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C–H/C–F functionalization by *E*-selective ruthenium (II) catalysis

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1. Introduction

Methods for the site-selective introduction of fluorine-containing moieties into organic molecules continue to be in high demand, because these structural motifs improve the solubility, bioavailability, and metabolic stability of biorelevant compounds [1,2]. As a consequence, approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine [3–7]. Recently, a significant impetus has been gained through the development of powerful tools that merge C–F cleavage [8,9] with C–H activation [10–24] strategies [25–28], as elegantly developed by Loh [29–31], Li [32–34], Wang [33], and Ackermann [35,36], among others [37]. In this context, we have reported on a (*Z*)-selective manganese-catalyzed transformation [36]. Within our program on sustainable ruthenium (II)-catalyzed [38–43] C–H activation [44,45], we hence became attracted to exploring complementary (*E*)-selective ruthenium-catalyzed [46] C–H/C–F functionalization. To this end, we have now unraveled the unique chemoselectivity of ruthenium (II) catalysis to enable a facile switch from a common C–H hydroarylation [47,48] manifold [49] toward challenging C–H/C–F functionalization-based C–H allylations (Fig. 1) [50–71], on which we wish to report. Salient features of our findings include (i) unprecedented ruthenium-catalyzed C–H/C–F functionalization, (ii) highly *E*-diastereoselective C–H/C–F functionalization, (iii) a removable [12,72] directing group approach, and (iv) mechanistic insights into ruthenium-catalyzed C–H/C–F functionalizations.

2. Results and discussion

2.1. Optimization

We initiated our studies by probing various reaction conditions for the envisioned C–H/C–F functionalization with ketimine **1a** (Table 1). Thus, a switch in chemoselectivity from the typical hydroarylation regime (entries 1 and 2) toward allylative C–H/C–F activation proved viable by the use of a phosphine ligand and K_2CO_3 as the base (entries 1–3). Robust ruthenium (II) catalysis was operative in a range of aprotic solvents, including toluene, *meta*-xylene, 1,4-dioxane, and cyclohexane (entries 1–8). The base K_3PO_4 led to slightly improved yields of the desired ketone **3aa** upon one-pot hydrolysis (entries 8 and 9). Among a variety of ligands, the triaryl phosphine P(4-C_6H_4F)$_3$ was identified as being optimal (entries 9–17), particularly when trimethoxyphenylketimine **1b** was used as the substrate (entry 17 vs. 18). The *E*/*Z*-diastereoselectivities were slightly influenced by the choice of the ligand, generally favoring the *E*-diastereomer.

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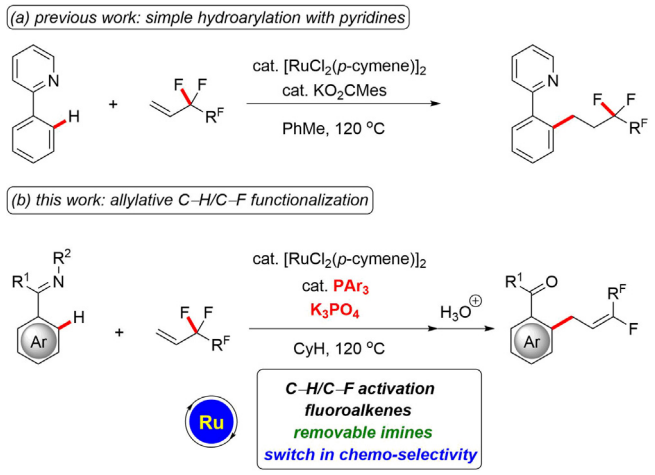
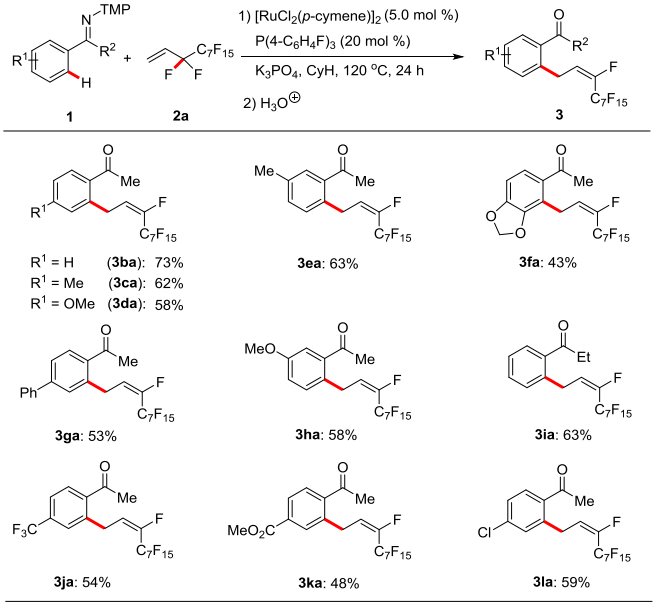


Fig. 1. Switch from hydroarylation to C–H/C–F functionalization by ruthenium (II) catalysis.



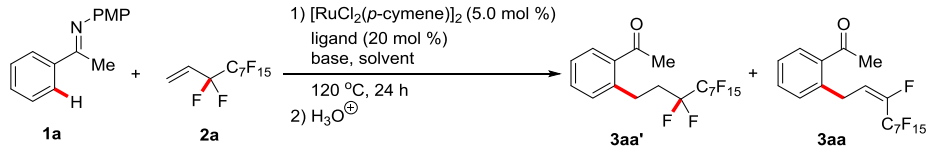
Scheme 1. C–H/C–F functionalization with ketimines **1** [73].

2.2. Reaction scope

With the optimized ruthenium (II)-catalyzed C–H/C–F functionalization in hand, we explored its versatility with differently substituted ketimines **1** (Scheme 1). The robust ruthenium (II) catalysis manifold proved to be tolerant of various valuable functional groups, such as chloro and ester substituents, which should prove invaluable for future late-stage diversification. The site selectivity of the C–H/C–F functionalizations in intramolecular competition experiments with meta-substituted arenes **1e**/**1h** was largely dominated by steric repulsion, unless a secondary directing group effect was exerted, as by dioxolone for ketone **3fa**. Generally, ruthenium (II) catalysis was characterized by high diastereo control, favoring the (*E*)-diastereomer with selectivities ranging from 2.3/1 to 5.3/1, while only very minor amounts of the corresponding hydroarylation products of less than 2% were observed [73].

The versatile ruthenium (II)-catalyzed C–H/C–F functionalization was not limited to alkene **2a** as the substrate. The perfluoroalkylalkenes **2** were likewise smoothly converted into the corresponding products **3**, exploiting the removable nature of the ketimine **1** within a user-friendly one-pot procedure (Scheme 2). Again, the C–H/C–F functionalization was characterized by high levels of chemo-, diastereo-, and position selectivities.

Table 1
Optimization of ruthenium (II)-catalyzed C–H/C–F functionalization.[a]



Entry	Ligand	Base	Solvent	*E*/*Z*	3aa′ [%]	3aa [%]
1	NaOAc	K_2CO_3	1,4-dioxane	–	85	–
2	–	KOH	1,4-dioxane	–	70	–
3	PPh_3	K_2CO_3	HFIP	–	–	–
4	PPh_3	K_2CO_3	PhMe	2.7	–	40
5	PPh_3	K_2CO_3	*m*-xylene	2.0	–	42
6	PPh_3	K_2CO_3	1,4-dioxane	2.0	–	45
7	–	K_2CO_3	CyH	–	–	–
8	PPh_3	K_2CO_3	CyH	2.5	–	42
9	PPh_3	K_3PO_4	CyH	2.8	–	53
10	PCy_3	K_3PO_4	CyH	2.0	–	8
11	dppf	K_3PO_4	CyH	–	–	–
12	$P(Cy)Ph_2$	K_3PO_4	CyH	2.7	–	35
13	$P(4\text{-}C_6H_4Cl)_3$	K_3PO_4	CyH	2.0	–	25
14	$P(4\text{-}C_6H_4Me)_3$	K_3PO_4	CyH	2.3	–	27
15	$P(4\text{-}C_6H_4OMe)_3$	K_3PO_4	CyH	3.0	–	28
16	$P(4\text{-}C_6H_4F)_3$	K_3PO_4	CyH	2.7	–	55
17[b]	$P(4\text{-}C_6H_4F)_3$	K_3PO_4	CyH	3.0	–	65
18[c]	$P(4\text{-}C_6H_4F)_3$	K_3PO_4	CyH	3.5	–	73

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), ligand (20 mol %), base (2.0 equiv), solvent (1.0 mL), 120 °C, 24 h, isolated yields.
[b] **2a** (1.5 mmol).
[c] TMP-ketimine **1b** (1.5 mmol) instead of PMP-ketimine **1a**. PhMe = toluene, HFIP = 1,1,1,3,3,3-hexafluoroisopropanol, CyH = cyclohexane, PMP = 4-methoxyphenyl, TMP = 3,4,5-trimethoxyphenyl.