafts reactions of highly electronically deactivated benzylic alcohols. *Angew. Chem., Int. Ed.* **2017**, *56*, 3085−3089. (c) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajooei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. Unlocking the Friedel−Crafts Arylation of Primary Aliphatic Alcohols and Epoxides Driven by Hexafluoroisopropanol. *Chem* **2021**, *7*, 3425−3441. (d) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. Friedel−Crafts Reaction of Benzyl Fluorides: Selective Activation of C-F Bonds as Enabled by Hydrogen Bonding. *Angew. Chem., Int. Ed.* **2014**, *53*, 13835−13839. (e) Muller, C.; Horký, F.; Vayer, M.; Golushko, A.; Lebœuf, D.; Moran, J. Synthesis of Functionalised Isochromans: Epoxides as Aldehyde Surrogates in Hexafluoroisopropanol. *Chem. Sci.* **2023**, *14*, 2983−2989. (f) Tang, R.-J.; Milcent, T.; Crousse, B. Friedel−Crafts Alkylation Reaction with Fluorinated Alcohols as Hydrogen-Bond Donors and Solvents. *RSC Adv.* **2018**, *8*, 10314−10317.

(13) Qi, C.; Gandon, V.; Lebœuf, D. Calcium (II)-Catalyzed Intermolecular Hydroarylation of Deactivated Styrenes in Hexafluoroisopropanol. *Angew. Chem., Int. Ed.* **2018**, *57*, 14245−14249.

(14) (a) Willot, M.; Chen, J.; Zhu, J. Combination of lithium chloride and hexafluoroisopropanol for Friedel-Crafts reactions. *Synlett* **2009**, *2009*, 577−580. (b) Mohamadpour, F. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) as a reusable promoting medium for the catalyst-free and green synthesis of dihydropyrano[2,3-c]pyrazole scaffolds. *Res. Chem.* **2024**, *9*, No. 101629. (c) Markwitz, M.; Labrzycki, K.; Łyczek, K.; Kuciński, K. Functionalization of Electron-Rich Secondary Benzyl Alcohols in HFIP: From Thioethers to Trisubstituted Methanes. *J. Org. Chem.* **2025**, *90*, 9513−9518.

(15) For very recent reports of 4-membered ring functionalization exploiting HFIP, see: (a) Sasmal, P.; Hazra, S.; Rajendra, T. N.; Saha, J.; Jain, R.; Kumar, R. HFIP-Promoted Strain-Release-Driven Functionalization of Azabicyclo[1.1.0]butanes with Heterocyclobutane Trichloroacetimidates. *Org. Lett.* **2026**, *28*, 3026−3032. (b) Huang, W.; Lin, Y.; Hsu, S.; Reddy, J. S.; Lin, S. Hexafluoroisopropanol-Enabled One-Step Access to Oxetanol and Azetidinol Scaffolds from Unprotected Indoles and Heteroarenes. *Adv. Synth Catal.* **2026**, *368*, No. e70304.

(16) *Dihydrobenzofurans are formed through the ortho-alkylation of phenols and intramolecular cyclisation, prevented with the di-ortho-substitution. See ref 5a.*

(17) Niggemann, M.; Meel, M. J. Calcium-Catalyzed Friedel−Crafts Alkylation at Room Temperature. *Angew. Chem., Int. Ed* **2010**, *49*, 3684−3687.

(18) McCubbin, J. A.; Krokhin, O. V. Organocatalyzed Friedel−Crafts arylation of benzylic alcohols. *Tetrahedron Lett.* **2010**, *51*, 2447−2449.

(19) Dryzhakov, M.; Richmond, E.; Moran, J. Recent advances in direct catalytic dehydrative substitution of alcohols. *Synthesis* **2016**, *48*, 935−959.

(20) In reactions with more electron rich aryloxetanols, two different related aldehydes were observed, albeit in low yields, which were distinguished from one another using HSQC and HMBC NMR spectroscopy (see SI for more details). The ratio of these varied depending on the electronic nature of the oxetanol substrates, and suggests the intermediacy of phenonium (see, Mayer, R. J.; Lebœuf, D. Harnessing Phenonium Ions in Synthesis. *Angew. Chem. Int. Ed* **2025**, *64*, e202516932. The formation of aldehyde b may proceed via Fe-assisted 1,2-migration of the preinstalled aryl group, concurrent with oxetane ring opening, to give a 1-hydroxy-3-aryl-propan-2-one. Subsequent 1,2-addition of an arene to the ketone, dehydration, and tautomerization would produce aldehyde b. This is also consistent with the observed formation of ketone 28c in the anisole/*para*-methoxylphenyloxetanol reaction (Figure S5). Alternatively, 1,2-migration may also occur from the isolated 3,3-diaryloxetane under Fe-activation, with subsequent hydride shift or elimination/tautomerization yielding aldehydes a and b, depending on the migrating aryl group (Figure S6)

(21) Higher yields were generally obtained for substrates with substituents that displayed electrophilic substituent constants (σ_p^+/σ_m^+) between $-0.31 < \sigma^+ < 0.15$, providing appropriate levels of stabilization of the carbocation (see SI). The 4-OMe substituent ($-0.31 < \sigma^+$) afforded somewhat lower yield, due to increased rearrangement processes. Oxetanols with substituents possessing $\sigma^+ > 0.15$ were either unproductive or afforded very low, but non-zero, isolated yield consistent with the poor stabilization of the carbocation intermediate. Brown, H. C.; Okamoto, Y. Electrophilic substituent constants. *J. Am. Chem. Soc.* **1958**, *80*, 4979−4987.

(22) *Throughout the examples investigated, aldehyde products were formed in varying amounts and isolated for characterization (See SI for full details of isolated aldehydes).*

(23) O'Donovan, D. H.; Aillard, P.; Berger, M.; de la Torre, A.; Petkova, D.; Knittl-Frank, C.; Geerdink, D.; Kaiser, M.; Maulide, N. C− H. activation enables a concise total synthesis of quinine and analogues with enhanced antimalarial activity. *Angew. Chem., Int. Ed.* **2018**, *57*, 10737−10741.

(24) Walter, F. R.; Veszelka, S.; Pásztói, M.; Péterfi, Z. A.; Tóth, A.; Rákhely, G.; Cervenak, L.; Ábrahám, C. S.; Deli, M. A. Tesmilifene modifies brain endothelial functions and opens the blood−brain/blood−glioma barrier. *J. Neurochem.* **2015**, *134*, 1040−1054.

(25) 15% of *ortho*-**30** and 9% of aldehydes were also formed, and readily separable by column chromatography.

(26) Keating, G. M.; Croom, K. F. Fenofibrate: a review of its use in primary dyslipidaemia, the metabolic syndrome and type 2 diabetes mellitus. *Drugs* **2007**, *67*, 121−153.

(27) Jiang, M.; Feng, L.; Feng, J.; Jiao, P. Catalytic asymmetric cycloadditions of silyl nitronates bearing α-aryl group. *Org. Lett.* **2017**, *19*, 2210−2213.

(28) For selected examples: (a) Li, W.; Werner, T. $B(C_6F_5)_3$-Catalyzed Michael Reactions: Aromatic C−H as Nucleophiles. *Org. Lett.* **2017**, *19*, 2568−2571. (b) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. Sequential One-Pot $InBr_3$-Catalyzed 1,4- then 1,2-Nucleophilic Addition to Enones. *J. Org. Chem.* **2002**, *67*, 3700−3704. (c) Alam, M. M.; Varala, R.; Adapa, S. R. Conjugate addition of indoles and thiols with electron-deficient olefins catalyzed by $Bi(OTf)_3$. *Tetrahedron Lett.* **2003**, *44*, 5115−5119.

(29) Zhang, H. B.; Liu, L.; Liu, Y. L.; Chen, Y. J.; Wang, J.; Wang, D. Triflic Acid−Catalyzed Michael Reactions of Indole and Pyrrole Compounds with α, β-Unsaturated Ketones in Water. *Synth. Commun.* **2007**, *37*, 173−181.

(30) Bhattacharya, A.; Shukla, P. M.; Maji, B. $Fe(OTf)_3$-catalysed Friedel−Crafts reaction of benzenoid arenes with α,β-unsaturated carbonyl compounds: easy access to 1,1-diarylalkanes. *R. Soc. Open Sci.* **2017**, *4*, No. 170748.

(31) Sun, Z.-M.; Zhang, J.; Manan, R. S.; Zhao, P. Rh (I)-catalyzed olefin hydroarylation with electron-deficient perfluoroarenes. *J. Am. Chem. Soc.* **2010**, *132*, 6935−6937.

(32) Kim, D.; Hong, S.; Lee, G. S. Direct $C(sp^2)$−H Alkylation of Unactivated Arenes Enabled by Photoinduced Pd Catalysis. *Nat. Commun.* **2020**, *11*, No. 5128.

https://doi.org/10.1021/acs.joc.6c00762
J. Org. Chem. XXXX, XXX, XXX−XXX

(33) Khan, J.; Taneja, N.; Yadav, N.; Hazra, C. K. Silane-Mediated, Facile C−H and N−H Methylation Using Formaldehyde. *Chem. Commun.* **2024**, *60*, 11367−11370.
(34) Dubois, M. A. J.; Begg, C. S.; Ma, T.-K.; Rojas, J. J.; White, A. J. P.; Choi, C.; Bull, J. A. Iron Catalyzed Friedel−Crafts Reactions of Unactivated 3-Aryl-oxetanols Exploiting HFIP Stabilization of Carbocations [preprint] *ChemRxiv*, March 30, 2026. DOI: 10.26434/chemrxiv.15001389/v1.



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