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Dehydrogenation at the Energetic Limit of β -Hydride Elimination

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Abstract

Alcohol is the Answer! 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 due to their instability.

Keywords

Ruthenium; Fluorine; Transfer Hydrogenation; Diastereoselectivity; Green Chemistry

Over 20% of approved pharmaceutical agents and 30–40% of 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 non-stabilized 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]

Under the conditions of redox-triggered carbonyl addition,^[6] alcohols serve as synthetic equivalents to their carbonyl congeners, enabling additions that would otherwise be unattainable due to 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 *via* 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 that combine to form products of addition.^[6] As the aldehyde is generated pairwise with an organometallic nucleophile it does not accumulate, 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 increased endothermicity of dehydrogenation, which being reversible 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)^[9] (Figure 2). Here, 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.^[10,11,12,13] 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 and the fluoroethanols **1a-1c** were treated with allene **2a** under conditions for the coupling of non-fluorinated alcohols to 1,1-disubstituted allenes (eq. 1).^[11e] Exposure of trifluoroethanol **1a** and allene **2a** to the ruthenium(II) catalyst derived *in situ* from the commercially available components $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ 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 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 adduct **3d** in 73% yield as a single diastereomer (eq. 1).

^aCited yields are of material isolated by silica gel chromatography. Stereoisomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. See supporting information for further experimental details.

Despite considerable effort to enhance conversion in the reactions of trifluoroethanol **1a** and difluoroethanol **1b** through variation of ligand, ruthenium precatalyst and other parameters, no significant improvement was possible. In contrast, for the reaction of fluoroethanol **1c** and allene **2a**, simply extending the reaction time allowed the desired adduct **3c** to be obtained in 75% isolated yield. In general, the coupling of fluorinated alcohols occurs under essentially the same conditions as non-fluorinated alcohols,^[11e] but longer reaction times are required. Thus, fluorinated alcohols **1c-1e** were each reacted with 1,1-disubstituted allenes **1c**, **1e-1g** to furnish the adducts **3c**, **3e-3s** in good yields (Table 1). Remarkably, in reactions of the saturated fluorinated alcohols **1c**, **1e-1g** with 1-methyl-1-aryl substituted allenes **2a**, **2c** and **2d**, complete levels of *anti*-diastereoselectivity are observed, as determined by ¹H NMR analysis of the crude reaction mixtures. Even for the phthalimidomethyl substituted

Our collective data suggests the following catalytic mechanism (Scheme 1).^[11] The ruthenium hydride complex derived from $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ and dippf engages in allene hydrometallation to form a nucleophilic allylruthenium complex. The stoichiometric reaction of $\text{HXRu}(\text{CO})(\text{PR}_3)_3$ ($\text{X} = \text{Cl}, \text{Br}$) 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 to the more stable complex **π -Allyl A**.^[11e,17] Carbonyl addition by way of the (*E*)- σ -allylruthenium complex through a chair-like 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 aldehyde, regenerating the ruthenium hydride to close the catalytic cycle.

distant from the carbinol position, a kinetic isotope effect of 0.9 is observed. These data suggest that for 4,4,4-trifluorobutanol **1f**, β -hydride elimination is no longer turn-over limiting and that an inverse secondary isotope effect, associated with turn-over limiting carbonyl addition, may be evident.

In summary, redox-triggered carbonyl addition *via* ruthenium catalyzed transfer hydrogenation allows stable, abundant fluorinated alcohols to serve as synthetic equivalents to intractable fluorinated aldehydes, representing a broad, new means of accessing diverse organofluorine compounds. As specifically shown, the ruthenium complex generated from $\text{HClRu}(\text{CO})(\text{PPh}_3)_3$ 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 improved second-generation catalyst for the direct C-H functionalization of fluorinated alcohols.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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versus

Figure 1.
Fluorinated alcohols vs. fluorinated aldehydes.

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

Scheme 1.

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

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.^a

^aCited yields are of material isolated by silica gel chromatography and represent the average of two runs. Isotopic composition was determined by ^1H and ^2H NMR analysis and HRMS. See supporting information for further experimental details.

Table 1

Ruthenium catalyzed hydrohydroxyalkylation of 1,1-disubstituted allenes **2a-2d** with fluorinated alcohols **1c**, **1e-1g** to form adducts **3c**, **3e-3s**.^a

R^1 1c, 1e-1g (100 mol %)	R^2 2a-2d (300 mol %)	$\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ (5 mol %) diippf (5 mol %) THF (1.0 M), 75 °C 48 Hr	3c, 3e-3p
1c , $\text{R}^1 = \text{CH}_2\text{F}$ 2a , $\text{R}^2 = \text{Ph}$	1e , $\text{R}^1 = \text{CH}_2\text{CF}_3$ 2b , $\text{R}^2 = \text{CH}_2\text{NPhth}$	1f , $\text{R}^1 = (\text{CH}_2)_2\text{CF}_3$ 2c , $\text{R}^2 = 4\text{-MeO-Ph}$	1g , $\text{R}^1 = \text{CH=CHCF}_3$ 2d , $\text{R}^2 = 3,5\text{-Cl}_2\text{-Ph}$
75% yield, 3c ^b >20:1 dr	77% yield, 3e >20:1 dr	92% yield, 3f >20:1 dr	87% yield, 3g ^d >20:1 dr
72% yield, 3h ^{b,c} 4:1 dr	65% yield, 3i ^f 5:1 dr	85% yield, 3j ^c 5:1 dr	87% yield, 3k ^{c,d} 6:1 dr
60% yield, 3l ^p >20:1 dr	86% yield, 3m >20:1 dr	88% yield, 3n >20:1 dr	68% yield, 3o ^d >20:1 dr
65% yield, 3p ^b >20:1 dr	85% yield, 3q >20:1 dr	89% yield, 3r >20:1 dr	80% yield, 3s ^d 20:1 dr

^aCited yields are of material isolated by silica gel chromatography and represent the average of two runs. Stereoisomeric ratios were determined by ¹H NMR analysis of crude reaction mixtures. See supporting information for further experimental details. ^b72 Hr 95 °C 0.1 M THF 0.05M THF.