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A modular synthesis of α-aryl β-perfluoroalkyl ketones via *N*-heterocyclic carbene catalysis

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A new general *de novo* synthesis of pharmaceutically important α-aryl β-perfluoroalkyl ketones has been disclosed. Compared with trifluoromethylation-initiated radical 1,2-aryl migration of α, α-diaryl allylic alcohol, this protocol employs a new strategy of biomimetic carbene catalysis to assemble alkene, aldehyde and perfluoroalkyl reagent, providing access to products with excellent flexibility of aryl unit and perfluoroalkyl group. This method also demonstrates excellent functional group compatibility, including some Grignard reagent sensitive groups.

α-Aryl ketone is an important motif which is found in a lot of biological active compounds.[1] As shown in Fig. 1, compound **1** is a selective endothelin A receptor antagonist having a IC_{50} value of 0.72 μmol[1a] and compound **2** was identified as potential small-molecule mediator of Foxm-DNA interaction which is relevant to human colorectal cancer.[1b] Replacing C-H bond with C-F bond is a common strategy in drug design and optimization, because this substitution will not markedly alter three-dimensional conformation of apparent molecule due to the very close volume between hydrogen and fluorine.[2] However, C-F bond is stronger and more lipophilic, and so the replacement will improve the stability of anti-metabolism and the ability of permeating biomembrane.[3] Hence, the development of new method for synthesizing fluorinated analogue of α-aryl ketone (for example, compound **3**) has significant meaning. It remains very diffcult to synthesize compound **3** incorporating partially fluorinated aliphatic moiety via direct fluorination.

The synthesis of α-aryl β-perfluoroalkyl ketones has attracted much attention over the past few years. Wu,[4a] Tu[4b] and Sodeoka[4c] independently reported that these fascinating molecules could be accessed via trifluoromethylation-initiated radical 1,2-aryl migration of α, α-diaryl allylic alcohol in 2013 (Fig. 1b). After that, great endeavors toward improving the original protocols were made, including cheaper trifluoromethylation reagent and milder reaction condition through light or electricity as the driving force of reaction, but several limitations still exist.[4-5] Firstly, migration is an electrically controlled process and electron-deficient aryl group migrates preferentially when R^1 (R^2) is meta or para substituent. However, ortho-substituted aryl ring migrates less effectively, regardless of whether R^1 (R^2) is electron-donating or electron-withdrawing group. Therefore, isomer of anti-migration rule is

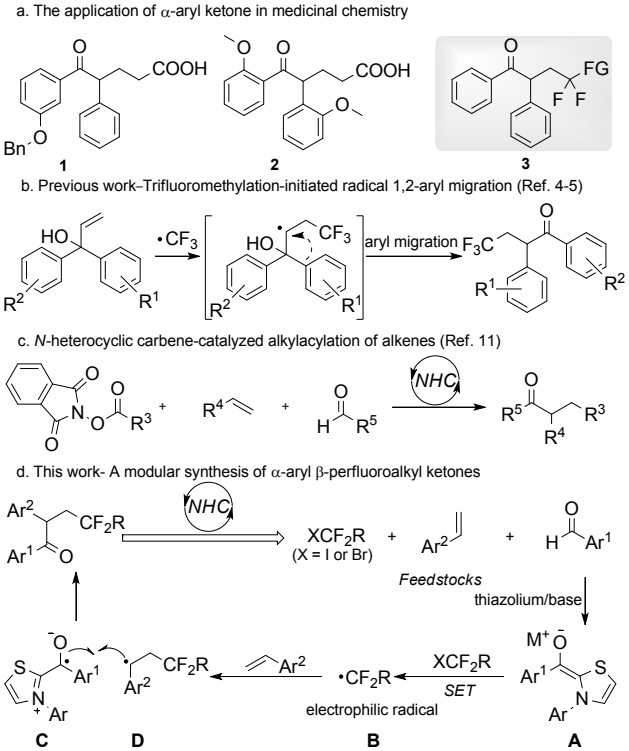

Fig. 1 The application of α-aryl ketone and synthetic strategies of α-aryl β-perfluoroalkyl Ketones

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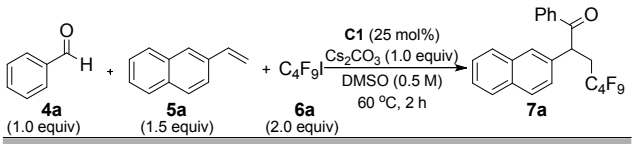
unattainable and the reaction has low selectivity for substrate with two electrically similar aryl groups. Secondly, these protocols can only introduce trifluoromethyl (CF_3) group with only one exception where difluoroalkyl group (CF_2CO_2R moiety) can be incorporated.[5b] At last, it takes three steps to synthesize α, α-diaryl allylic alcohol from aldehyde and the usage of Grignard reagent during the preparation of starting material also limits the available pattern of substituent in aryl motif of α -aryl β-perfluoroalkyl ketones. Therefore, it is highly desirable to develop new method for accessing this structural array with excellent flexibility of aryl unit and perfluoroalkyl group from readily available starting materials.

We envisaged a modular synthesis of α-aryl β-perfluoroalkyl ketone from alkene, aldehyde and perfluoroalkyl reagent that may address the synthetic issues (Fig. 1d).[6] In contrast to previous strategy which provides carbonyl group via intramolecular aryl group migration, aldehyde is directly employed as carbonyl source. This should be a great challenge, because aldehyde is neither a nucleophile nor a good SOMOphile due to the difficulty of forming energy-uphill oxygen radical.[7] However, the participation of carbene catalyst will enable this unconventional disconnection. The Breslow intermediate **A** formed from aldehyde and carbene precusor in the presence of base should be a strong reductant (Fig. 1d).[8] The fast SET process between the Breslow intermediate **A** and perfluoroalkyl halide will yield the intermediate **C** and electrophilic radical **B** which can be fastly added to electron-rich alkene to produce nucleophilic radical **D**.[9] The C-C bond is formed through the recombination of the resulting radicals **C** and **D**. Like the terminating step of most *N*-heterocyclic carbene catalyzed reactions, the acyl group is introduced along with the regeneration of carbene catalyst.[10]

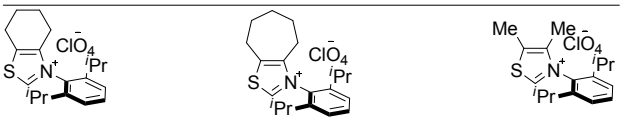
We began our studies by examining the reaction of benzaldehyde **4a**, 2-vinylnaphthalene **5a** with perfluorobutyl iodide **6a**. Inspired by *N*-heterocyclic carbene catalyzed alkylacylation of alkenes reported by Ohmiya and coworkers (Fig. 1c),[11] we examined the use of thiazolium as carbene precursor. Thiamine diphosphate acts as a coenzyme to catalyze the decarboxylation of pyruvate in nature, [12] which enables the application of thiazolium-based carbene catalyst to organic synthesis. Although the reductive potential of the corresponding Breslow intermediate **A** (-0.7 to -1.0 V vs SCE)[13a-b] is higher than that of perfluorobutyl iodide (-1.27 V vs SCE),[14] a fast electron transfer will be feasible because the cation motif of the intermediate **A** may activate the carbon iodine bond of perfluorobutyl iodide to overcome this endergonic event.[15] After a careful screening, we identified optimal conditions using 25 mol% of carbene precusor **C1**[16] and 1.0 equivalent of Cs_2CO_3 as base in DMSO to provide product **7a** in 80% yield by ^{1}H NMR (Table 1, entry 1). Lowering the Cs_2CO_3 loading or using other base instead of Cs_2CO_3 led to decreased yields (entries 2 and 3). Thiazoliums **C2** and **C3** are not as effective as **C1** albeit with similar conversion (entries 4 and 5). Compound **7a** was obtained in lower yield when reducing the **C1** loading to 10 mol% (entry 6). Carrying out the reaction in less polar CH_3CN, the reaction delivered compound **7a** in 27% yield (entry 7).

Table 1 Optimization studies on acylperfluoroalkylation of alkene[a]



4a (1.0 equiv) **5a** (1.5 equiv) **6a** (2.0 equiv) **7a**

Entry	Variation from "standard" conditions	Conv. (**4a**, %)	Yield (**7a**, %)
1	none	97	80 (78)
2	0.5 eq base	63	45
3	K_2CO_3	77	41
4	**C2**	98	53
5	**C3**	98	70
6	10% of **C1**	65	44
7	CH_3CN	69	27



C1 **C2** **C3**

[a]Reaction performed on 0.2 mmol scale. Yield of 7a determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. The isolated yield is given in parenthesis.

With the optimized condition in hand, we investigated the scope of acylperfluoroalkylation of alkene (Table 2). A number of perfluoroalkyl reagents were effective partners, delivering compounds **7a**-**7d** in 40-81% yields. This demonstrates the versatility of our protocol in terms of introducing perfluoroalkyl group. We also investigated the reaction employing various aldehydes. A range of benzaldehydes which bear substituents at the para or meta position including acetyl, methoxy, ester, and nitrile were well tolerated, affording compounds **7e**-**7h** in 39-71% yields. For heteroaryl aldehydes, the reaction proceeded well to provide compounds **7i**-**7l** in 43-75% yields. Ortho-substituted aromatic aldehyde such as 2-bromobenzaldehyde was not a suitable subtrate and we could only detect a trace of product under the optimized condition. Next, we focused on investigating the scope of alkenes. Various styrenes incorporating electron-withdrawing or electron-donating substituents at the aryl motif were found to participate in the reaction, giving the corresponding products **7m**-**7r** in 55-84% yields. Employing alkenes substituted heteroaryl groups as substrates, the reaction proceeded well to provide compounds **7s**-**7u** in 58-91% yields. The reaction afforded compound **7w** and **7x** in 63 and 68% yields by flexibly choosing suitable aldehyde and alkene as reaction partners, which were obtained as a 1.8: 1 inseparable mixture of regioisomers according to previous report.[5f] It is noteworthy that the method is compatible with some Grignard reagent sensitive groups (**7e**, **7j, 7l** and **7u**). The result is very meaningful because it would take additional protection/deprotection steps to prepare α, α-diaryl allylic alcohol employed as starting material in the aryl migration strategy. However, this protocol is ineffective for simple aliphatic alkene.

To demonstrate the synthetic utility of our protocol, we targeted the synthesis of difluorinated analogue of compound **1** which is a selective endothelin A receptor antagonist. Performing with 3-(benzyloxy)benzaldehyde, styrene and ethyl

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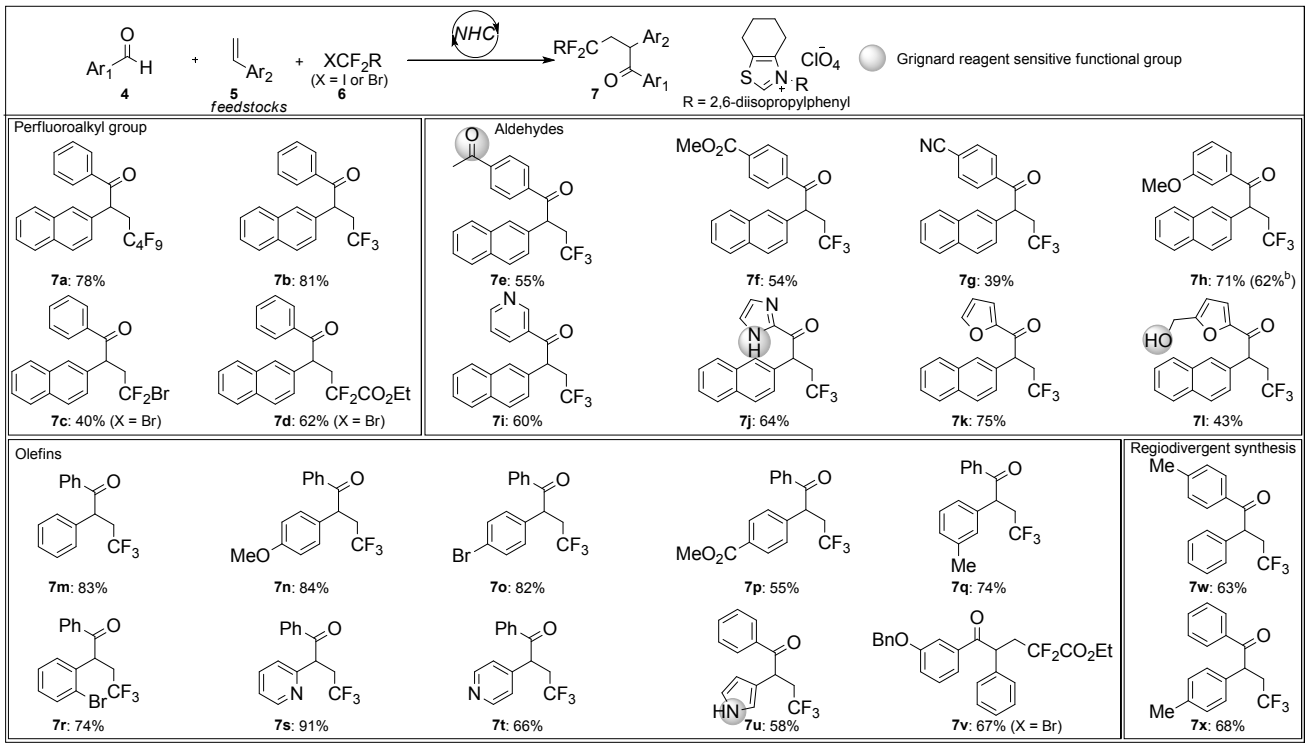
Table 2 Scope for carbene catalyzed three component reaction of alkene, aldehyde and perfluoroalkyl reagents[a]

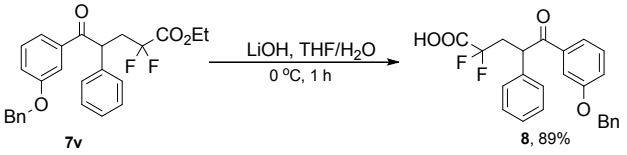


[a]The reaction was performed with carbene catalyst precursor **C1** (25 mol%), aryl aldehyde (0.2 mmol, 1.0 equiv),aryl alkene (1.5 equiv), perfluoroalkyl reagent (2.0 equiv) and cesium carbonate (1.0 equiv) in DMSO at 60 °C. All yields are isolated yields. [b]1.84 mmol of 3-methoxybenzaldehyde was used.

bromodifluoroacetate under standard condition, the corresponding product **7v** was obtained in 67% yield (Table 2). Hydrolysis of ester group afforded the target compound **8**. For compound **1**, the introduction of two fluorine didn't notably affect the volume of molecule but modify the pka value of carboxyl group.

In order to shed light on this new three component reaction， we performed some mechanistic experiments. The reaction was inhibited by the radical scavengers BHT and TEMPO，which demonstrates radical intermediate is involved in mechanistic pathway. Combing with previous studies on redox potential of the Breslow intermediate **A**, we tend to believe the above mentioned mechanism in Fig. 1 is reasonable.

Scheme 1 The synthesis of difluorinated analogue of compound **1**



The major limitation of our protocol is high catalyst loading which is an issue for a lot of carbene-catalyzed reactions (~ 20 mol%).[10] When a lower catalyst loading was used, the reaction stoped at a lower conversion even if prolonging reaction time or increasing reaction temperature, which indicates catalyst deactivation during reaction.[17] However, effort of separating byproduct to probe the mechanism of catalyst deactivation was unfruitful.

In summary, we have reported a new strategy of preparing α-aryl β-perfluoroalkyl ketones in moderate to good yields. The striking feature of our protocol is that flexibile construction of aryl unit and perfluoroalkyl group from simple precursors which free the synthesis from the intrinsic dilemma in trifluoromethylation-initiated radical 1,2-aryl migration of α, α-diaryl allylic alcohol. Seeking robust catalyst and strategy of controlling entioselectivity for the reaction are underway in our lab.

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Conflicts of interest

There are no conflicts to declare.

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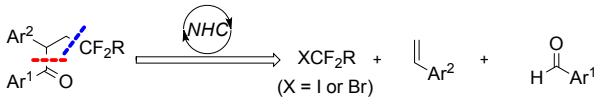

flexibile introduction of aryl unit and perfluoroalkyl group

A new strategy of assembling alkene, aldehyde and perfluoroalkyl reagent under the catalysis of *N*-heterocyclic carbene afforded valuable α-aryl β-perfluoroalkyl ketone.