Cobalt-Catalysed Enantioselective C(sp^3)–C(sp^3) Coupling

Y. Fu *et al. Nat. Catal.* **2021**, *4*, 901-911.

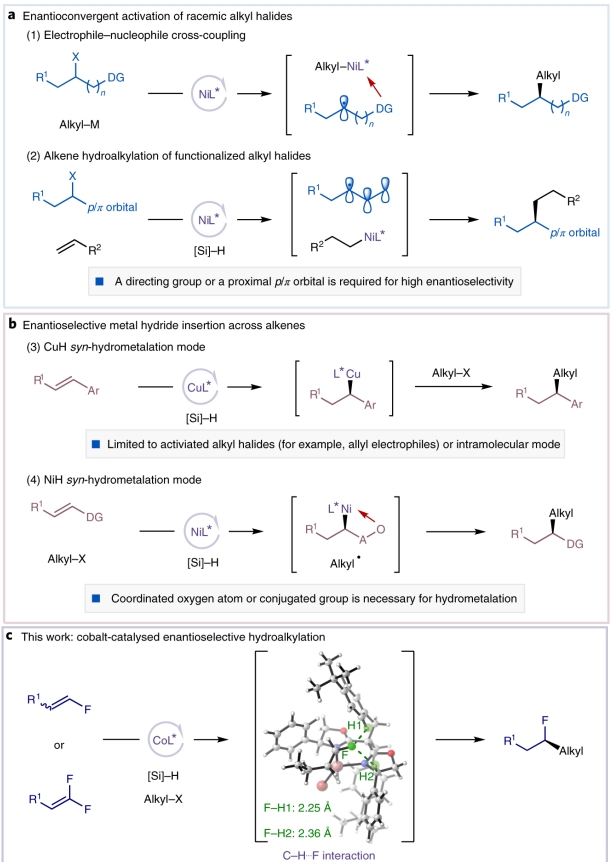
Introduction

Formation of alkyl–alkyl bond is one of the most attractive tools for building molecules. Herein, the authors report a cobalt-catalysed enantioselective C(sp^3)–C(sp^3) coupling reaction. The highly selective transformation with good efficiency, the wide substrate scope, and the fluoro-substituted stereocentre provides an outstanding resolution in the field of biochemical and pharmaceutical industry.

Previous Works

The strategy to the construction of an enantioenriched product has attracted numerous attentions since decades ago. A radical pathway starts from the activation of racemic alkyl halides is well studied (**Fig.1a**). The substrate must be bearing a suitable group to assist during the stereo-determining step such as a Lewis-basic directing group or a p/π orbital, which restrict the diversity/availability of substrate.

On the other hand, the route involves a metal hydride insertion has also been established well (**Fig. 1b**). For example the copper-hydride-catalysed hydroalkylation of internal alkynes is a widely used method, but is limited to activated alkyl halides. Very recently, a nickel-hydride-catalysed hydroalkylation was reported. In which, an oxygen directing group-stabilized intermediate is the key for stereo-determination. Such requirement of directing group, again, restrict the diversity of substrate.

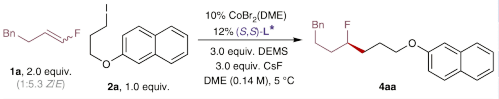


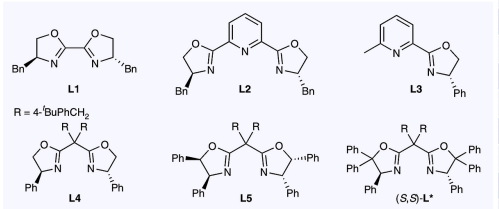
This Work

Cobalt, one of those low-toxic and economic metals, plays an important role in homogeneous catalysis like C–C bond formation, but rarely in enantioselective version. Herein, the authors report the cobalt-catalysed enantioselective hydroalkylation with the help of a cobalt-hydride system. The C–H···F interaction gives stabilising effect on the key intermediate which promotes this highly regio- and enantioselective transformation. Furthermore, the C–F on the stereocentre of product demonstrates the potential of access towards various pharmaceuticals and bioactive molecules (**Fig. 1c**)

> Optimisation of Conditions

Fluorine-containing fragment plays a significant role in organic reaction and biochemistry not only due to its biological activity, but also the incorporation with substrate. Thus, a fluorine-substituted substrate is chosen for the reaction, herein is **1a**, to react with alkyl iodide **2a**.





reactions were carried out under an argon atmosphere. Conditions: 1a (2.0 equiv.), 2a (1.0 equiv.), cobalt catalyst (10 mol %), ligand L* and L1–L5 (12 mol%), silane (3.0 equiv.), base (3.0 equiv.), solvent (0.14 M), 5 °C, 12 h. 0.1 mmol scale. ^{19}F NMR yield. Benzotrifluoride was used as an nternal standard. The e.e. value was determined by HPLC. [a]Isolated yield in parentheses. [b]15 °C.

Entry	Variants	Yield (%)	e.e. (%)
1	None	90 (85 *isolated*)	97
2	**L1**, **L2** or **L3**	trace	–
3	**L4**	37	91
4	**L5**	52	91
5	$CoCl_2$	64	96
6	CoI_2	35	96
7	$Co(acac)_2$	trace	–
8	$CoCl(PPh_3)_3$ or CoF_3	trace	–
9	PMHS	71	97
10	$MeEt_2SiH$	trace	–
11	Cs_2CO_3	40	98
12	KF	76	98
13	LiO*t*-Bu	17	85
14	1,4-Dioxane	23	91
15	Diglyme	86	96
16	DMA	8	59
17	MeCN, DCE or *i*-Pr_2O	trace	–

The standard conditions give 85% isolated yield and 97% of ee (**entry 1**). Ligand screening revealed the inefficiency of **L1**, **L2**, and **L3** (**entry 2**). Ligand **L4** and **L5** give moderate yield and slightly decreased ee (**entries 3-4**). Other cobalt(II) halides maintain high ee but yields are lower (**entries 5-6**). However, $Co(acac)_2$ is totally inert in this reaction (**entry 7**). Cobalt(I) and cobalt(III) are also inactive for this transformation (**entry 8**). Oxygen-bearing silanes like PMHS is applicable but $MeEt_2SiH$ is not capable (**entries 9-10**). Cs_2CO_3 and KF as base could maintain high ee but diminish yields (**entries 11-12**). But, both yield and ee are reduced by LiO*t*-Bu as base (**entry 13**). 1,4-Dioxane retains the selectivity but gives very low yield (**entry 14**). Diglyme is an equally good solvent for this reaction (**entry 15**) DMA is not suitable due to the low yield and ee of result (**entry 16**). However, lower-polarity solvents like MeCN, DCE or *i*-Pr_2O are totally inert (**entry 17**).

> Substrate Scope

With optimised conditions in hand, the authors investigated the substrate scope of both alkyl halides and fluoroalkenes.

In **substrate scope I (alkyl halide)**, this methodology shows a wide combability upon various enantio-non-pure alkyl bromides and iodides, provides moderate to good yields and reasonable ee. Those substrates include alkyl halides containing an ether, aryl ester, alkyl ester, trifluoromethyl, carbamate and keto carbonyl groups. Heterocycles containing substrates were also tolerated. Halogens containing substrates were also applicable. Natural product-derivatives were also feasible. In some cases, even different ratio of *E*/*Z* of substrates were investigated and all gave good yields and enantioselectivity.

In **substrate scope II (fluoroalkene)**, reactions proceeds with moderate to good yields and high enantioselectivity from numerous fluoroalkene, regardless of *E*- or *Z*-majored substrates were utilized. A broad set of synthetically valuable functional groups including arenes, furans, carbamates, phthalimides, sulphonamides, esters, internal alkenes, acetals, and many heterocycles were perfectly tolerated. Also some drug derivatives were also tested and giving good results.

To further demonstrate the utility of this methodology, the synthetic route of **4Br** was given in the bottom, which requires multiple steps to access the racemic product. However, this protocol could achieved the asymmetric synthesis of **4Br** by a shorter procedure.

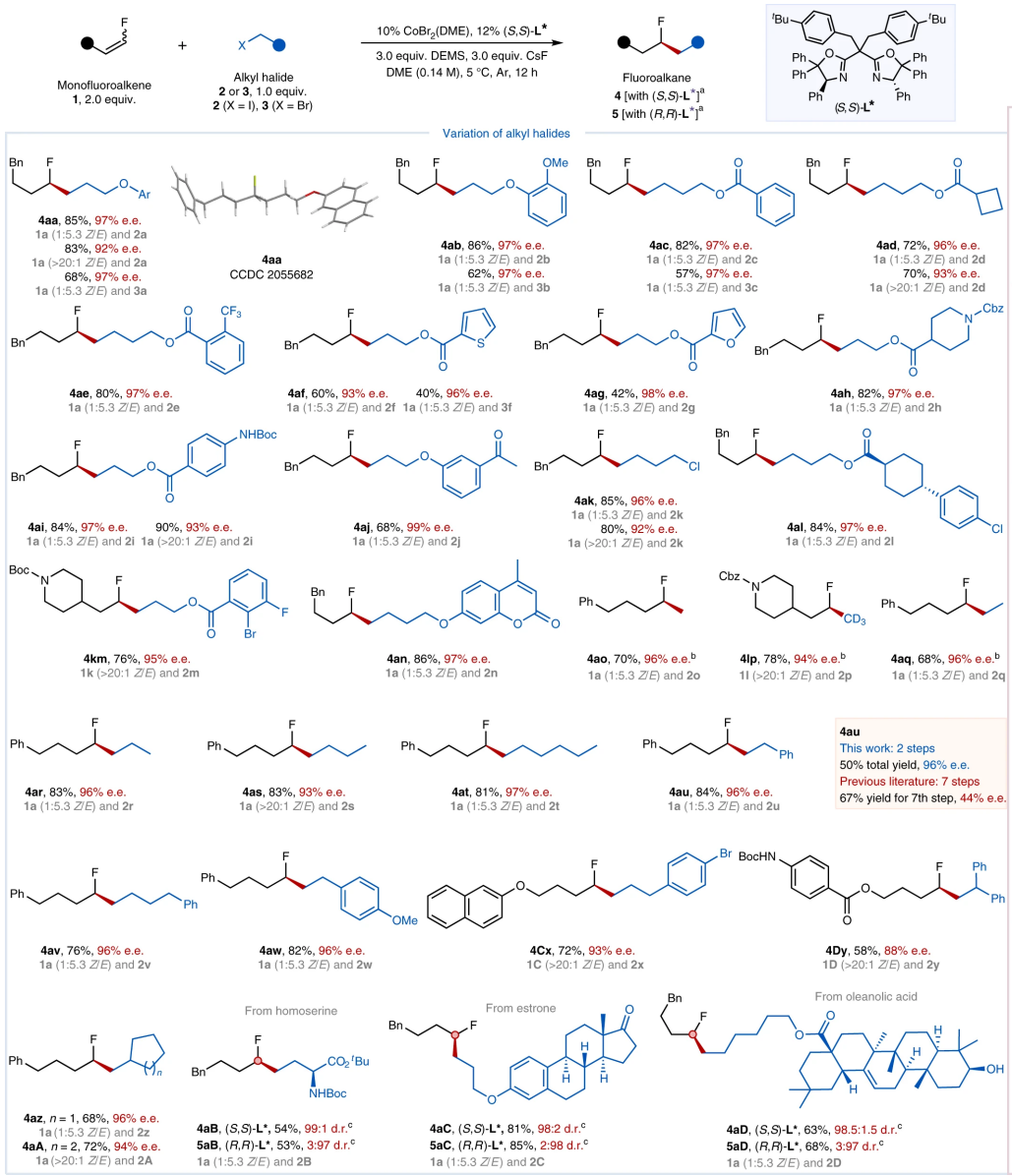


Fig. 3 | Scope of monofluoroalkenes in hydroalkylation. [a]Standard conditions as shown in Table 1 (0.2 mmol scale; isolated yield). [b]Diastereocentres are marked with a spherical symbol. d.r. and e.e. values were determined by HPLC or SFC. Ar, 2-naphthyl; Bz, benzoyl; Ts, tosyl; Martin's reagent, 1,1-dihydro-1,1,1-triacetoxy-1,2-benzoiodooxol-3(1*H*)-one; MOMO, methoxymethyl.

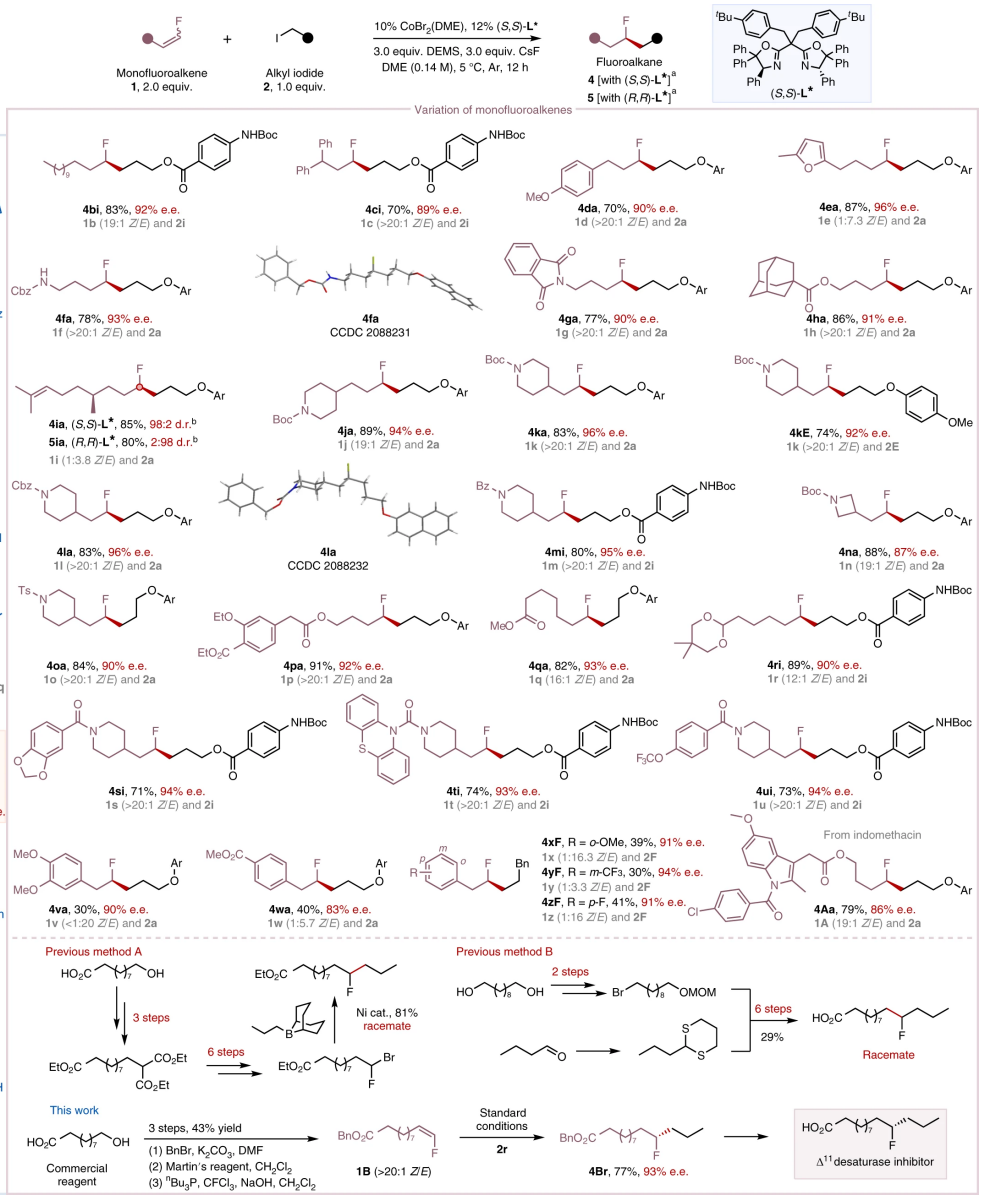


Fig. 2 | Scope of alkyl halides in hydroalkylation. [a]Standard conditions as shown in Table 1 (0.2 mmol scale; isolated yield). [b]Fluoroalkane **1** (1.0 equiv.) and alkyl iodide **2** (2.0 equiv.) were used. [c]Diastereocentres are marked with a spherical symbol. d.r. and e.e. values were determined by HPLC or supercritical fluid chromatography (SFC). Bn, benzyl; Ar, 2-naphthyl; Cbz, carbobenzyloxy; Boc, *t*-butoxycarbonyl; d.r., diastereomeric ratio.

> Mechanistic Study

Fig. a: When use **3G** which is containing a cyclopropane moiety, as the alkyl bromide into reaction conditions, only a mixture of ring-opened product **4aG** were obtained instead of ring-retained product **4aG'**. Moreover, when 6-iodohex-1-ene (**2H**) was subjected, cyclised product **4aH** as well as uncyclised product **4aH'** were obtained, and the uncyclised/cyclised ratio has a linear relationship with the concentration of cobalt catalyst (**see Fig. a, bottom**).

Fig. b: Thus, D-labelling experiment was conducted using Ph_2SiD_2 to study the stereochemistry. As a result, no H/D exchange observed in α position and observed only in β position. Furthermore, fluoroalkene **1d** featuring two different ratio of *E*/*Z* were used in the D-labelling, and the *E*/*Z* ratio and diastereoselectivity of product just matched the substrates in each case. Those results indicated a *syn*-hydrometalation of Co–H species occurring to the fluoroalkene with in a highly regio and enantioselective manner.

Fig. c: Kinetic isotope effect (KIE) experiments were performed with Ph_2SiH_2/Ph_2SiD_2 and a primary kinetic D isotope effect was found since the k_H/k_D value was 1.76. On the other hand, comparative experiment using **1a**/d_1-**1a** gave a 0.82 k_H/k_D value, which indicated a secondary kinetic D isotope effect.

Fig. d (1): A linear relationship was revealed between the enantio-purities of ligand and the corresponding product. Base on it, the combination of cobalt and the chiral ligand is probably involved in the *syn*-hydrometalation step.

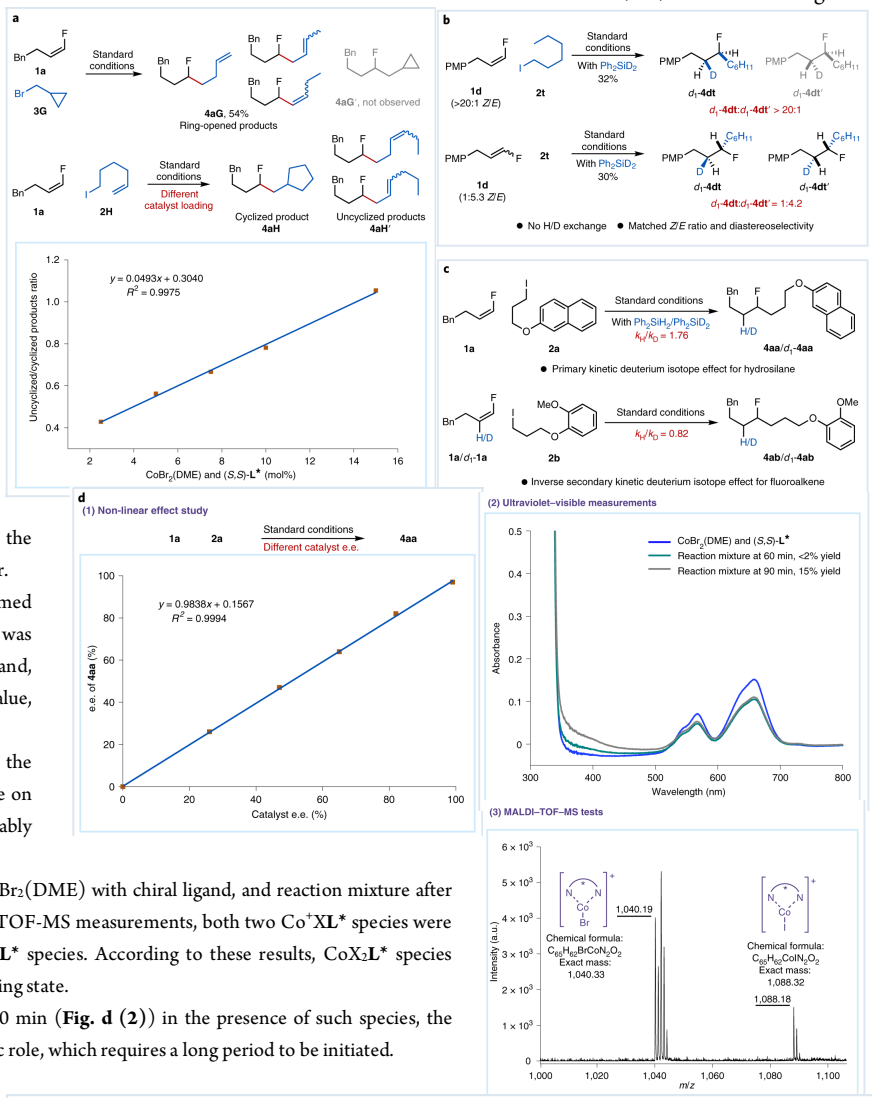


Fig. d (2)&(3): UV measurements of simple mixture of $CoBr_2$(DME) with chiral ligand, and reaction mixture after several time shown a mostly-matched curve. Also in MALDI-TOF-MS measurements, both two Co^+XL^* species were detected (X = Br, I), which indicated the presence of CoX_2L^* species. According to these results, CoX_2L^* species probably present in the reaction mixture thus might be the resting state.

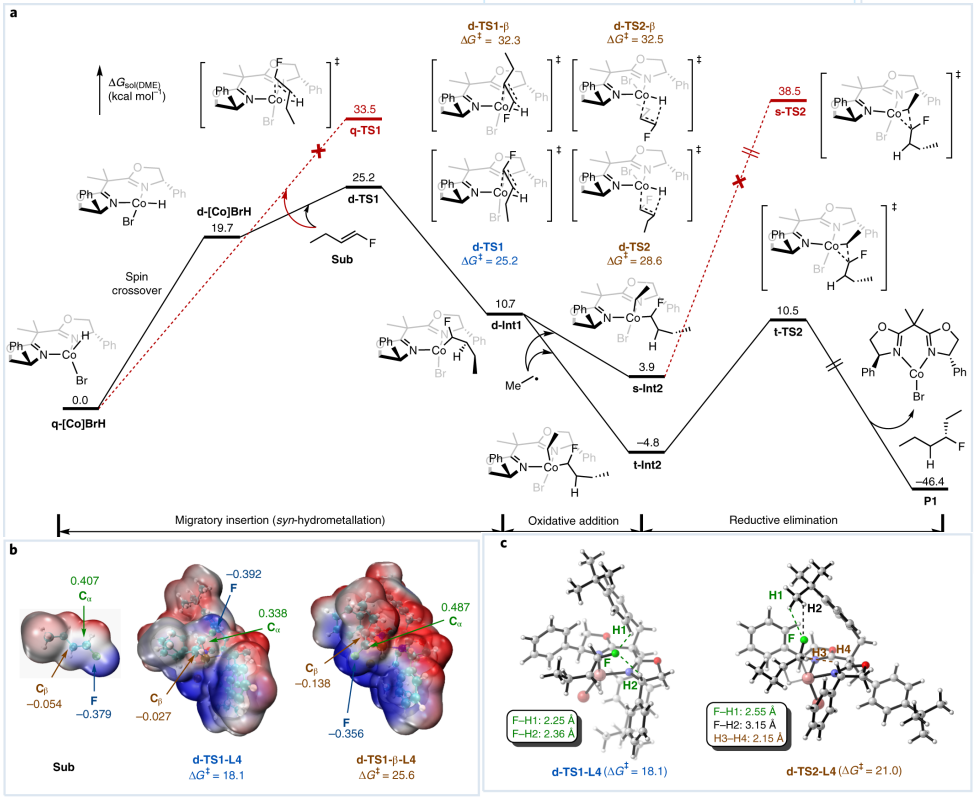
However, from the low yield of reaction mixture after 60/90 min (**Fig. d (2)**) in the presence of such species, the authors suggested that a Co–H species plays the actual catalytic role, which requires a long period to be initiated.

> Computational Study

a. At beginning of a simple mode, **q-[Co]BrH** is more stable than **d-[Co]BrH**, but migratory insertion is kinetically more feasible from doublet state (**q-TS1** vs **d-TS1**), thus a spin crossover is proposed. Four TSs in migratory insertion step were calculated, and the differences of Gibbs free energy clearly revealed the regio- and enantioselectivity of this step (**d-TS1** vs **other three**). Migratory insertion intermediate **d-Int1** next undergoes oxidative addition with alkyl radical to form **s-Int2** and **t-Int2**. The following reductive elimination prefers **t-Int2** due to its lower energy, to finally give the product.

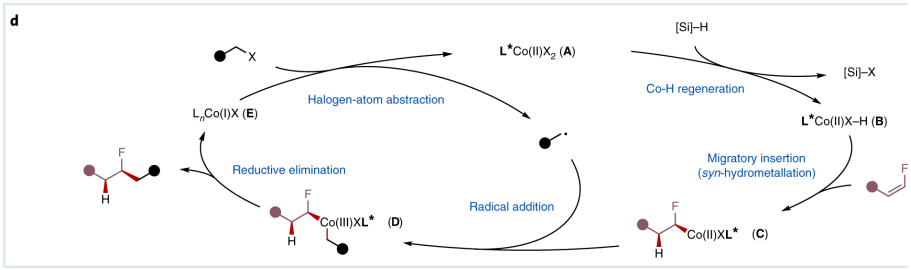
b. Energy barriers of substrate and two regioselective TSs of migratory insertion step were shown with actually used ligand **L4**. The regioselectivity at the fluoroalkene substrate (α vs β) is clearly revealed by the energy gap between **d-TS1-L4** and **d-TS1-β-L4** (18.1 vs 25.6). Moreover, the electron density on substrate increases in both case when Co–C bond forms at α or β position, while highly electronegative α-fluorine carbon could accelerate this step, and resulted in a lower energy on **d-TS1-L4** (18.1 vs 25.6).

c. Stereoselectivity was also studied based on two TSs of migratory insertion step and were shown. Indeed the energy gap could explain the stereoselectivity between **d-TS1-L4** and **d-TS2-L4** (18.1 vs 21.0). Moreover, in **d-TS1-L4** , the **F---H1** and **F---H2** interactions favour this TS. On the other hand, **F---H** distances become longer so that ineffective, and H3---H4 repulsion in **d-TS2-L4** will further destabilise this TS.



> Proposed Mechanism

Based on those results, a plausible mechanism is proposed in **Fig. d**. Co–H species **B** is formed from **A** in the presence of silane. Next, migratory insertion to fluoroalkene generate alkyl-Co species **C**. Then oxidative addition with alkyl radical forms dialkyl-Co species **D**, which releases the product and Co(I) via reductive elimination. Consequently, Co (II) is regenerated from Co(I) by halogen-atom abstraction.



> Defluorinative Hydroalkylation

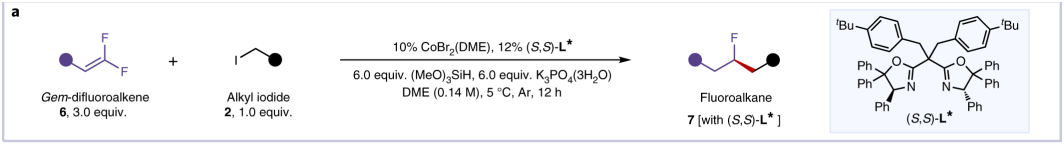
When use difluoroalkene as the substrate, a defluorinative hydroalkylation was found to proceed with maintaining the excellent enantioselectivity to give chiral fluoroalkane (**Fig. a**).

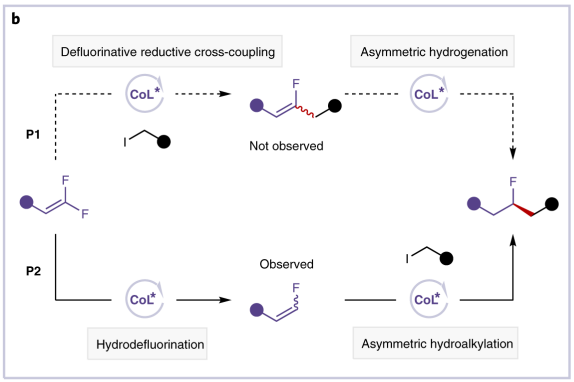
Two possible pathways were proposed in **Fig. b**. Pathway **P1** suggests a defluorinative reductive cross-coupling with alkyl iodide to form racemic alkyl-alkenyl fluoride, followed by asymmetric hydrogenation to finally give chiral product. In Pathway **P2** is shown a hydrodefluorination to form racemic alkenyl fluoride, then upon asymmetric hydroalkylation with alkyl iodide to give chiral product.

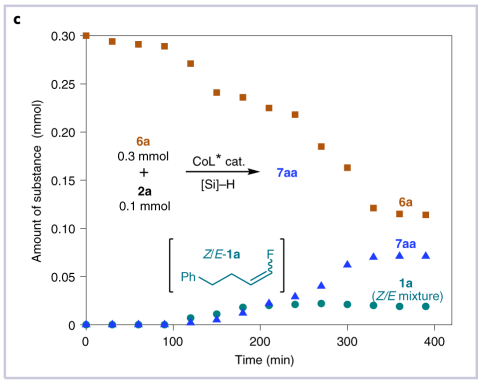
In actual experimental process, only racemic alkenyl fluoride from **P2** was detected, makes the second pathway highly possible.

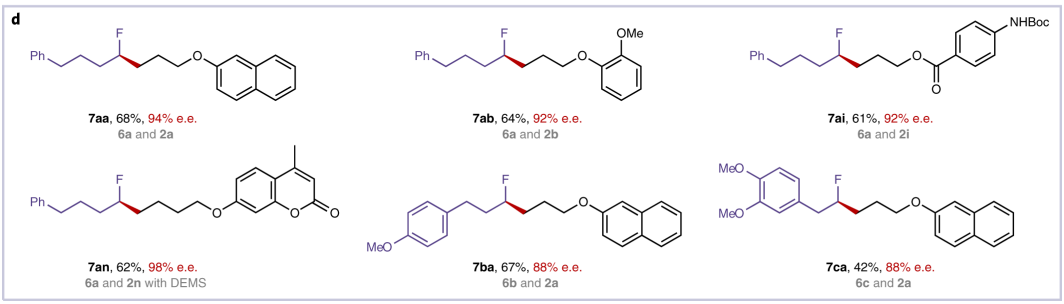
An NMR-tracking experiment in **Fig. c** further revealed this proposal, in which racemic alkenyl fluoride intermediate **1a** generates during consumption of substrate.

Finally, a simple substrate scope is shown in **Fig. d** to demonstrate this developed methodology featuring high efficiency and regio-/enantioselectivity.







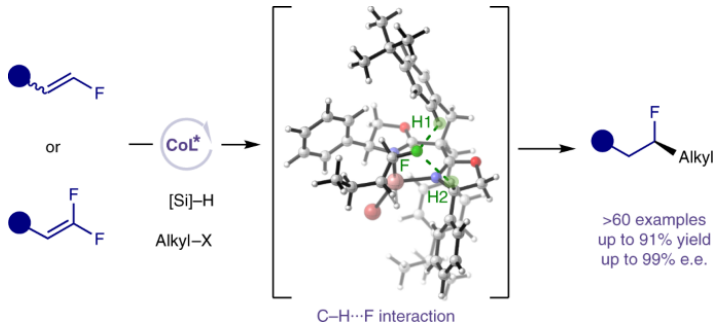


Conclusion & My Comment

The authors herein develop a cobalt-catalysed C(sp^3)–C(sp^3) reaction between fluoroalkenes and alkyl halides. This efficient reaction allows the highly regio- and enantioselective formation of product bearing a fluorine-substituted chiral centre.

The enantioselectivity is achieved by using the fluoroalkene substrate. In the key transition state, a significant interaction between (carbon)–hydrogen atom and fluorine atom create a stabilising effect to promote the stereo-determining step.

As an assistance/tool for understanding, the authors utilise density functional theory (DFT) calculation to demonstrate those effect on both steric and electronic aspects.



Furthermore, the fluorine-featuring substrate is not only assisting in the stereo-determining step, but also gives product with a fluorine atom at the chiral centre. Given the widely usage of fluorine-containing chemicals in drugs and bioactive molecules, this methodology will expand a new and wider platform in the field of pharmaceutical and biochemical industry, in my opinion.

Also, the use of cobalt which is one of the less toxic and low-expense metals, provides a more economic pathway for this type of transformation.