Allylic Compounds

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Ruthenium-Catalyzed C–C Coupling of Fluorinated Alcohols with Allenes: Dehydrogenation at the Energetic Limit of β-Hydride Elimination**

*Brannon Sam, Tom Luong, and Michael J. Krische**

Abstract: *Ruthenium(II) complexes catalyze the C–C coupling of 1,1-disubstituted allenes and fluorinated alcohols to form homoallylic alcohols bearing all-carbon quaternary centers with good to complete levels of diastereoselectivity. Whereas fluorinated alcohols are relatively abundant and tractable, the corresponding aldehydes are often not commercially available because of their instability.*

Over 20% of the approved pharmaceutical agents and 30–40% of the commercially available agrochemicals are organofluorine compounds.[1] Accordingly, many powerful methods for the introduction of fluorine and fluorine-containing functional groups have been developed.[2] Remarkably, despite years of intensive investigation, there is a surprising paucity of methods for the addition of nonstabilized *C*-nucleophiles to fluorinated aldehydes,[3] and, to our knowledge, metal-catalyzed additions of *C*-nucleophiles to fluorinated aldehydes are largely restricted to carbonyl–ene, Mukaiyama aldol, and Friedel–Crafts reactions.[4] These methodological deficiencies likely stem from the intractability of fluorinated aldehydes and their propensity to engage in self-condensation or suffer reduction upon exposure to main-group organometallics such as Grignard reagents.[3a,b] In contrast, the corresponding fluorinated alcohols are stable, abundant, and relatively inexpensive; so much so they are often used as solvents, cosolvents, or additives in chemical synthesis (Figure 1).[5]

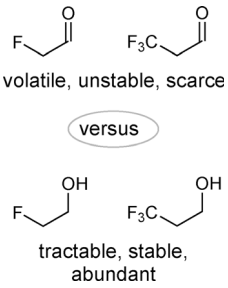


Figure 1. Fluorinated alcohols versus fluorinated aldehydes.

Under the conditions of redox-triggered carbonyl addition,[6] alcohols serve as synthetic equivalents to their carbonyl congeners, thus enabling additions that would otherwise be unattainable because of the intractability of the corresponding aldehydes. For example, 1,3-dialdehydes are relatively unstable, yet the corresponding 1,3-diols are highly tractable and can be used in catalytic enantioselective double allylations or crotylations by redox-triggered carbonyl addition.[7] In such redox-triggered carbonyl additions, hydrogen is transferred from alcohols to π-unsaturated reactants to generate transient carbonyl–organometal pairs which combine to form products of addition.[6] As the aldehyde is generated pairwise with an organometallic nucleophile it does not accumulate, thus mitigating competing decomposition. The feasibility of engaging fluorinated alcohols in redox-triggered carbonyl addition was rendered uncertain by three issues: a) the relatively high strength of carbinol C–H bonds in fluorinated alcohols,[8] b) the reversibility and increased endothermicity of dehydrogenation, which would shorten the lifetime of the transient aldehyde,[9] and c) the large destabilizing effect of fluoroalkyl groups on the transition state for β-hydride elimination (up to 15 kcal mol^{-1})[9] (Figure 2).

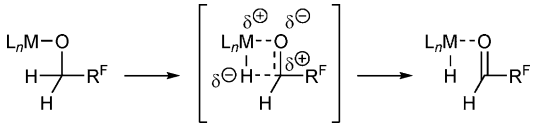
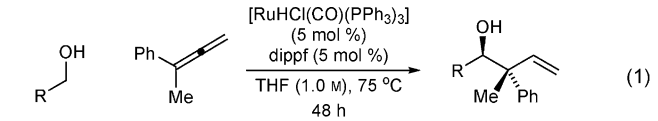


Figure 2. Inductive fluoroalkyl moieties raise the energetic barrier to β-hydride elimination in dehydrogenations of fluorinated alcohols.

Herein, we report that certain fluorinated alcohols are capable of participating in redox-triggered carbonyl allylation, as illustrated by their regio- and diastereoselective ruthenium catalyzed C–C coupling to 1,1-disubstituted allenes to furnish adducts bearing all-carbon quaternary stereocenters.[10–13] Further, through a series of experiments, including competition kinetics, we demonstrate that the alcohol dehydrogenation events in these processes occur near the energetic limit of β-hydride elimination.

In initial experiments, ethanol (**1d**) and the fluoroethanols **1a–c** were treated with the allene **2a** under reaction conditions for the coupling of nonfluorinated alcohols to 1,1-disubstituted allenes [Eq. (1)].[11e] Exposure of trifluoro-



(1)

1a, R = CF_3
1b, R = CHF_2
1c, R = CH_2F
1d, ethanol (100 mol %)

2a (300 mol %)

3a, R = CF_3, not detected
3b, R = CHF_2, <5% yield, 2:1 d.r.
3c, R = CH_2F, 60% yield, >20:1 d.r.
3d, R = CH_3, 73% yield, >20:1 d.r.

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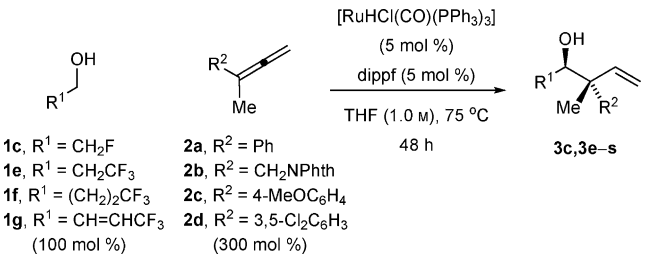
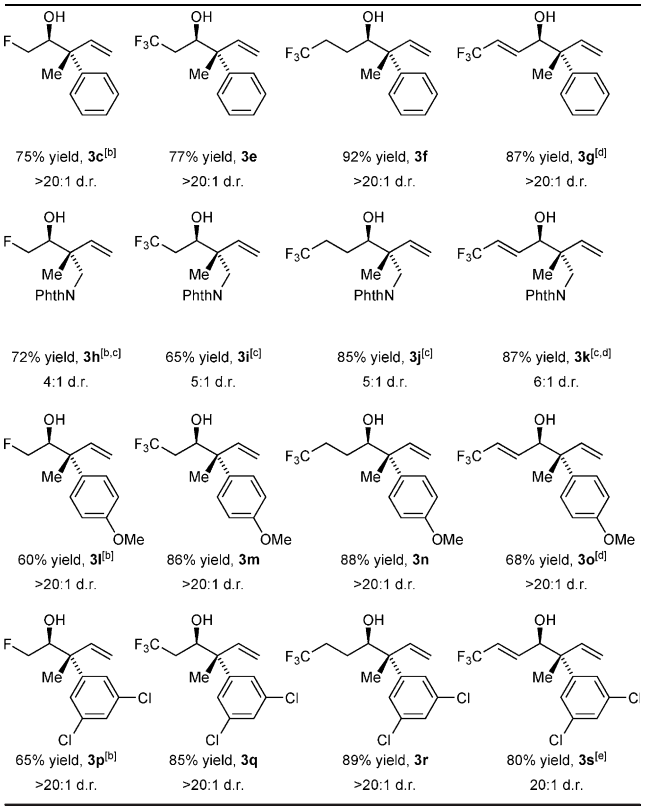
ethanol (**1a**) and **2a** to the ruthenium(II) catalyst, derived in situ from the commercially available components [H(Cl)Ru(CO)(PPh_3)$_3$] and dippf [bis(diisopropylphosphino)ferrocene], in THF (solvent) at 75 °C did not provide any detectable quantity of the desired adduct **3a**. However, as anticipated based on the relative transition-state energies for β-hydride elimination,[9] reaction efficiency increases with a decreasing degree of fluoro substitution. The reaction of difluoroethanol (**1b**) and fluoroethanol (**1c**) delivered the desired adducts **3b** and **3c** in less than 5% and 60% yield, respectively, whereas the reaction of ethanol itself provided the adduct **3d** in 73% yield as a single diastereomer [Eq. (1); cited yields are of material isolated by silica gel chromatography. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. See the Supporting Information for further details; THF = tetrahydrofuran].

Despite considerable effort to enhance conversion in the reactions of **1a** and **1b** through variation of the ligand, ruthenium precatalyst, and other parameters, no significant improvement was possible. In contrast, for the reaction of **1c** and **2a**, simply extending the reaction time allowed the desired adduct **3c** to be obtained in 75% yield upon isolation. In general, the coupling of fluorinated alcohols occurs under essentially the same reaction conditions as for nonfluorinated alcohols,[11e] but longer reaction times are required. Thus, the fluorinated alcohols **1c** and **1e–g** were each reacted with the 1,1-disubstituted allenes **2a–d** to furnish the adducts **3c** and **3e–s** in good yields (Table 1). Remarkably, in reactions of **1c** and **1e–g** with the 1-methyl-1-aryl-substituted allenes **2a**, **2c**, and **2d**, complete levels of *anti*-diastereoselectivity are observed, as determined by ^{1}H NMR analysis of the crude reaction mixtures. Even for the phthalimidomethyl-substituted allene **2b**, good levels of *anti*-diastereoselectivity (4:1–6:1 d.r.) are evident in the formation of the adducts **3h–k**. For other dialkyl-substituted allenes, the transient (*E*)- and (*Z*)-σ-allylruthenium intermediates are quite similar in energy, thus resulting in lower diastereoselectivity. Conversion of the trifluoromethylated allylic alcohol **1g** into the adducts **3g**, **3k**, **3o**, and **3s** is noteworthy, as fluorinated allylic alcohols are known to undergo internal redox isomerization upon exposure to closely related ruthenium(II) catalysts.[14] The organofluorine compounds generated using the present catalytic methods raise numerous possibilities in terms of synthetic applications. For example, as illustrated in the conversion of **3i** into the β-amino ester **5i**, novel CF_3-containing nonproteinogenic amino acids are readily accessible [Eq. (2); cited yields are of material isolated by silica gel chromatography. See the Supporting Information for further details; DMAP = 4-(*N*,*N*-dimethylamino)pyridine].[15]

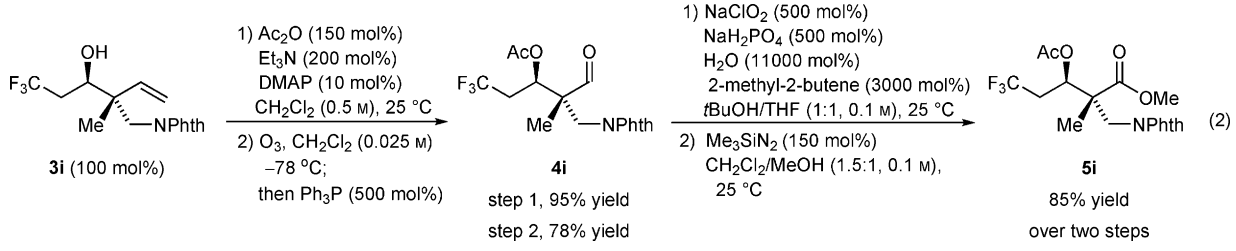
Table 1: Ruthenium-catalyzed hydrohydroxyalkylation of 1,1-disubstituted allenes (**2a–d**) with fluorinated alcohols (**1c** and **1e–g**) to form the adducts **3c** and **3e–s**.[a]

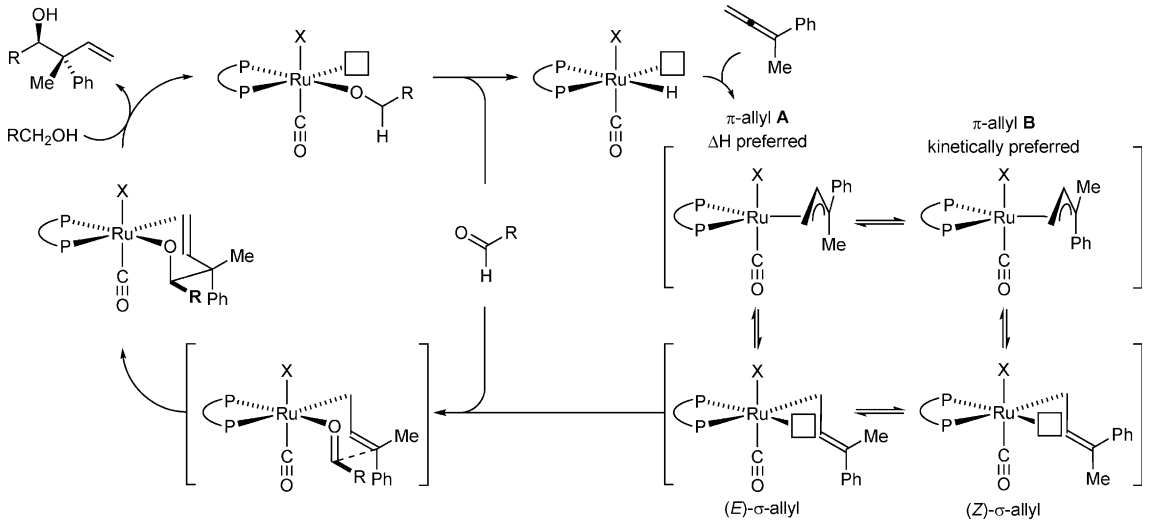




[a] Cited yields are of material isolated by silica gel chromatography and represent the average of two runs. Stereoisomeric ratios were determined by ^{1}H NMR analysis of crude reaction mixtures. See the Supporting Information for further experimental details. [b] 72 h. [c] 95 °C. [d] 0.1 M THF. [e] 0.05 M THF.

Our collective data suggests the following catalytic mechanism (Scheme 1).[11] The ruthenium hydride complex derived from [H(Cl)Ru(CO)(PPh_3)$_3$] and dippf engages in allene hydrometallation to form a nucleophilic allylruthenium complex. The stoichiometric reaction of [H(X)Ru(CO)-

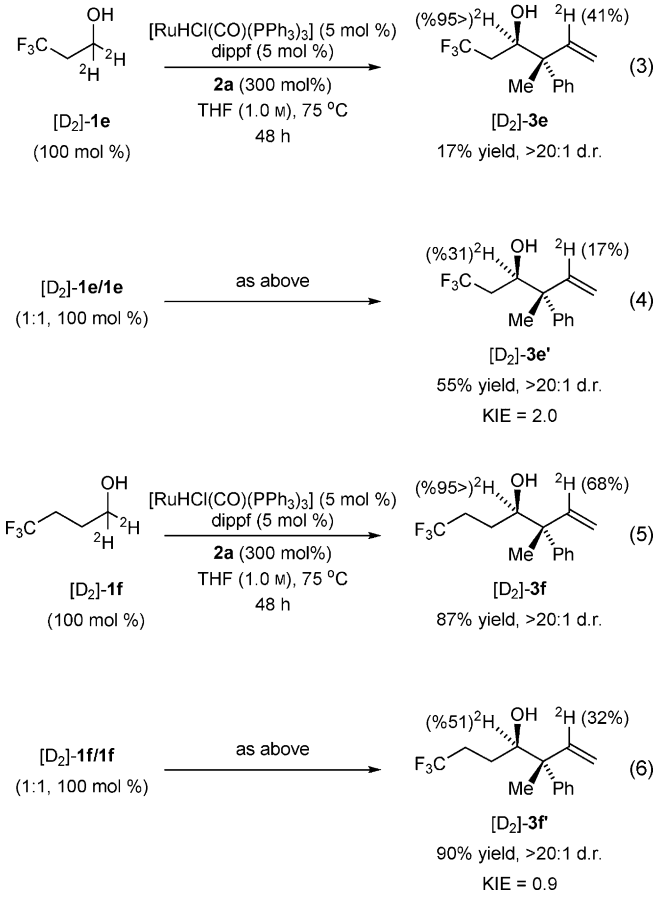




Scheme 1. General catalytic mechanism for the redox-triggered coupling of primary alcohols with allenes.

$(PR_3)_3$] (X = Cl, Br) with allenes or dienes to furnish π-allylruthenium complexes has been described.[16] Although hydrometallation from the allene π-face proximal to the smaller methyl group is anticipated to be kinetically preferred, rapid isomerization of π-allyl **B** enables conversion into the more stable complex π-allyl **A**.[11e,17] Carbonyl addition by way of the (*E*)-σ-allylruthenium complex through a chairlike transition structure forms the *anti*-diastereomer. Protonolysis of the resulting homoallylic ruthenium alkoxide with a reactant alcohol releases the product and provides a primary ruthenium alkoxide, which upon β-hydride elimination delivers the aldehyde, thus regenerating the ruthenium hydride to close the catalytic cycle.

To corroborate the anticipated effects of fluorination on the β-hydride elimination event,[9] a series of competition kinetics experiments were undertaken (Scheme 2). Coupling of the [D_2]3,3,3-trifluoropropanol ([D_2]-**1e**), which is fully deuterated at the carbinol position (i.e., > 95 % ^{2}H), with **2a** under standard reaction conditions delivered [D_2]-**3e** in 17 % yield [Eq. (3)]. For [D_2]-**3e**, deuterium is completely retained at the carbinol position, thus suggesting that the secondary alcohol product is inert with respect to dehydrogenation. Incomplete deuterium incorporation at the interior vinylic position of [D_2]-**3e** (41 % ^{2}H) may be due to β-hydride elimination of the allylruthenium intermediate to form diene byproducts, which are detected in the crude reaction mixture and may account for the requirement of excess allene. Adventitious water also may diminish the extent of deuterium incorporation.[18] The relatively low yield of the isolated [D_2]-**3e** compared to the non-isotopically labeled material **3e** already suggests that the dehydrogenation events involving either the alcohols [D_2]-**1e** or **1e** are turnover limiting. Indeed, when this transformation is conducted using equimolar quantities of **1e** and [D_2]-**1e**, a primary kinetic isotope effect of 2.0 is observed in the formation of [D_2]-**3e'** [Eq. (4)]. Furthermore, when an analogous set of experiments was performed on [D_2]-4,4,4-trifluorobutanol ([D_2]-**1f**) [Eqs. (5) and (6)], for which the inductive CF_3 moiety is more distant from the carbinol position, a kinetic isotope effect of 0.9 is observed. These data suggest that for **1f**, β-hydride elimination is no longer turnover limiting and that an inverse



Scheme 2. A transition from turnover-limiting β-hydride elimination to turnover-limiting carbonyl addition in the redox-triggered couplings of fluorinated alcohols **1e** and **1f**, respectively, as corroborated by competition kinetics. Cited yields are of material isolated by silica gel chromatography and represent the average of two runs. Isoptopic composition was determined by ^{1}H and ^{2}H NMR analysis and HRMS. See the Supporting Information for further experimental details.

secondary isotope effect, associated with turnover limiting carbonyl addition, may be evident.

In summary, redox-triggered carbonyl addition by ruthenium-catalyzed transfer hydrogenation allows stable, abundant fluorinated alcohols to serve as synthetic equivalents to intractable fluorinated aldehydes, thus representing a broad, new means of accessing diverse organofluorine compounds. As specifically shown, the ruthenium complex generated from $[H(Cl)Ru(CO)(PPh_3)_3]$ and dippf catalyzes the C–C coupling of 1,1-disubstituted allenes with fluorinated alcohols to form homoallylic alcohols bearing all-carbon quaternary centers with good to complete levels of diastereoselectivity. As corroborated by competition kinetics, the partial positive charge accumulating in the transition state for β-hydride elimination of the ruthenium alkoxide poses an increasingly significant energetic barrier for alcohols bearing increasingly inductive fluoroalkyl groups [Eq. (1)]. This insight into the critical role of β-hydride elimination will guide the design of an improved second-generation catalyst for the direct C–H functionalization of fluorinated alcohols.

Keywords: allylic compounds · diastereoselectivity · fluorine · hydrogenation · ruthenium

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