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Highly Efficient "On Water" Catalyst-Free Nucleophilic Addition Reactions Using Difluoroenoxysilanes: Dramatic Fluorine Effects[**]

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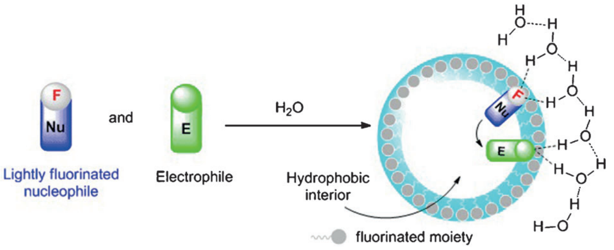
Dedicated to Professor Li-Xin Dai on the occasion of his 90th birthday

***Abstract:** A remarkable fluorine effect on "on water" reactions is reported. The C−F⋯H−O interactions between suitably fluorinated nucleophiles and the hydrogen-bond network at the phase boundary of oil droplets enable the formation of a unique microstructure to facilitate on water catalyst-free reactions, which are difficult to realize using nonfluorinated substrates. Accordingly, a highly efficient on water, catalyst-free reaction of difluoroenoxysilanes with aldehydes, activated ketones, and isatylidene malononitriles was developed, thus leading to the highly efficient synthesis of a variety of α,α-difluoro-β-hydroxy ketones and quaternary oxindoles.*

Since the landmark work of Sharpless and co-workers,[1a] "on water" catalysis has been established as a powerful strategy in organic synthesis.[1] It is very important to explore the potential of this methodology in the synthesis of value-added products, as water is a cheap, safe, and an environmentally benign solvent. Generally, on water reactions rely on the heterogeneity of reaction mixtures, and the rate acceleration is related to the unique chemistry between water and reactants at the phase boundary, where hydrogen-bonding interactions play an important role.[1] Many organic reactions have been tried under on water conditions to improve synthetic efficiency, however, the influences of fluorine substitution[2] on a reaction under such conditions remains to be explored.[3] In contrast to the hyper-hydrophobicity of highly fluorinated compounds, a single fluorine substitution on an aliphatic chain actually reduces the hydrophobicity.[2] Accordingly, we envisioned that C−F⋯H−O interactions[4] might bring about beneficial effects to on water reactions.

For example, through the interactions with hydrogen-bond networks at the phase boundary, the fluorinated moiety of the nucleophile and the hydrophilic part of the electrophile might be organized at the periphery of the oil droplet, while the hydrophobic part is positioned within the hydrophobic interior (Scheme 1). As a result, the free hydroxy groups at the interface can only stabilize both the reactants and the transition state,[1i] but importantly, they organize both reaction partners into a favorable orientation to facilitate the desired reaction. Therefore, it is possible to take advantage of such effects to develop on water reactions, which could not be realized by using nonfluorinated nucleophiles, even in the absence of any catalyst, to enable the synthesis of valuable fluorinated products.[5]



Scheme 1. Schematic of the fluorine effects on on water reactions.

This hypothesis, along with our previous finding that C−F⋯H−N interactions dramatically affected the cyanation of ketimines,[6ab] encouraged us to explore the possible effects of fluorine substitution on on water reactions as part of our work on selective introduction of fluoroalkyl groups.[6] The difluoroenoxysilane **1**[7] (for structures see Table 1) was used as the ideal fluorinated nucleophile to initiate our study because it only contained a CF_2 group as the hydrophilic part, and could simplify the analysis. The on water, catalyst-free aldol reaction using **1** was first examined, in view of the versatility of the product α,α-difluoro-β-hydroxy ketones **3**,[8] for the synthesis of difluoromethylated compounds[9] which are of current interest in medicinal research.[10] In addition, while several Lewis acid catalyzed protocols are known,[7a,8ab] a metal-free version is lacking, and an on water, catalyst-free method would avoid heavy-metal contamination of the products. It should also be noted that although much progress had been made in the Lewis acid catalyzed aldol reaction of nonfluorinated trimethylsilyl (TMS) based nucleophiles in

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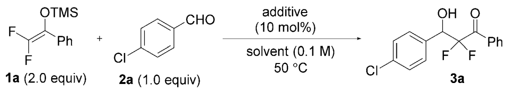
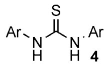
water,[11a] the corresponding on water, catalyst-free processes are rare and limited to the reactions using highly active aldehydes or TMS-based nucleophiles.[11b–d]

To our delight, the on water reaction of **1a** with the aldehyde **2a** was complete within 10 hours at 50 °C to give the product **3a** in 85 % yield (entry 1, Table 1). Remarkably, the reaction was much more efficient than those run in organic solvents (see the Supporting Information). We had previously discovered that 4-dimethylaminopyridine (DMAP) could effectively activate **1** to react with isatins or β,γ-unsaturated α-ketoesters in THF,[6de] however, it catalyzed the present reaction very slowly (entry 2). The thiourea **4** [Ar = 3,5-$(CF_3)_2C_6H_3$][12] was inefficient as well, thus affording **3a** in only 43 % yield, even after six days (entry 3). These results unambiguously showed that the development of a metal-free protocol of this reaction was not trivial. The heterogeneity proved to be very important,[13] as the homogeneous reaction using a mixed solvent of THF/H_2O (7:1, v/v) gave **3a** in a low yield (entry 4). The use of a Brønsted acid might affect the microenvironment at the phase boundary, thus leading to a reduced yield. For example, the use of $PhSO_3H$ decreased the yield of **3a** from 85 % to 70 % (entry 1 versus entry 5). The use of a surfactant,[14] either *p*-dodecylbenzenesulfonic acid or sodium dodecyl sulfonate, to improve the reaction efficiency was tried, but resulted in no positive result (entries 6 and 7), possibly because of the interference of the surfactant on the microenvironment of the reaction. Noticeably, no reaction took place under solvent-free conditions (entry 8), thus indicating the rate acceleration was not a result of the increase in the effective concentration of the reactants.

Table 1: Representative results.

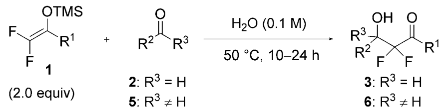


Entry[a]	Solvent	Additive	*t* [h]	Yield [%][b]
1	H_2O	–	10	85
2	THF	DMAP	72	10
3	THF		144	43
4	THF/H_2O[c]	–	24	21
5	H_2O	$PhSO_3H$	10	70
6	H_2O	4-$C_{12}H_{25}C_6H_4SO_3H$	10	77
7	H_2O	$C_{12}H_{25}SO_3Na$	10	79
8	neat	–	10	–

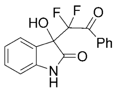
[a] On a 0.25 mmol scale. [b] Yield of isolated product. [c] THF/H_2O (7:1, v/v). THF = tetrahydrofuran.

The scope of this on water, catalyst-free protocol with respect to the difluoroenoxysilanes **1** and aldehydes **2** was then examined by running the reaction at 50°C (Table 2). First, it should be pointed out that this catalyst-free, on water protocol could be used for preparative synthesis, as demonstrated by a scaled up reaction using 6.0 mmol of **2a**, which afforded **3a** in 1.55 grams with 86 % yield (entry 2). Generally, the benzaldehydes **2a–i** worked well with **1a** to give the products **3a–i** in good to high yield (entries 1–10). 2-Naphthyl aldehyde (**2j**) provided the product **3j** in 62 % yield (entry 11), and thiophene-2-carbaldehyde (**2k**) gave the desired product **3k** in lower yield as well (entry 12). The aliphatic aldehyde **2l** gave **3l** in higher yield by using saturated NaCl (aq.) as the solvent. Both aryl and aliphatic difluoroenoxysilanes (**1a–f**) worked well with **2a** to give the corresponding products **3a** and **3m–q** in good yield (entries 1 and 14–18), but the aryl-substituted **1a–e** gave the corresponding products in higher yields. The activated ketones **5**, such as isatins and β,γ-unsaturated α-ketoesters, were also viable substrates for this on water reaction, thus giving the desired products **6a–h** in high yield.

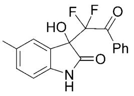
Table 2: Substrate scope of Mukaiyama aldol reaction.



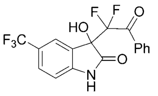
Entry[a]	R^1	R^2	**3**	Yield [%][b]
1	**1a**: Ph	**2a**: *p*-ClC_6H_4	**3a**	85
2[c]	**1a**: Ph (6.0 mmol)	**2a**: *p*-ClC_6H_4	**3a**	86
3	**1a**: Ph	**2b**: *o*-ClC_6H_4	**3b**	78
4	**1a**: Ph	**2c**: *m*-ClC_6H_4	**3c**	80
5	**1a**: Ph	**2d**: *p*-$NO_2C_6H_4$	**3d**	94
6	**1a**: Ph	**2e**: *p*-$CF_3C_6H_4$	**3e**	84
7	**1a**: Ph	**2f**: *p*-CNC_6H_4	**3f**	80
8	**1a**: Ph	**2g**: Ph	**3g**	64
9	**1a**: Ph	**2h**: *m*-MeC_6H_4	**3h**	76
10	**1a**: Ph	**2i**: *p*-$MeOC_6H_4$	**3i**	61
11	**1a**: Ph	**2j**: 2-naphthyl	**3j**	62
12	**1a**: Ph	**2k**: thienyl	**3k**	48
13[d]	**1a**: Ph	**2l**: $PhCH_2CH_2$	**3l**	33
14	**1b**: *p*-ClC_6H_4	**2a**: *p*-ClC_6H_4	**3m**	94
15	**1c**: *m*-MeC_6H_4	**2a**: *p*-ClC_6H_4	**3n**	93
16[e]	**1d**: 2-naphthyl	**2a**: *p*-ClC_6H_4	**3o**	66
17	**1e**: *p*-$MeOC_6H_4$	**2a**: *p*-ClC_6H_4	**3p**	85
18	**1f**: $PhCH_2CH_2$	**2a**: *p*-ClC_6H_4	**3q**	59



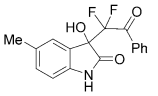
6a: 91%



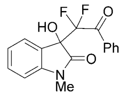
6b: 84%



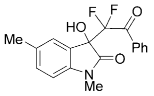
6c: 87%



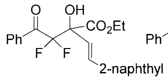
6d: 85%



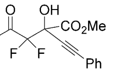
6e: 96%



6f: 99%



6g: 62%

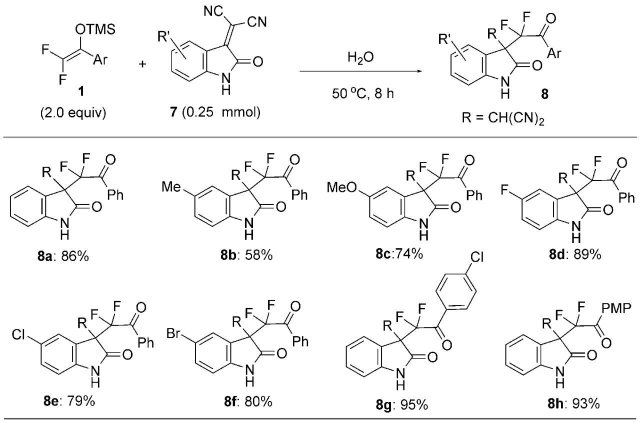


6h: 82%

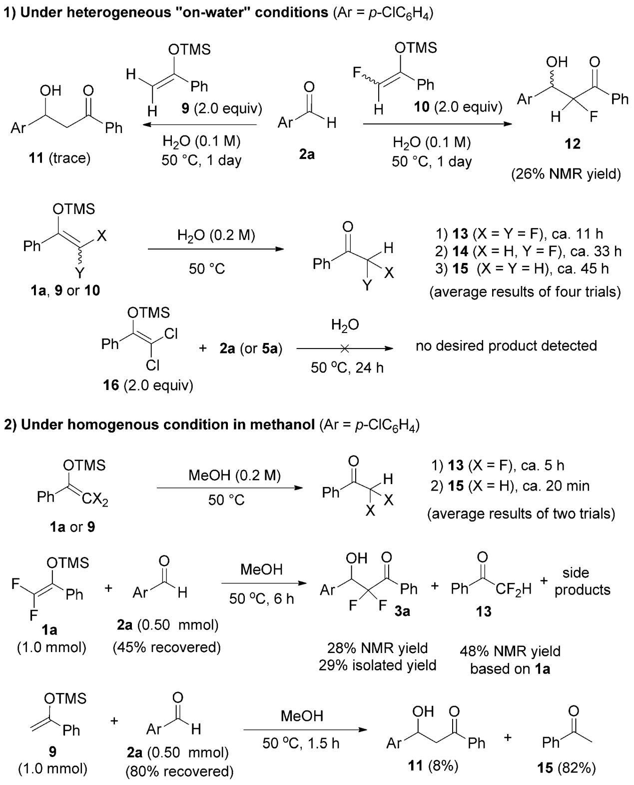
[a] On a 0.25 mmol scale. [b] Yield of the isolated product. [c] On a 6.0 mmol scale. [d] Saturated NaCl (aq.) as the solvent and on a 1.0 mmol scale. [e] Used 1.2 equiv of **1d**.

The α,α-difluoro-β-hydroxy ketones **3** are versatile building blocks, and could be readily transformed into difluoromethylated hydroxy esters, diols, *anti*-2,2-difluoropropane-1,3-diols, aminoalcohol, and 3,3-difluoroazetidine (for full substrate scope of Mukaiyama aldol reaction and the product elaborations, see the Supporting Information).

Interestingly, an unprecedented Mukaiyama–Michael addition of the difluoroenoxysilanes **1** to the isatylidene malononitriles **7** worked well on water, thus allowing efficient construction of the quaternary oxindoles **8** featuring a CF_2 group at the C3-position (Scheme 2). Remarkably, this reaction represents a rare example of on water, catalyst-free construction of quaternary carbon centers.[1] It should be noted that the synthesis of quaternary oxindoles is of current interest[15] because of the need for privileged scaffolds in medicinal research.



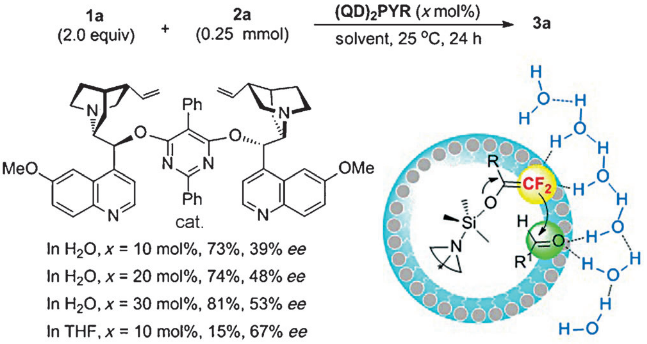
Scheme 2. Mukaiyama–Michael addition using **1**.



The high efficiency of these catalyst-free, on water reactions of difluoroenoxysilanes is impressive, and obviously resulted from the difluorine substitution, as revealed by the following control experiments. First, the on water reaction of the nonfluorinated silyl enol ether **9** and **2a**, although not reversible,[16] gave only trace amounts of the product **11**, with almost complete hydrolysis of **9**. In contrast, the presence of enough fluorine atoms on the enol silyl ether was also important, as the monofluorinated analogue **10** reacted with **2a** sluggishly to give **12** in only 26% yield (NMR) under the same reaction conditions. Noticeably, the difluoroenoxysilane **1a** hydrolyzed at a much faster rate than both **9** and **10** in the absence of the aldehyde **2a**. These observations could not be explained by the reactivity difference between **9** and **1a**, because although there is a difference in reactivity, it is not that significant (**9** is two times more reactive than **1a** in palladium-catalyzed arylation reactions,[7d] but is less reactive in a Brønsted acid catalyzed Mannich reaction[7g]). In addition, although chlorine is highly electronegative, the dichloroenoxysilane **16** failed to react with **2a** or the isatin **5a** to give the desired aldol adduct. More surprising results came from the homogeneous reactions run in MeOH. Despite the methanolysis of **9** within 20 minutes, the reaction of the nonfluorinated **9** and **2a** gave the adduct **11** in 8% yield upon isolation, and is in sharp contrast to the fact that only trace amounts of **11** were detected under on water conditions, even though it took about 45 hours for the complete hydrolysis of **9** under on water conditions. In addition, while both C–F···H–O interactions and hydrogen-bonding activation of **2a**[17] could be expected, the homogeneous reaction of **1a** and **2a** in MeOH provided **3aa** in only 29% yield, accompanied by side products (see the Supporting Information for detailed discussion).

To account for why the reaction of **1a** and **2a** proceeded much more efficiently on water (heterogeneous) than in MeOH (homogeneous), but that of **9** and **2a** worked substantially better in MeOH than under on water conditions, we propose that oil droplets, formed from **1a** and **2a** on water, have a microstructure different from those formed between **9** and **2a**. Through the hydrogen-bonding interactions with both the CF_2 group of **1** and the carbonyl group of **2**, as suggested in Scheme 1, the network of hydroxy groups at the phase boundary elegantly preorganizes both reaction partners to react with each other. Without such organization through C–F···H–O interactions, the microstructure of the oil droplets derived from **9** and **2a** might result in an unfavorable orientation of the reactants, thus making it difficult for **9** to approach the aldehyde and leading to almost complete hydrolysis of **9**.

According to this mechanistic insight, the hydrophobic TMS moiety of **1** should be positioned within the interior of the oil droplet. Therefore, it was possible to use a chiral Lewis base to activate **1a** from the interior of the droplet and cooperate with the hydrogen-bonding interactions at the periphery to realize asymmetric synthesis. Indeed, when $(QD)_2PYR$[18] was used, **3aa** was obtained in 73% yield and 39% *ee*. Increasing the loading of $(QD)_2PYR$ from 10 mol% to 30 mol% resulted in the increase of the *ee* value of **3aa** from 39 to 53%,[19] possibly because $(QD)_2PYR$ was dis-



persed into more oil droplets, thus reducing the background reaction. The rate acceleration effect of the on water conditions was obvious, as reaction in THF gave **3aa** in only 15 % yield, albeit in 67 % *ee*. These results further support the proposed mechanism, even though there is ample room for further improvements on the *ee* value of **3**. It should be also noted that the organocatalytic asymmetric aldol reaction of **1** with aldehydes is unprecedented.[20]

The crucial role of the C–F···H–O interactions in the C–C bond-formation step of this protocol was further supported by density functional theory (DFT) calculations using a five-water model. The Gibbs free-energy profile and the optimized structures of the transition state (TS) are shown in Figure 1. The results reveal that in the transition-state $\mathbf{TSII}_{(5\,H_2O)}$, a short C–F···H–O contact[4] (bond length 2.219 Å; bond angle of F···H–O, 145°) does indeed exist between dangling free OH groups of the five-water assembly and the CF_2 moiety of **1a**, together with double hydrogen bonds between the carbonyl group of the aldehyde and water. On one hand, hydrogen-bonding interactions activated **2a** and stabilized the negative charge developed at the oxygen atom in the transition state. On the other hand, the C–F···H–O interactions effectively organized **1a** in a favorable orientation for the reaction. Such cooperative hydrogen-bonding interactions decreased the total activation energy by 10.3 kcal mol^{-1}, from 33.6 kcal mol^{-1} (calculations based on a three-water model optimized TS in which only hydrogen-bonding interactions between water and **2a** existed) to 23.3 kcal mol^{-1}. Calculations also revealed that without the assistance of water the reaction proceeded through a concerted mechanism with a reaction barrier of up to 41.6 kcal mol^{-1}. These results further showed the importance of C–F···H–O interactions in lowering the activation barrier. Not unexpectedly, the transition state of the reaction using **9** and the dichloroenoxysilane **16** was not located, possibly because of the lack of effective C–F···H–O interactions with water. For computational methods, data, and a detailed discussion, see pages 34–56 of the Supporting Information.

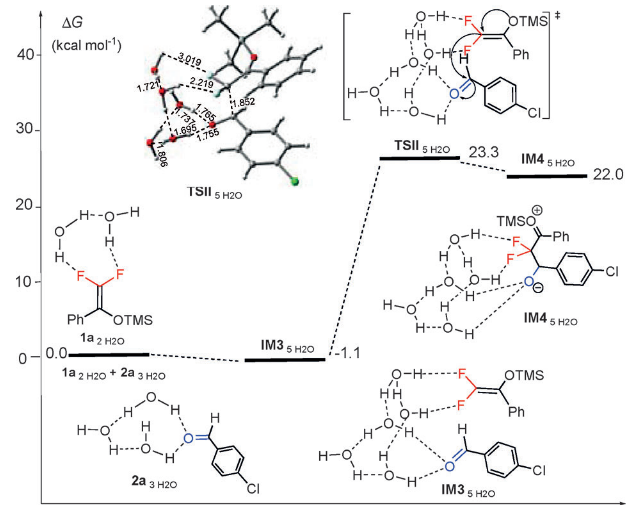


Figure 1. DFT calculations using a five-water model.

In conclusion, we have demonstrated, by experimental and theoretical studies, that the C–F···H–O interactions between the fluorinated nucleophile and the hydrogen-bond network at the phase boundary are able to cooperate with the hydrogen-bonding activation of the electrophile to facilitate on water reactions, which are unattainable by using non-fluorinated substrates. An on water, catalyst-free reaction of the difluoroenoxysilanes **1** with aldehydes, activated ketones, and isatylidene malononitriles was developed, thus allowing highly efficient synthesis of valuable α,α-difluoro-β-hydroxy ketones and quaternary oxindoles. Further investigation of this dramatic fluorine effects in other on water reactions is now in progress in our laboratory.

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at the begining of reaction	at the end of reaction

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