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Enantioselective Synthesis of Chiral Organofluorine Compounds: Alcohol-Mediated Hydrogen Transfer for Catalytic Carbonyl Reductive Coupling

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ABSTRACT: Alcohol-mediated carbonyl addition has enabled catalytic enantioselective syntheses of diverse fluorine-containing compounds without the need for stoichiometric metals or discrete redox manipulations. Reactions of this type may be separated into two broad categories: redox-neutral hydrogen autotransfer reactions, wherein lower alcohols and π-unsaturated pronucleophiles are converted to higher alcohols, and corresponding 2-propanol-mediated carbonyl reductive couplings.

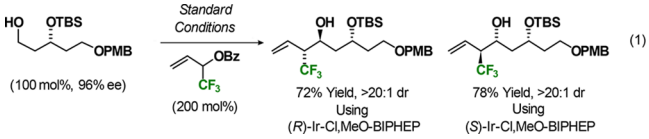
KEYWORDS: *fluorine, iridium, ruthenium, enantioselective catalysis, carbonyl addition, hydrogen transfer*

I. INTRODUCTION

Because of the favorable biological properties of organofluorine compounds, fluorinated structural motifs appear ubiquitously across commercial pharmaceutical and agrochemical ingredients,[1] and many powerful methods now exist for their synthesis.[2] In the course of our ongoing exploration into transfer hydrogenative carbonyl addition,[3] we have developed a suite of catalytic enantioselective methods for the formation of chiral organofluorine compounds wherein π-unsaturated reactants are converted to transient organometallic nucleophiles via alcohol-mediated hydrogen transfer. Two reactions types have emerged: hydrogen autotransfer processes, wherein primary alcohols serve as both the reductant and the carbonyl proelectrophile (enabling conversion of lower alcohols to higher alcohols), and related 2-propanol-mediated reductive couplings of discrete carbonyl reactants. Such transfer hydrogenative carbonyl additions may be differentiated from "borrowing hydrogen" processes, which promote formal alcohol substitution.[4] Most importantly, unlike many classical carbonyl additions, the present alcohol-mediated processes are noncryogenic and circumvent the use of stoichiometric organometallic reagents, which pose issues of safety, require multistep syntheses, and generate stoichiometric quantities of metallic byproducts. In this review, we provide a comprehensive survey of catalytic enantioselective methods for the synthesis of chiral organofluorine compounds via alcohol-mediated carbonyl addition with an emphasis on preparative capabilities (Scheme 1). For detailed discussions of reaction mechanism and stereochemical models, the reader is referred to the primary literature citations.

II. CHIRAL ORGANOFLUORINE COMPOUNDS VIA ALCOHOL-MEDIATED CARBONYL ADDITION

In 2008, cyclometalated π-allyliridium *C,O*-benzoate complexes bound by chiral chelating phosphines were shown to catalyze highly enantioselective alcohol-mediated carbonyl allylations[5] and crotylations[6] using allyl acetate and α-methyl allyl acetate, respectively, as pronucleophiles. In 2011, using a cyclometalated π-allyliridium *C,O*-benzoate complex modified by (*R*)-Cl,MeO-BIPHEP, related carbonyl (α-trifluoromethyl)allylations using α-trifluoromethyl allyl benzoate as the pronucleophile were developed (Scheme 2).[7] In reactions conducted from the alcohol oxidation level, moderate to good yields of the CF_3-bearing homoallylic alcohols were generated with excellent levels of *anti*-diastereo- and enantioselectivity. When 2-propanol was used as the terminal reductant under otherwise equivalent conditions, an identical set of adducts was accessible from the aldehyde oxidation level with comparable levels of *anti*-diastereo- and enantioselectivity. Finally, in carbonyl (α-trifluoromethyl)allylations of enantiomerically enriched chiral γ-stereogenic alcohols, high levels of catalyst-directed stereoinduction were observed (eq 1).



(1)

To illustrate the utility of the reaction products, the compound obtained upon (α-trifluoromethyl)allylation of 1,4-aminobutanol was transformed into two useful *N*-containing building blocks (Scheme 3). Specifically, exposure of the product to ozone followed by $NaBH_4$ furnished a 1,3-diol, which was converted to the indicated *p*-toluenesulfonate in a site-selective fashion. Conversion of the *p*-toluenesulfonate to the CF_3-bearing piperidine was then accomplished in accordance with a related literature procedure.[8,9] Alternatively, the *p*-toluenesulfonate can be eliminated, and the resulting olefin can be subjected to diastereoselective ruthenium-catalyzed hydrogenation to provide the *syn*-trifluoroisopropyl-substituted secondary alcohol as a single diastereomer.[10]

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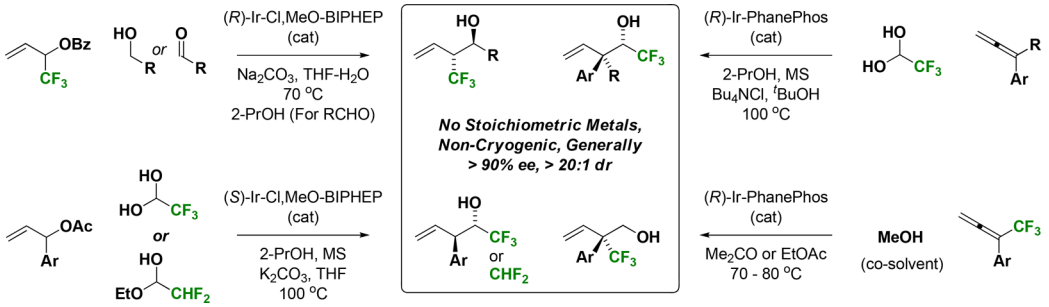
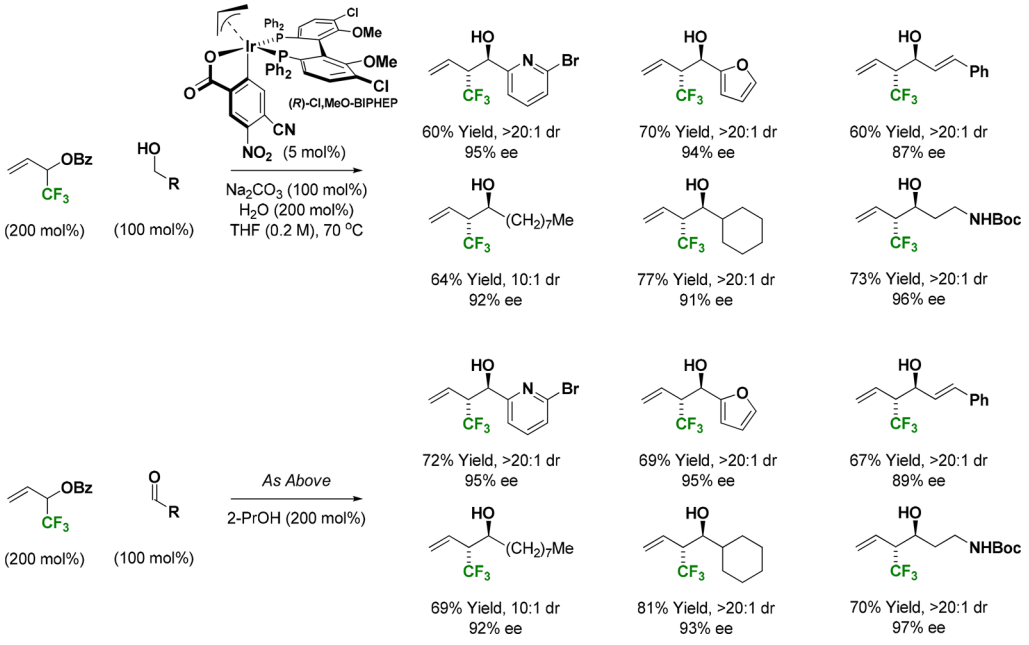
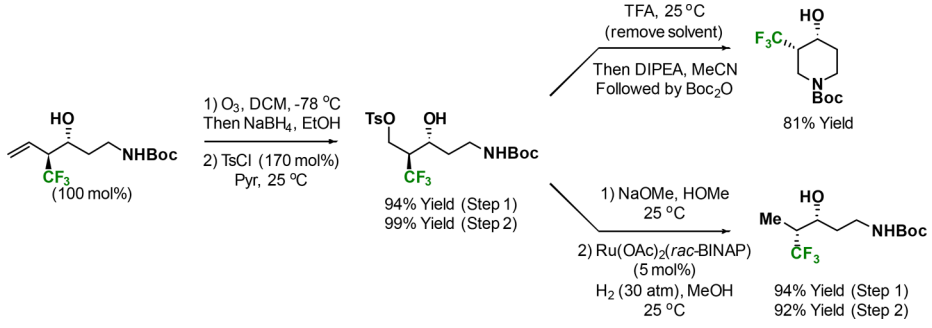
Scheme 1. Organofluorine Compounds via Enantioselective Alcohol-Mediated Carbonyl Addition



Scheme 2. *anti*-Diastereo- and Enantioselective Iridium-Catalyzed Carbonyl (α-Trifluoromethyl)allylation



Scheme 3. CF_3-Bearing Building Blocks Obtained via (α-Trifluoromethyl)allylation of Aminobutanol



The cyclometalated π-allyliridium *C,O*-benzoate complex modified by (*R*)-Cl,MeO-BIPHEP was also effective in promoting highly enantioselective carbonyl (2-fluoro)-allylations (Scheme 4).[11] With commercially available (2-fluoro)allyl chloride as the pronucleophile, benzylic, allylic, and aliphatic alcohols were converted to the corresponding homoallylic alcohols in good to excellent yields with uniformly high levels of enantioselectivity. When 2-propanol was used as the terminal reductant under otherwise identical conditions, corresponding aldehyde reductive couplings of (2-fluoro)allyl chloride occurred with roughly equivalent levels of enantioselectivity (not shown). In all cases, small quantities of defluorinated side products were observed (3−10% yield), which were easily removed upon chromatographic isolation of the product. Diastereoselective hydrogenation of the vinyl fluoride-containing products was readily achieved at ambient pressures of hydrogen gas using the Crabtree catalyst.[12] In this way, *syn*-3-fluoro-1-alcohols were formed from primary alcohols in the absence of stoichiometric organic or metallic byproducts.

Commercially available solutions of fluoral hydrate or difluoroacetaldehyde ethyl hemiacetal (75 wt % in water or 90 wt % in ethanol, respectively) can be utilized in highly *anti*-diastereo- and enantioselective carbonyl (α-aryl)allylations

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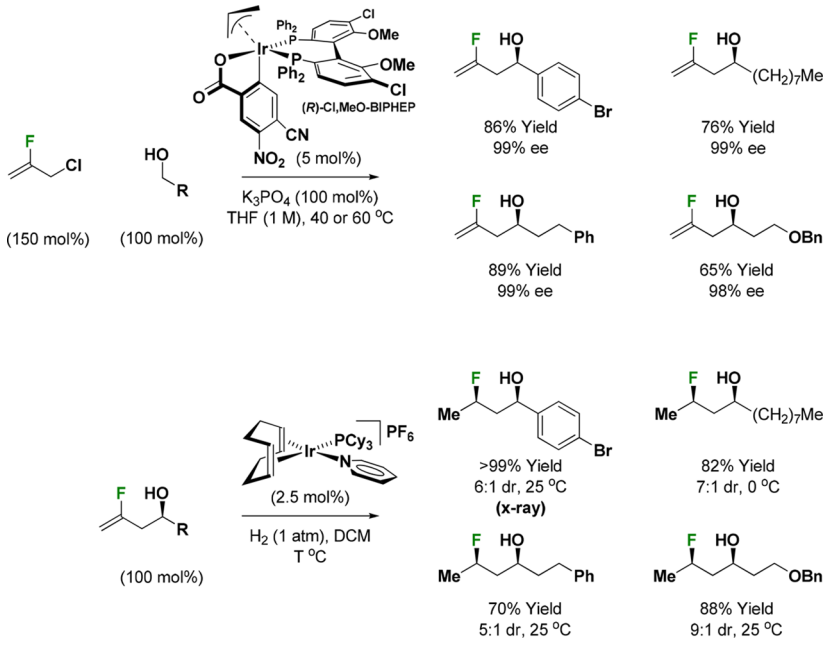
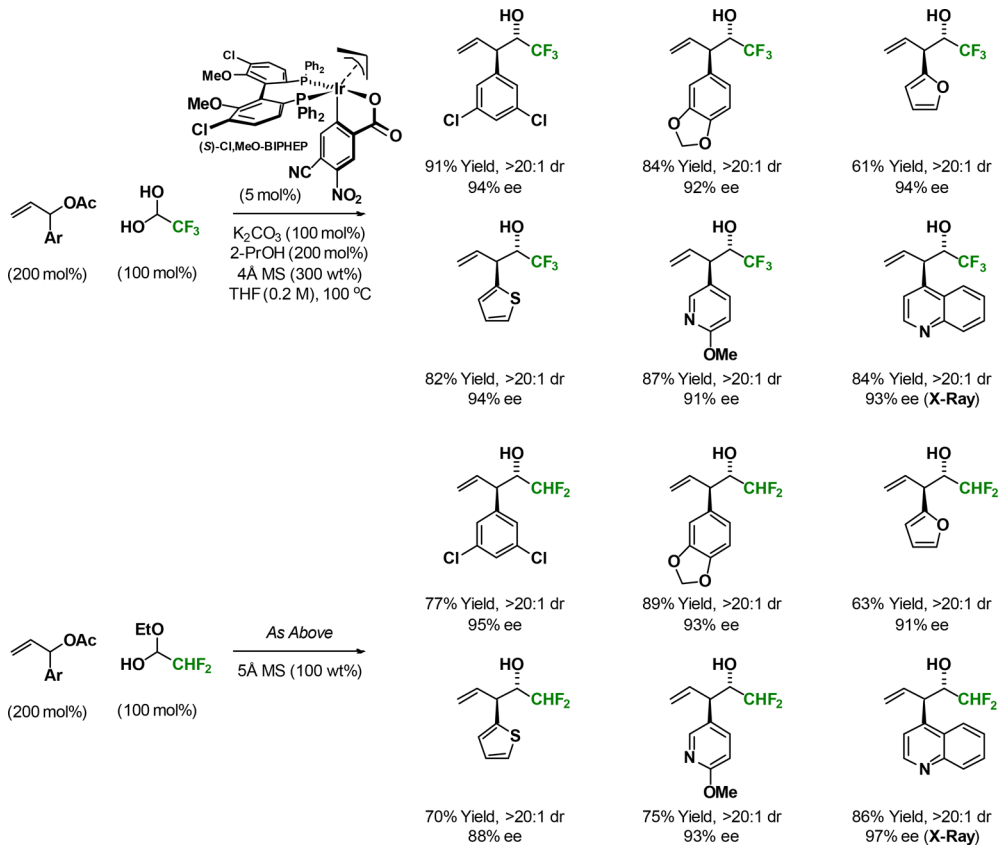
Scheme 4. Enantioselective Iridium-Catalyzed Carbonyl (2-Fluoro)allylation



Scheme 5. *anti*-Diastereo- and Enantioselective Iridium-Catalyzed Carbonyl (α-Aryl)allylation of Fluoral Hydrate and Difluoroacetaldehyde Ethyl Hemiacetal



(Scheme 5).[13] Again, the chromatographically purified cyclometalated π-allyliridium *C,O*-benzoate complex modified by (*S*)-Cl,MeO-BIPHEP was identified as the catalyst of choice. Using 2-propanol as the terminal reductant and molecular sieves to remove water and ethanol results in (α-aryl)allylation of both fluoral and difluoroacetaldehyde in good to excellent yields with high levels of diastereo- and enantioselectivity. These results are significant, as nearly all enantioselective metal-catalyzed additions to fluoral require anhydrous conditions involving in situ generation of gaseous fluoral, which is acutely toxic. The hydrate and hemiacetal solutions are less hazardous than their gaseous counterparts. Addition-

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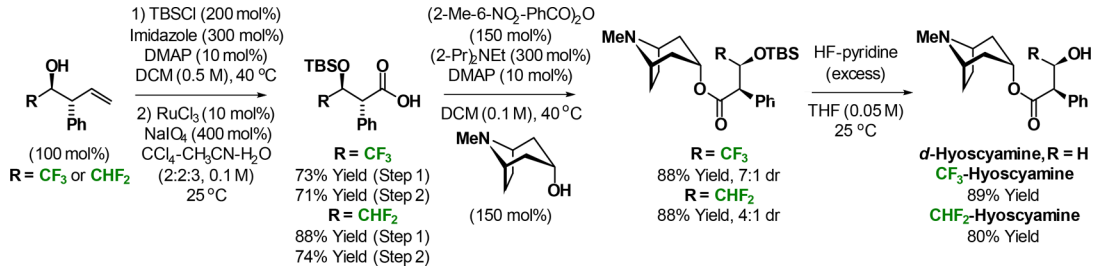
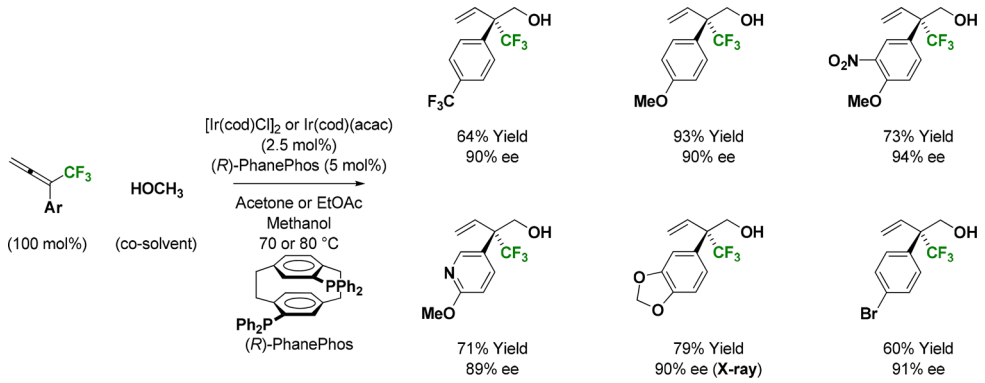
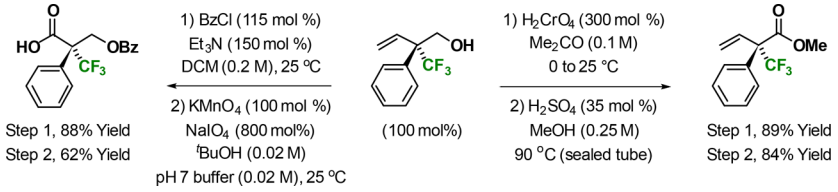
Scheme 6. Syntheses of CF_3- and CHF_2-Bearing Derivatives of *d*-Hyoscyamine (*dextro*-Atropine)



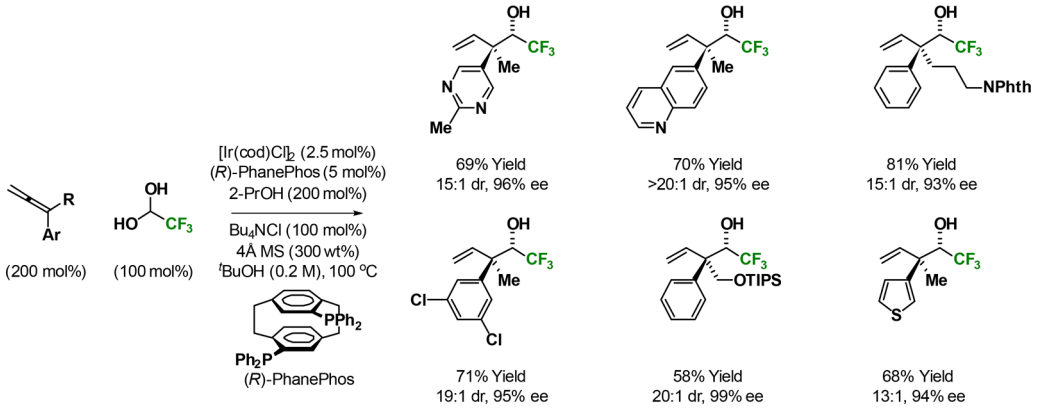
Scheme 7. Enantioselective Iridium-Catalyzed Reductive Coupling of Methanol with CF_3-Substituted Allenes via Hydrogen Autotransfer



Scheme 8. Syntheses of Enantiomerically Enriched Carboxylic Acids That Incorporate CF_3-Bearing Quaternary Carbon Stereocenters



Scheme 9. Enantioselective Iridium-Catalyzed Reductive Coupling of Fluoral with Allenes Mediated by 2-Propanol



ally, there is surprising paucity of catalytic enantioselective methods for the formation of CHF_2-bearing stereocenters.[14] The ability to engage fluoral hydrate and difluoroacetaldehyde ethyl hemiacetate in highly *anti*-diastereo- and enantioselective (α-aryl)allylation enabled concise routes to di- and trifluoromethylated derivatives of the FDA-approved alkaloid *d*-hyoscyamine (*dextro*-atropine) (Scheme 6).[15]

The use of methanol as a feedstock in metal-catalyzed C−C coupling is an important objective in chemical synthesis.[16] Following the development of non-asymmetric allene−methanol C−C couplings,[17] it was found that iridium complexes modified by PhanePhos catalyze the enantioselective reductive coupling of CF_3-substituted allenes with methanol via hydrogen autotransfer.[18,19] Products of hydrohydroxymethylation are formed exclusively as the branched

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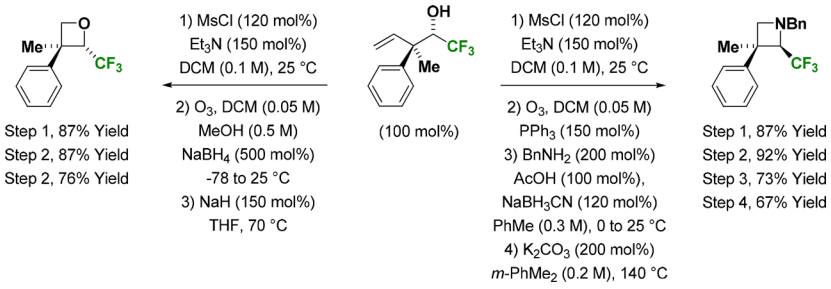
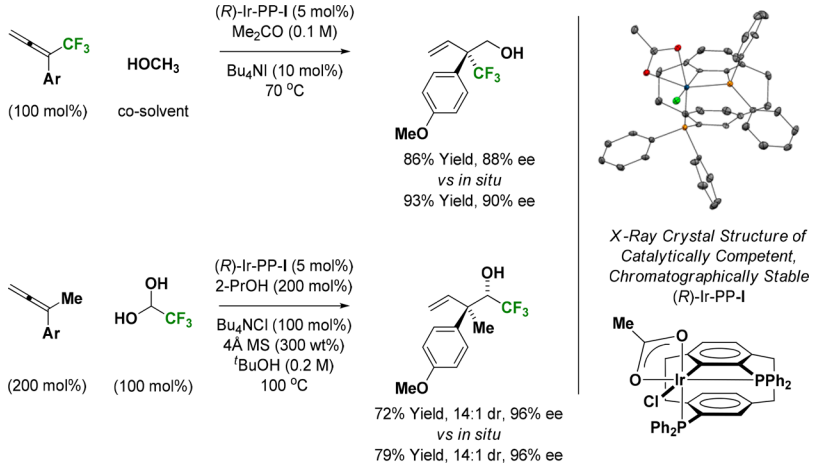
Scheme 10. Synthesis of an Enantiomerically Enriched CF_3-Substituted Oxetane and CF_3-Substituted Azetidine



Scheme 11. Catalytically Competent Cyclometalated Iridium−PhanePhos Complex (*R*)-Ir-PP-I



regioisomers with excellent levels of enantiomeric enrichment (Scheme 7). In this process, methanol dehydrogenation provides formaldehyde and an iridium hydride. Allene hydrometalation then delivers an allyliridium species that undergoes formaldehyde addition to furnish a homoallylic iridium alkoxide. Alkoxide exchange with another equivalent of methanol releases the product and closes the catalytic cycle. This transformation enables the catalytic enantioselective formation of acyclic CF_3-bearing quaternary carbon stereocenters without stoichiometric metals or byproducts.[20] The utility of this method was highlighted in syntheses of chiral carboxylic acids that incorporate CF_3-bearing quaternary carbon stereocenters (Scheme 8).

Iridium complexes modified by PhanePhos are also effective catalysts for the 2-propanol-mediated reductive coupling of 1,1-disubstituted allenes with fluoral (Scheme 9).[21] In this way, branched CF_3-substituted secondary alcohols bearing acyclic quaternary carbon stereocenters[20] are formed with high levels of *anti*-diastereo- and enantioselectivity. The utility of this method was illustrated by the construction of CF_3-substituted oxetanes and azetidines (Scheme 10). The oxetane formation proceeds via secondary to primary methanesulfonate transfer, which accounts for the divergent diastereoselectivity of these processes. Iridium−PhanePhos complexes were uniquely effective in the allene-mediated C−C coupling described herein.[18,21] Investigations of the reaction mechanism suggested that the chromatographically stable cyclometalated iridium−(*R*)-PhanePhos complex (*R*)-Ir-PP-**I** is the active catalyst. Generation of the cyclometalated complex in situ provides a slightly more active catalyst that does not incorporate the bidentate acetate counterion, which appears to impede conversion (Scheme 11).

III. SUMMARY AND OUTLOOK

Carbonyl addition has played a fundamental role in chemical synthesis since the inception of organic chemistry as a field. However, traditional methods have typically relied on the use of stoichiometric carbanions, which must be preformed and deployed under cryogenic conditions and incur issues of safety, waste generation, and functional group compatibility. By harnessing the reducing power of alcohols, we have demonstrated that carbonyl additional can be accomplished from *transient* organometallic nucleophiles in the absence of stoichiometric metals under noncryogenic conditions.[3] As summarized herein, adaptation of these methods for the synthesis of chiral organofluorine compounds enables access to novel fluorine-containing compounds that would otherwise be difficult to prepare. For application of this chemistry on scale, it will be important to reduce the catalyst loadings, as successfully accomplished in related iridium-catalyzed alcohol aminations.[22] The focus of future studies will be on the development of related C−C couplings, including alcohol-mediated carbonyl arylations and related cross-electrophile reductive couplings.

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Notes

The authors declare no competing financial interest.

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