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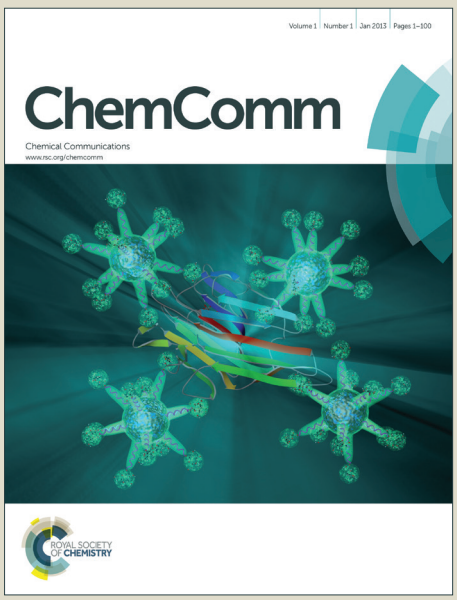

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A simple base-mediated synthesis of diverse functionalized ring-fluorinated 4*H*-pyran via double direct C-F substitutions†

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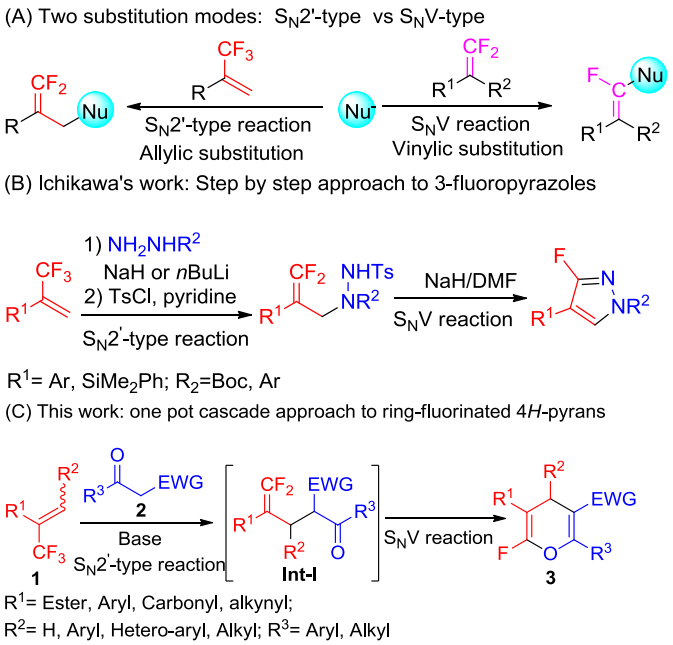
A straightforward and efficient approach to structurally diverse and synthetically useful ring-fluorinated 4*H*-pyrans via a simple base-mediated cascade reaction of readily available trifluoromethylated alkenes with 1,3-dicarbonyl compounds was developed. The key events of this reaction involve two consecutive C-F substitutions under very mild conditions.

Owing to the nature of the C-F bond with high bond energy, the activation or cleavage of C-F bond to produce more valuable fluorinated or non-fluorinated organic compounds poses considerable challenge in organic synthesis[1] Therefore, the development of mild and effective methods for the C-F bond transformations, in particular, those transformations of readily available starting materials, have received much attention in past years.[2-3] 2-Trifluoromethyl-1-alkenes and terminal *gem*-difluoroalkenes received considerable attention due to their readily availabe and high reactivity with nucleophiles through S_N2' reaction or S_NV reaction processes, which provide an excellent opportunity to synthesize synthetically valuable and structure diversity partially fluorinated or non-fluorinated compound$_s$ (Scheme 1A).[4] For example, Ichikawa and co-workers have recently developed an elegant step by step approach to 3-fluoropyrazoles from simple 2-aryl-3,3,3-trifluoroprop-1-enes and hydrazine by combination of two types of substitutions (Scheme 1B).[5] The first substitution is the S_N2'-type reaction of 3,3,3-trifluoroprop-1-enes with lithio- or sodio-hydrazines affording *gem*-difluoroalkenes, the other substitution is a S_NV reaction via a normally disfavored 5-*endo-trig* cyclization process according to Baldwin's rules.[6] This disfavored cyclization might be promoted by intramolecular vinylic addition-elimination process.[4b] With respect to step- and atom-economy, the one-pot cascade approach to flurorinated heterocycles by the combination of two types of substitution of C-F bonds is considered to be the most straightforward and efficient one but with considerable challenge.

As a continuation of our interest in the chemistry of 2-trifluoromethyl-1, 3-enynes with functional nucleophiles,[7] we envisioned that terminal or internal trifluoromethylated alkenes **1** might readily react with bisnucleophiles such as 1,3-dicarbonyl compounds **2** to afford diverse functionalized ring-fluorinated 4*H*-



Scheme 1. Background and concept of monofluorine 4*H*-pyran construction.

pyrans **3** via a one-pot tandem reaction through intermediate **Int-I** under simple basic reaction conditions (Scheme 1C). It is well known that 4*H*-Pyrans have been identified as potential and specific IKCa channel blockers[8] that are proposed as potential therapeutic agents for diseases such as sickle cell anaemia, secretory diarrhoea, cystic fibrosis, autoimmune diseases and restenosis.[9] In addition, fluorine-containing organic molecules often possess elevated reactivity, lipophilicity, and bioactivity compared to their nonfluorinated counterparts.[10] Among the compounds bearing fluorine atoms, ring-fluorinated heterocycles containing only one fluorine atom (monofluorinated heterocycles) constitute an important family of organic compounds with a wide array of applications ranging from drugs to multi-ton industrial intermediates.[11] However, to

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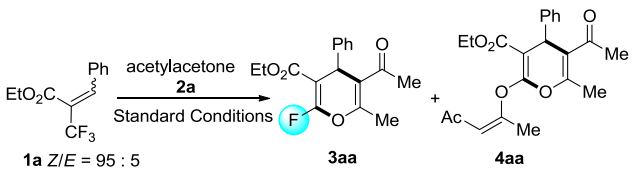
the best of our knowledge, the methods for the synthesis of ring-monofluorinated 4*H*-pyrans have not been well explored to date.[12]

To validate the above hypothesis, ethyl 3-phenyl-2-(trifluoromethyl)acrylate **1a** was used as model substrate, which could be easily prepared from readily available α-iodo-α,β-unsaturated esters and methyl fluorosulphonyldifluoroacetate.[13] After numerous attempts, we are pleased to find that the reaction of acetylacetone **2a** with **1a** could deliver the desired monofluorinated 4*H*-pyran **3aa** in 73% isolated yield under the standard conditions: K_2CO_3, DMF, RT (Table 1, entry 1). It should be noteworthy that the molar ratio of starting materials has dramatic effects on the selectivity of **3aa** and byproduct **4aa** (Table 1, entries 2-5). Byproduct **4aa** was formed via the further unusual *O*-conjugate S_NV reaction of **3aa** with **2a**. The *Z*-alkene geometry of **4aa** was confirmed by NOE experiment (*see* ESI) , which is consistent with fact that linear β-diketones exist predominantly in the *cis*-enol form.[14] The use of 4 Å molecular sieves was slightly effective to give a relative higher yield of **3aa** (Table 1, entry 4 vs entry 5). All other tested solvents, either polar or nonpolar solvents such as THF, CH_3CN, Toluene and DCM resulted in lower yields or shutting down the reaction (Table 1, entries 6-9). The screening of other inorganic or organic bases could not give better results (Table 1, entries 10-13).

Table 1. Initial reaction discovery and optimization[a]

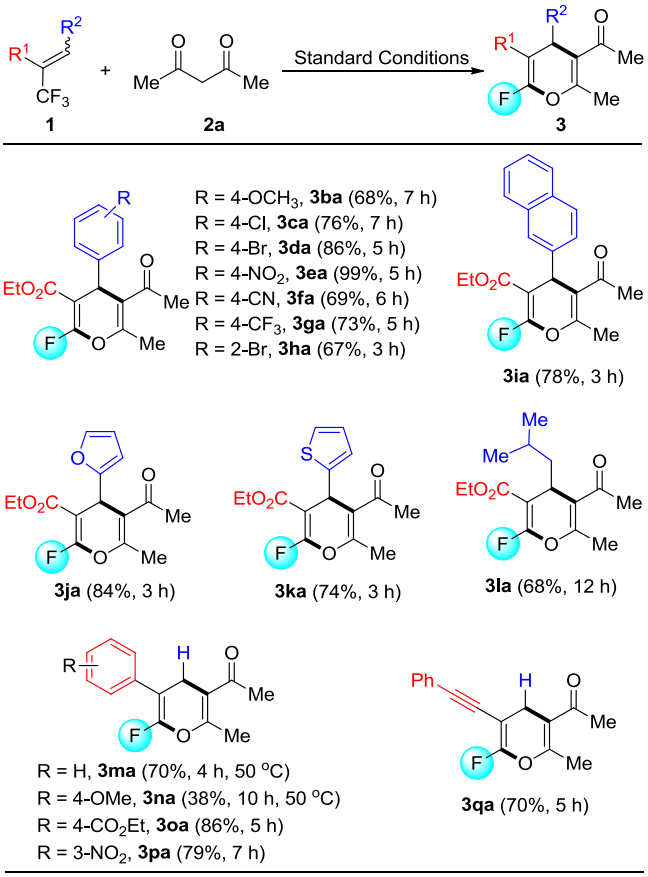


1a *Z*/*E* = 95 : 5 **3aa** **4aa**

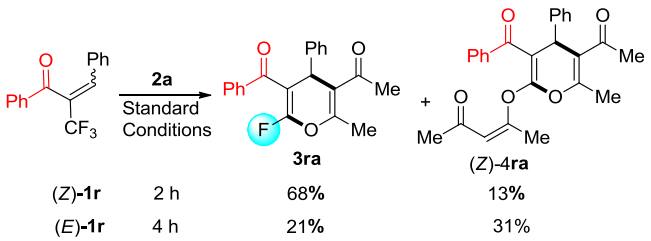
Entry	Variation from standard conditions	**3aa** (%)[b]	**4aa** [%][b]
1	none	80 (73)	0
2	**1a** : **2a** = 2 : 1	70	trace
3	**1a** : **2a** = 1.5 : 1	64	9
4	**1a** : **2a** = 1 : 1.5	56	16
5	**1a** : **2a** = 1 : 1.5[c]	50	12
6	CH_3CN instead of DMF	15	8
7	THF instead of DMF	9	0
8	Toluene instead of DMF	0	0
9	DCM instead of DMF	0	0
10	NaOH instead of K_2CO_3	48	trace
11	Na_2CO_3 instead of K_2CO_3	67	trace
12	DBU instead of K_2CO_3	24	trace
13	Et_3N instead of K_2CO_3	0	0

[a] Standard Conditions: **1a** (3.0 equiv), **2a** (0.2 mmol), K_2CO_3 (1.2 equiv), 4 Å MS (100 mg), DMF, RT, 6 h, Ar. [b] The NMR yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard; yields of isolated product are shown in parentheses. [c] 4 Å MS was not added.

With the standard reaction conditions in hand, we next examined the substrate scope and limitation of this reaction. Firstly, the reaction scope was investigated by variation of the component of trifluoromethylated alkenes **1** (Scheme 2). There are several points noteworthy: (1) The substituent R^1 has a significant impact on present transformation, the reaction with substrates **1** bearing electron-withdrawing R^1 group such as ester group proceeded smoothly under standard reaction



Scheme 2. Scope of trifluoromethylated alkenes **1**



Scheme 3. The reaction of **1r** with acetylacetone **2a**

conditions, delivering the desired fully substituted ring-monofluorinated 4*H*-pyrans **3** in moderate to excellent yields (Scheme 2, **3ba-3la**). A range of various electron-donating and -withdrawing substituted aryl, heteroaryl and even alkyl group could be well introduced to the 4-position of the pyrans (Scheme 2, **3ba-3la**); (2) If R^1 ester group was switched to aryl group, the electron-withdrawing substituents on the aryl group is beneficial to the reaction and higher yields could be obtained (Scheme 2, **3ma-3pa**); (3) Substituted alkynyl group could also be used as activating group and the desired product **3qa** bearing a synthetically useful alkyne moiety was isolated in 70% yield. The structure of **3qa** was unambiguously confirmed by X-ray crystallography;[15] (4) Additionally, it should be emphasized that in most cases byproduct **4** could not be detectable. However, the reactions of (*Z*)-**1r** or (*E*)-**1r** derived from α, β-unsaturated ketone with **2a** would afford not only the desired mono-fluorinated 4*H*-pyran **3ra** but also the defluorination adduct (*Z*)-**4ra** in 13% and 31% yield, respectively. The (*Z*)-isomer exhibited more reactive than the (*E*)-isomer in terms

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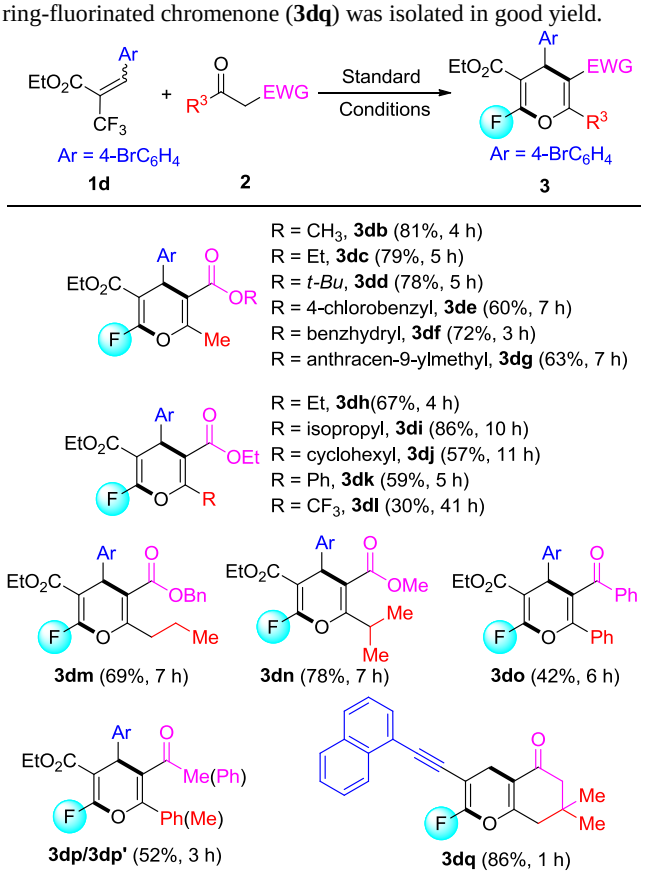
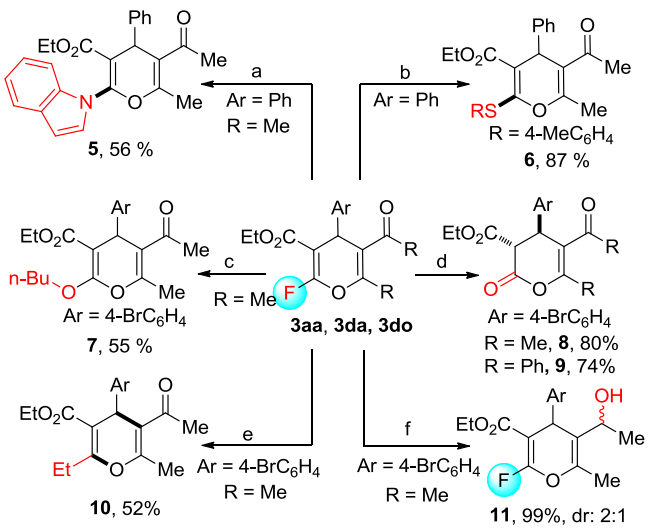
of reaction time and the yield of monofluorinated 4*H*-pyran formation. It was also interesting to find that (*Z*)-**1r** would undergo isomerization to the corresponding (*E*)-**1r** under basic conditions[16] while the isomerization of (*Z*)-**4ra** took place under weak acidic conditions (in $CDCl_3$, NMR tube) (Scheme 3).[14a]

The substrate scope of this transformation is also pretty general with respect to 1,3-dicarbonyl compounds. A broad spectrum of *β*-ketoesters, acyclic and cyclic *β*-diketones, could be employed to afford the desired structurally diverse functionalized monofluorinated 4*H*-pyrans in moderate to good yields (Scheme 4, **3db**-**3dq**). The effects of substitution on ester group could be negligible; for example, changing the ester group from methyl to ethyl (**3dc**), *tert*-butyl (**3dd**), 4-chlorobenzyl (**3de**), 3-benzhydryl (**3df**) or anthracen-9-ylmethyl (**3dg**) had no impact on the yield of the reaction. Notably, when the nonsymmetrical diketone 1-phenylbutane-1, 3-dione (**2p**) was subjected to the standard reaction conditions, two isomes (**3dp** and **3dp'** in 26% and 27% yield, respectively) were isolated.[17] Gratifyingly, cyclic *β*-diketone were also efficient for present transformation and the desired bicyclic ring-fluorinated chromenone (**3dq**) was isolated in good yield.



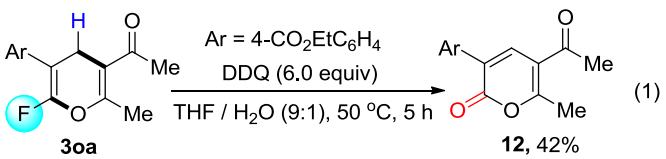
Scheme 4. Scope of 1,3-dicarbonyl compounds **2**.

To highlight the synthetic utilities of this transformation, several selective transformations of the representative monofluorinated 4*H*-pyran **3aa, 3da**, **3do**, and **3oa** were showcased in Scheme 5 and Equation 1. The results show that ring-monofluorinated 4*H*-pyrans are a versatile organic building blocks in organic synthesis. For example, treatment of **3aa** with 1*H*-indole or 4-methylbenzenethiol as *N*- or *S*-based nucleophiles, indole or thiophenol incorporated 4*H*-pyran **5** or **6** was obtained in 56%, 87% isolated yield, respectively. Alcohol could also be used as *O*-based nucleophiles, 4*H*-pyran **3da** react readily with lithium butoxide to afford alkyloxy-substituted 4*H*-pyran **7** in 55% isolated yield. Interestingly, synthetic valuable enol lactones[18] **8** and **9** could be delivered in 80% and 74% yield, respectively, by treatment of **3da** and **3do** with *n*-Bu_4NOAc in DMF via a consecutive addition-elimination process followed by hydrolysis and isomerization. The structure and the relative stereochemistry were established by X-ray crystallography analysis of enol lactone **9** as a *trans*-isomer.[15] Notably, Grignard reagent such as ethylmagnesium bromide could undergo chemoselective nucleophilic substitution of fluorine atom rather than nucleophilic addition to ketone. For instance, treatment of **3da** with ethylmagnesium bromide at -20 °C gave ethyl substituted 4*H*-pyran **10** in 52% isolated yield. Furthermore, the ketone could be selectively reduced by $NaBH_4$ at room temperature, with vinylic C-F bond untouched, leading to **11** in almost quantitative yield with moderate diastereo-selectivity. Furthermore, monofluorinated 4*H*-pyran **3oa** could undergo oxidative defluorination to afford high functionalized *α*-pyrone derivative **12** in 42% isolated yield upon treatment with DDQ in THF and water as solvent. It is well known that *α*-pyrone is a privileged structural motif frequently found in a number of natural products, pharmaceutical compounds, as well as useful building blocks in organic synthesis.[19] Thus, our new developed synthetic methodology for ring-fluorinated 4*H*-pyrans synthesis also provide an alternative synthetic route to high substituted enol lactone or *α*-pyrone derivatives, two types of important building blocks in organic synthesis.



Conditions: a) 1. indole, CH_3MgBr, THF, RT; 2. **3aa**, THF, RT, 1 h; b) 4-methylbenzenethiol, K_2CO_3, 4Å MS, DMF, 50 °C, 3 h; c) BuOH (1.2 equiv.), BuLi (1.2 equiv.), -20 °C-RT, THF, 3 h; d) *n*-Bu_4NOAc (1.5 equiv.), DMF, RT, 2 h; e) EtMgBr (1.2 equiv.), THF, -20 - 0 °C, 3 h; f) $NaBH_4$, MeOH, RT, 0.5 h.

Scheme 5. Synthetic transformations of pyrans **3aa**, **3da** and **3do.**



In summary, we have developed a one-step synthetic approach to structurally diverse functionalized and synthetic valuable ring-fluorinated 4*H*-pyrans via simple base-mediated

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cascade reaction of trifluoromethylated alkenes with 1,3-dicarbonyl compounds. The key events of this reaction involve two consecutive C-F substitutions (intermolecular S_N2'-type reaction and subsequent intramolecular S_NV reaction) in one step synthetic approach under very mild conditions. The structural nature and electronic properties of trifluoromethylated alkenes have dramatic effect on product diversity. Synthetic transformations revealed that this types of compounds can be used as versatile building blocks in organic synthesis. Further studies include further application of this new synthetic protocol and design new reactions of trifluoromethylated alkenes are currently underway in our laboratory and will be reported in due course.

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† Electronic Supplementary Information (ESI) available: Complete experimental procedures and characterization data for all new compounds. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/c000000x/

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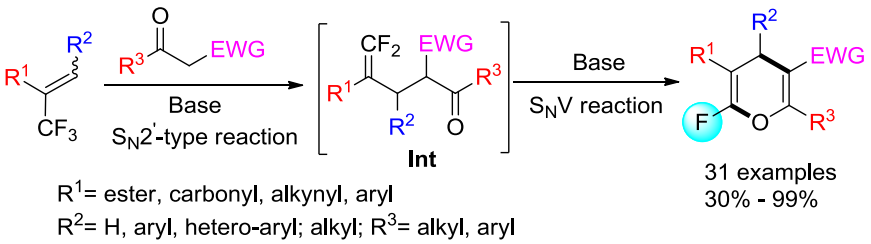

A simple base-mediated synthesis of diverse substituted ring-fluorinated 4*H*-pyran (monofluorinated 4*H*-pyrans) from trifluoromethylated alkenes and 1,3-dicarbonyl compounds was developed.

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