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Highly selective difluoromethylations of β-keto amides with $TMSCF_2Br$ under mild conditions

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Abstract

Without employing any transition metal and other additives, efficient methods for selective difluoromethylations of β-keto amides with $TMSCF_2Br$ reagent have been developed under alkaline and open-air conditions. This protocol allows a convenient access to various α-difluoromethyl β-keto amides with excellent yields (up to 93%) and high C/O regioselectivities (up to 99:1). The C/O selectivity of β-keto amides could be easily reversed and controlled by simply changing the base. This protocol can be easily scaled up and the C-difluoromethylation product could be reduced into amino-alcohol derivatives. Moreover, the first enantioselective electrophilic difluoromethylation of β-keto amides has been achieved by phase-transfer catalysis.

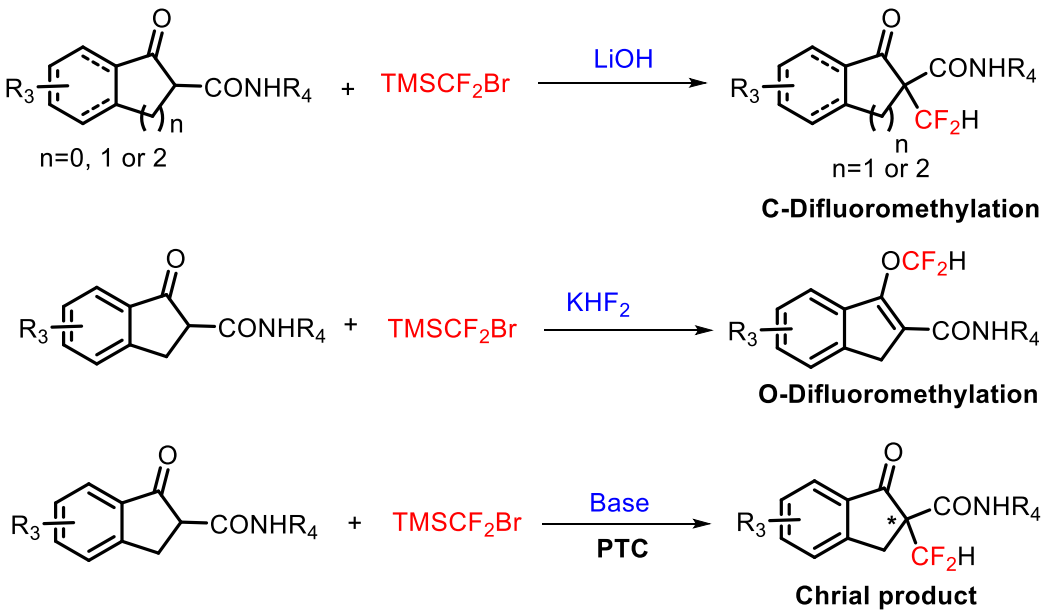
Keywords

Difluoromethylation, β-Keto amides, C/O selectivity, Asymmetric synthesis

Introduction

Fluorinated molecules play an increasingly important role within pharmaceuticals and materials science [1]. Among them, the difluoromethyl (CF_2H) group, an analog of well-recognized trifluoromethyl (CF_3) group, has attracted considerable attention because it can act as a surrogate of a hydroxyl or a thiol group, and a lipophilic hydrogen bond donor [2]. Furthermore, this fascinating group (CF_2H) could modulate the lipophilicity of a molecule that may increase the drug's metabolic stability [3]. Because of this, the introduction of the difluoromethyl group into leading drug candidates has become a powerful strategy for new drug discovery. On this account, many marketed drugs contained the CF_2H skeletons, such as soft PDE4 inhibitor Roflumilast (medicine for pneumonia) and the proton pump-inhibiting drug Pantoprazole [4-5]. Therefore, it is highly desirable to develop efficient methods to introduce the CF_2H motif into organic molecules. Until now, numerous methods have been developed to access CF_2H-containing molecules [6]. Although metal-photoredox catalysis and transition metal catalysis are effective means [7], the difluorocarbene-mediated electrophilic difluoromethylations are still attractive and straightforward strategies for preparation of difluoromethylated compounds [8]. However, most of these reactions are focused on the difluoromethylation of heteroatoms, such as *O*-, *S*-, *N*-, *P*- and *Se*-nucleophiles [9]. However, the difluoromethylation of *C-H* nucleophiles is sparse, remains an area with limited success. Furthermore, β-keto esters are widely used nucleophiles and the development of controlling C/O regioselectivities were problematic. Recently, efficient difluoromethylations with high C/O selectivities were achieved by the groups led by Hu [10], Shibata [11], Shen [12], Liu [13] using different kinds of difluoromethylating reagents. Compared with the β-keto esters, β-keto amides are still challenging

substrates, possibly due to the lower acidity of the α-hydrogen, and the reactivity towards difluorocarbene is largely underexplored or unknown. In Hu's work, only one example of β-keto amide was showed to react with difluorocarbene, and the yield of the difluoromethylated product was low [10]. Moreover, there are no examples of direct difluoromethylation of the *N-H* contained β-keto amides as far as we know. Therefore, the development of a general method for efficient difluoromethylation of various β-keto amides with readily available reagent is highly desirable. Herein, we reported an efficient method for the highly regioselective difluoromethylation of β-keto amides, and the C/O selectivity of β-keto amides could be easily reversed and controlled. Moreover, the enantioselective C-difluoromethylation of β-keto amides could be achieved by phase-transfer catalysis. (Scheme 1).



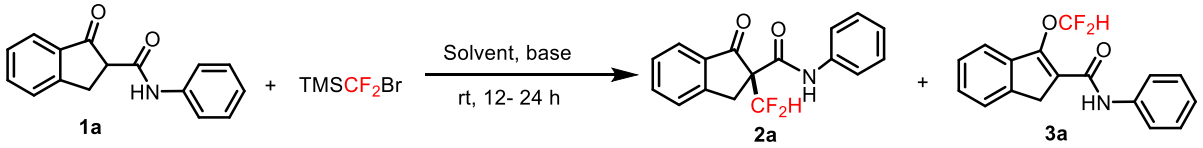
Scheme 1. Direct difluoromethylation of β-keto amides.

Results and Discussion

The discovery of simple and efficient systems for efficient difluoromethylation of various *C-H* nucleophiles with readily available reagent is a highly desirable task in

Chemistry[14]. To develop a new and convenient method for the C-difluoromethylation of β-keto amides, we investigated the α-difluoromethylation of 1-indanone derived β-keto amide **1a** using the readily available reagent $TMSCF_2Br$, a difluorocarbene reagent originally introduced by Hu,[8c,10] as the difluorocarbene precursor. First, we screened several bases with CH_2Cl_2 in the presence of $TMSCF_2Br$. Organic bases such as DBU and Et_3N were ineffective in this transformation (Table 1, entries 1, 2). We found that inorganic bases such as KOH and NaOH could promote this reaction, but with moderate yields and C-O regioselectivities (Table 1, entries 3, 4). Then we found that an inorganic base, LiOH, favourably controlled C/O regioselectivity (C/O = 92:8) in 78% yield (Table 1, entry 5). However, the performance of other bases such as CsOH, K_2CO_3, Li_2CO_3, KO*t*Bu and LiO*t*Bu were inferior compared with LiOH (Table 1, entries 6-10). Other organolithium regents such as *n*-BuLi and LiHMDS could not promote this difluoromethylation (Table 1, entries 11-12). The choice of solvent was also very important. Hexane, THF, DMF and Et_2O all gave unsatisfactory results both in terms of yields and regioselectivities (Table 1, entries 13-16). To our delight, we found toluene could improve the yield and C/O selectivity obviously (Table 1, entry 17). Other reaction parameters such as temperature, concentration and other additives were also screened (for more details, see Table S1 in the ESI†). Subsequently, further improvement was observed in toluene by using 1.5 equiv. of $TMSCF_2Br$ in the presence of LiOH (3.0 equiv.) in 2 mL toluene at 15°C for 24 h. Under the optimized reaction conditions, the C-difluoromethylation product **2a** was obtained with excellent C/O selectivity (C/O = 98:2) in 91% yield (Table 1, entry 18).

Table 1: Optimization of the reaction conditions for the C-difluoromethylation of β-keto amide **1a**[a].



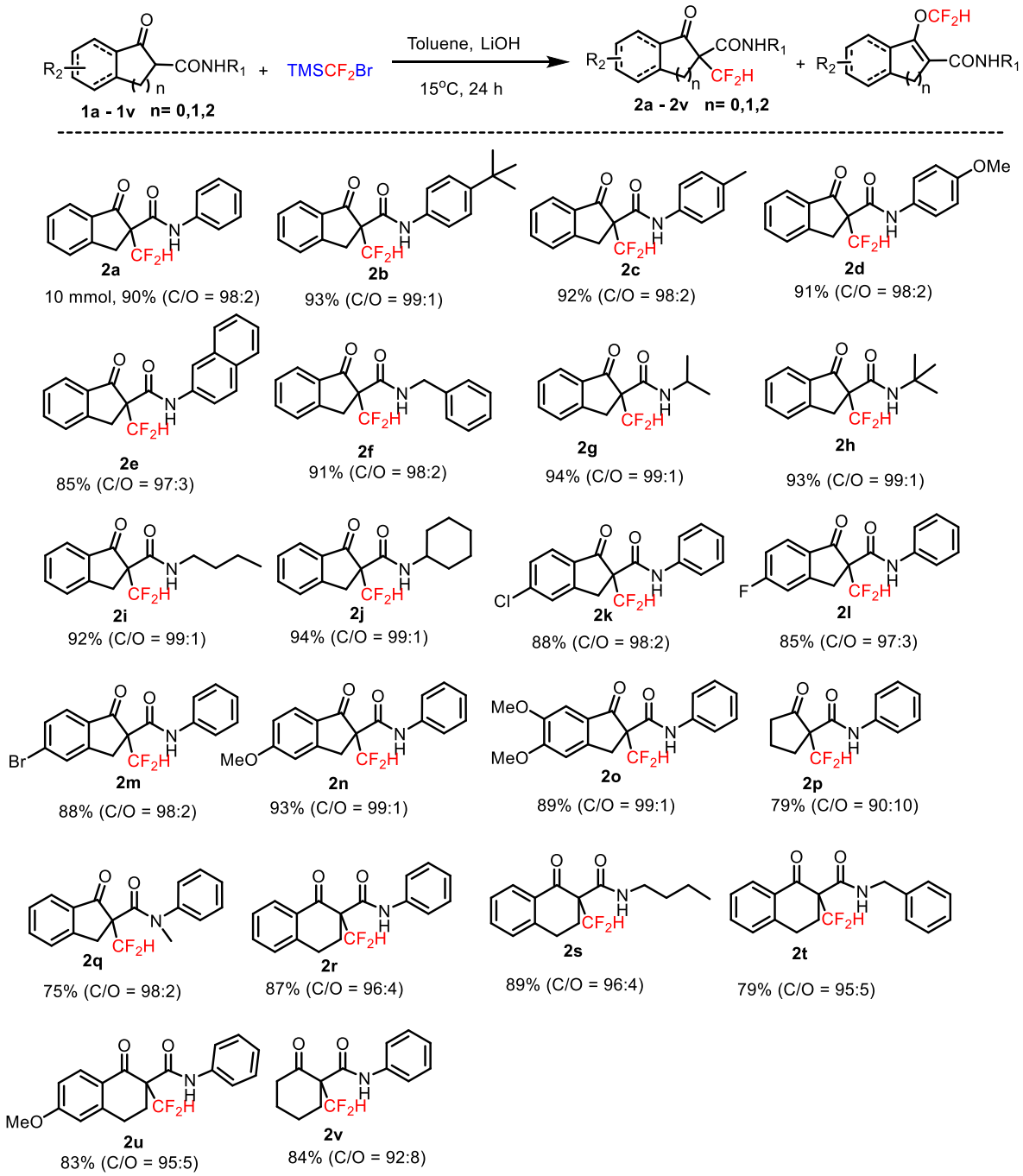
Entry	Solvent	Base	Time (h)	Yield (%) [b]	C/O [c]
1	CH_2Cl_2	DBU	12	Trace	Nd
2	CH_2Cl_2	Et_3N	24	Trace	Nd
3	CH_2Cl_2	KOH	24	37	71/29
4	CH_2Cl_2	NaOH	24	42	67/33
5	CH_2Cl_2	LiOH	24	78	92/8
6	CH_2Cl_2	CsOH	24	46	81/19
7	CH_2Cl_2	K_2CO_3	24	Trace	Nd
8	CH_2Cl_2	Li_2CO_3	24	Trace	Nd
9	CH_2Cl_2	KO*t*Bu	24	43	86/14
10	CH_2Cl_2	LiO*t*Bu	24	56	88/12
11	CH_2Cl_2	*n*-BuLi	24	Trace	Nd
12	CH_2Cl_2	LiHMDS	12	Trace	Nd
13	Hexane	LiOH	24	45	88/12
14	THF	LiOH	12	58	91/9
15	DMF	LiOH	24	Trace	Nd
16	Et_2O	LiOH	12	72	88/12
17	Toluene	LiOH	12	85	96/4
18[d]	Toluene	LiOH	24	91	98/2

[a] The reaction of **1a** (0.1 mmol) with $TMSCF_2Br$ (2.0 equiv.) was carried out in the presence of a base (3.0 equiv.) in solvent (0.1 M) at rt. [b] Yield of isolated product. [c]

^{19}F NMR with trifluorotoluene as the internal standard. [d] The reaction of **1a** (0.1 mmol) with $TMSCF_2Br$ (1.5 equiv.) was carried out in the presence of LiOH (3.0 equiv.) in 2.5 mL toluene at 15°C.

With the optimized reaction conditions in hand, the scopes of the difluoromethylation of β-keto amides were explored to evaluate the generality of the process (Scheme 2). First, we investigated the substituents at the amide sides. Aniline-derived substrates containing 4'-Me, 4'-MeO, 4'-*t*-Bu and aryl derivatives containing naphthyl and benzyl group could be converted into the corresponding products **2a**-**2f** in good yields (78-94%) and up to 99:1 C/O selectivities. It is worth mentioning that we scaled up the α-difluoromethylation of β-keto amide **1a** to the gram scale. Under the standard conditions, 10 mmol of β-keto amides (**1a**) reacted smoothly with 15 mol of $TMSCF_2Br$ and gave 2.70 g (90% yield) of **2a** with 98:2 C/O selectivity after 16 h. Compounds **1g**-**1j**, with aliphatic amido groups, affording the corresponding products **2g**-**2j** in good yields (92%-94%) and excellent C/O selectivities (99:1). Next, we extended the procedure to substrates which have halogen atoms and electron-donating groups on the aromatic ring of the indanone scaffold. Under mild conditions, **1k**-**1m** which have halogen substituents were nicely converted into the corresponding products in 85-88% yields and excellent C/O selectivities (99:1). Furthermore, when methoxy groups were introduced (**1n** and **1o**), the reactions proceeded smoothly and the desired products were obtained with 89-93% yields. Interestingly, the five-membered cyclopentanone derived substrate **1p** could be converted into the α-difluoromethylation prodcuts with 79% yield and 90:10 C/O selectivity. Compound **1q** which has methyl and phenyl in the N-position, afforded **2q** in 75% yield and 98:2 C/O selectivity under the optimized reaction conditions. Then the scope of 1-tetralone-derived β-keto amides **1r**-**1u** were then examined, and the desired products

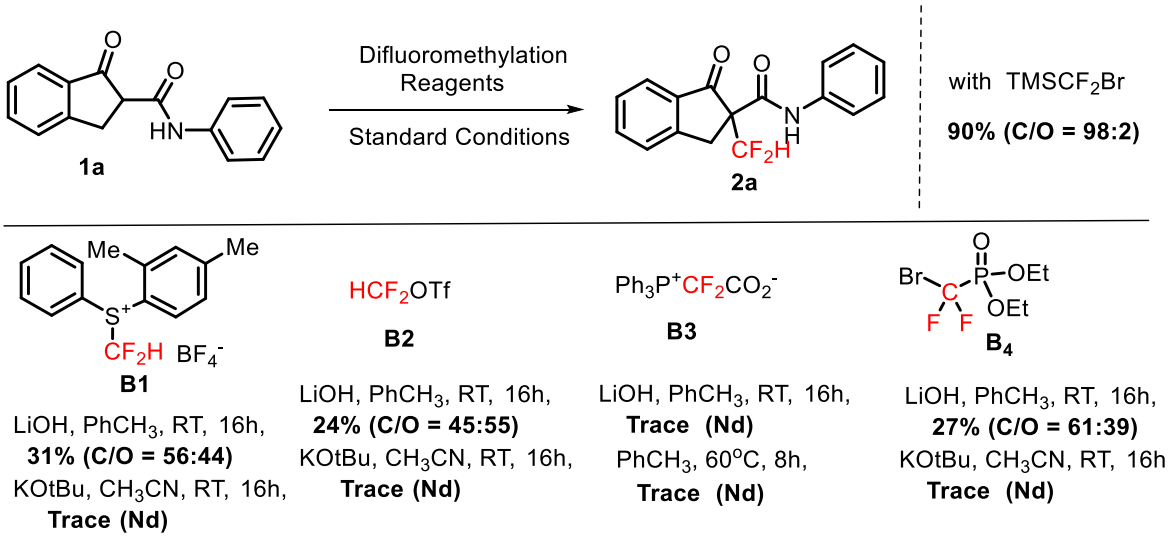
were obtained with 79-89% yields and up to 96:4 C/O selectivities. To our delight, the six-membered cyclohexanone derived substrate **1v** was nicely converted into the corresponding product **2v** with 84% yield and 92:8 C/O selectivity. Ultimately, such a simple and efficient method for α-difluoromethylation showed good substrate tolerance for indanone and 1-tetralone-derived β-keto amides.



Scheme 2. Substrate scope of the α-difluoromethylation of β-keto amides. *Reaction conditions* (unless otherwise specified): the reactions were performed with β-keto

amide (0.1 mmol), $TMSCF_2Br$ (0.13 mmol), LiOH (0.3 mmol), and 2.5 mL toluene at 15°C for 16 h.

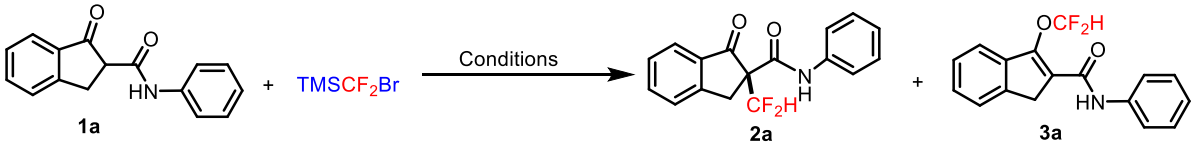
Inspired by these exciting results, we turned our attention to the unique reactivity of $TMSCF_2Br$ and carried out some comparison experiments using other difluoromethylation reagents **B1**-**B4**. β-Keto amide **1a** was selected as a model substrate. As described in Scheme 3, $TMSCF_2Br$ can difluoromethylate **1a** to give product **2a** in 90% yield and 98:2 C/O selectivity. However, under the optimized and modified reaction conditions, the S-difluoromethyl sulfonium salt **B1** [15], the difluoromethyl ethers **B2** [16], the phosphine yelide type of difluoromethylation reagent **B3** [17], and the diethyl (bromodifluoromethyl)-phosphonate **B4** [18] showed low reactivities towards **1a**, and desired product **2a** was formed in low yields (0-31%) and C/O selectivities. These results highlights the unique feature and advantage of $TMSCF_2Br$ as a privileged difluorocarbene precursor for this C-difluoromethylation of β-keto amides.



Scheme 3. The reactivity of different difluoromethylation reagents towards **1a**.

The controlling of O/C regioselectivities was also significant, and we envisioned that the regioselectivity of $TMSCF_2Br$ towards O site could be enhanced under different reaction conditions. For the β-keto amide **1a**, under standard conditions,

only C-difluoromethylated product **2a** was formed in 90% yield and 98:2 C/O selectivity; Then we noticed that alcohols can react with :CF_2 directly without predeprotonation [19]. So we used the weakly acidic KHF_2 as the reaction promotor, CH_2Cl_2 and H_2O as the mixed solvents, we were pleased to see that the O-difluoromethylated product **3a** was obtained in 83% yield and 8:92 C/O selectivity at 40℃ for 12 h. These findings indicated that the C/O selectivity of β-keto amides could be easily controlled by simply changing the reaction conditions, it also highlighted $TMSCF_2Br$ as a unique and versatile difluorocarbene reagent (Scheme 4).

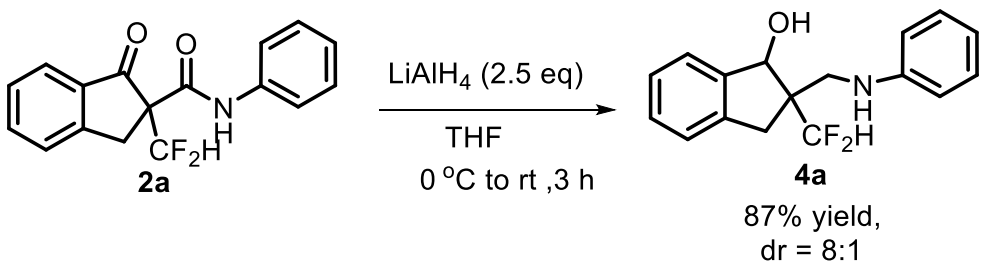


Conditions A: **1a** (0.1 mmol), LiOH (3.0 equiv), $PhCH_3$ (2.5 mL), $TMSCF_2Br$ (1.5 equiv), RT, 16h. — 90% (C/O =98:2) — Nd

Conditions B: **1a** (0.3 mmol), KHF_2 (6.0 equiv), CH_2Cl_2 (0.3 mL), H_2O (0.3 mL), $TMSCF_2Br$ (3.0 equiv), 40°C, 12h. — Nd =8:92) — 83% (C/O

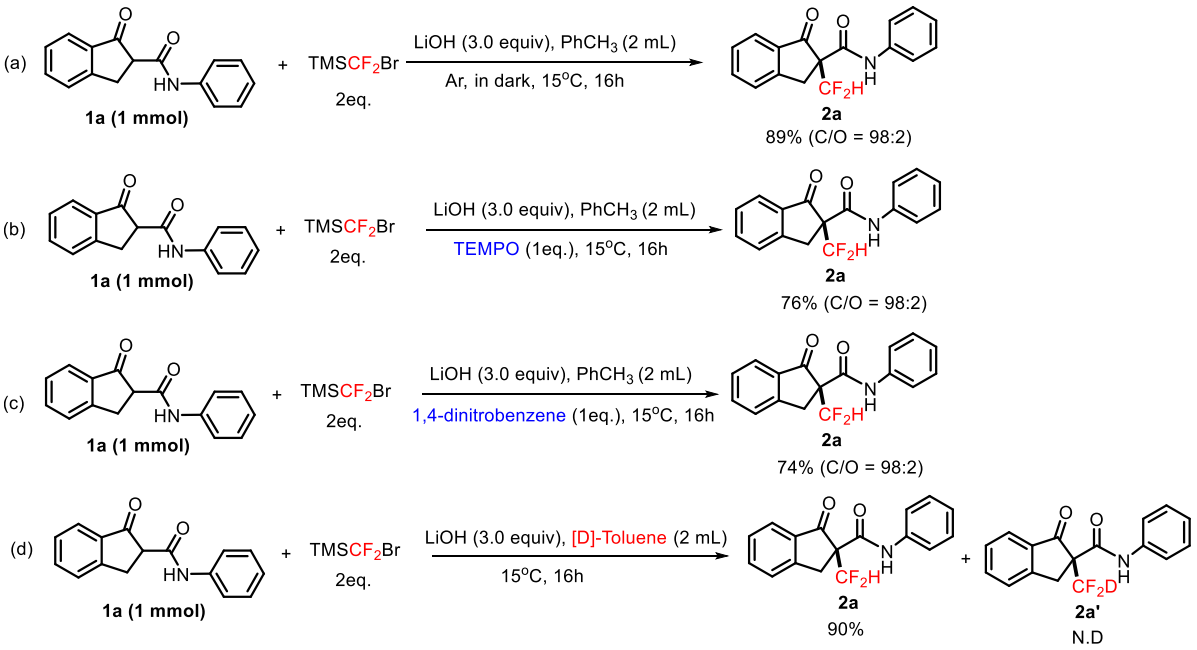
Scheme 4. Divergent transformations of β-keto amide **1a**. for controlling C/O selectivity.

The synthetic application of the C-difluoromethylation product **2a** was further demonstrated (Scheme 5). To our delight, the amino-alcohol derivative **4a** could be easily obtained by reduction with $LiAlH_4$ in THF in 87% yield with 8:1 dr, which highlighted the practicability of this transformation.



Scheme 5. Synthetic utilization of C-difluoromethylation product **2a**.

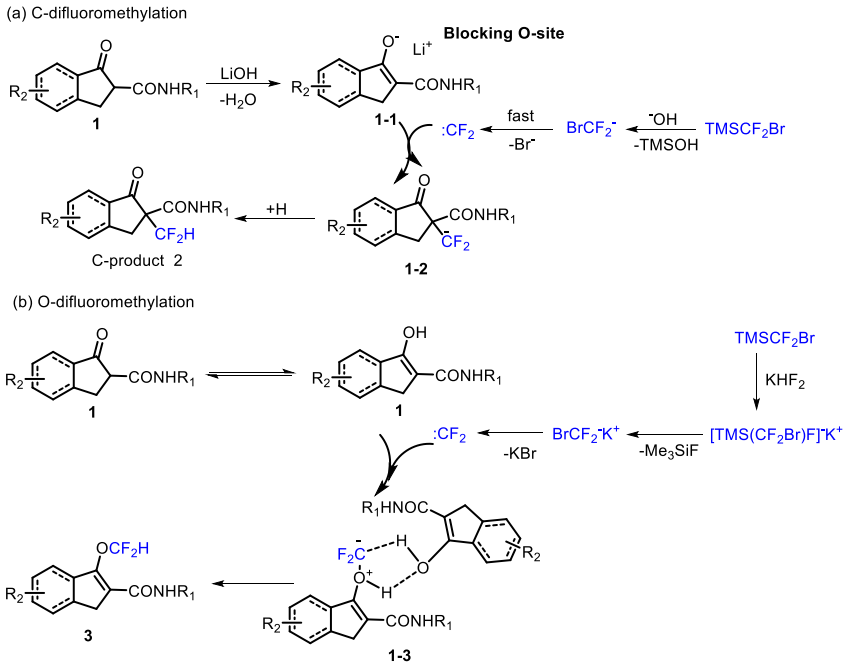
To gain insight into the reaction mechanism, some control experiments were performed (Scheme 6). We found that, the reaction performed well in an argon atmosphere and in the dark, which suggested the aerobic oxidation [20] and photo-oxidation [21] were not involved in this reaction. The yield of **2a** was not significantly decreased in the presence of radical inhibitor TEMPO and SET inhibitor 1, 4-dinitrobenzene, which indicated that a radical process did not occur in this reaction system. Furthermore, no deuterated product was detected when deuterated toluene was used as solvent (see Scheme 6d). These results clearly suggested that the difluorocarbene pathway of the capturing proton from substrate **2** to produce nondeuterated C-difluoromethylation product is predominant.



Scheme 6. Controlled experiments for the C-difluoromethylation of β-keto amide.

On the basis of these experiments and the related reported work, we proposed a possible mechanism for the difluoromethylation of β-keto amide. For the C-selective difluoromethylation, the CF_2Br anion was generated via initial desilylation by base (such as HO^-), Then α-elimination of CF_2Br anion occurred and it is fragmented to

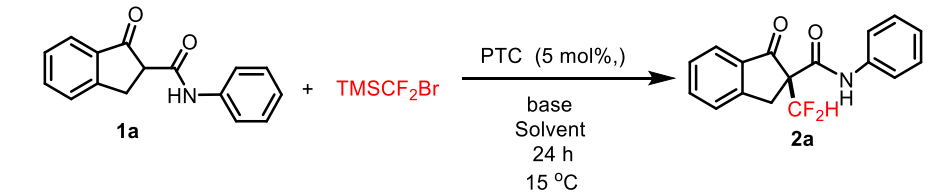
generate difluorocarbene. The protonation of CF_2Br anion is much slower than its fragmentation to difluorocarbene [22]. Then difluorocarbene was prone to be captured by the carbon-site of enolate intermediate **1-1**. Based on the Pearson acid base concept [23], a strong affinity between hard Li^+ and the hard oxygen-site in enolate **1-1** helped to block the approaching CF_2 carbene from the O-site. Then the final C-difluoromethylation product **2** could be generated by capturing hydrion of **1-2** [11]. A plausible mechanism for the O-difluoromethylation with $TMSCF_2Br$ was also proposed based our results and the previous studies on reaction of carbenes with hydroxyl groups [19, 24]. $TMSCF_2Br$ could be activated by KHF_2 to form a pentacoordinate silicate intermediate at the oil-water interface, In the organic phase, $BrCF_2K$ is released from the pentacoordinate silicate intermediate, and then splits into KBr and the singlet difluorocarbene. The latter species interacts with two alcohol molecules to form a five-membered complex with oxonium character **1-3** [25], which eventually undergoes double proton transfer to deliver the difluoromethyl ether and regenerate one O-selective difluoromethylation product **3** (Scheme 7).

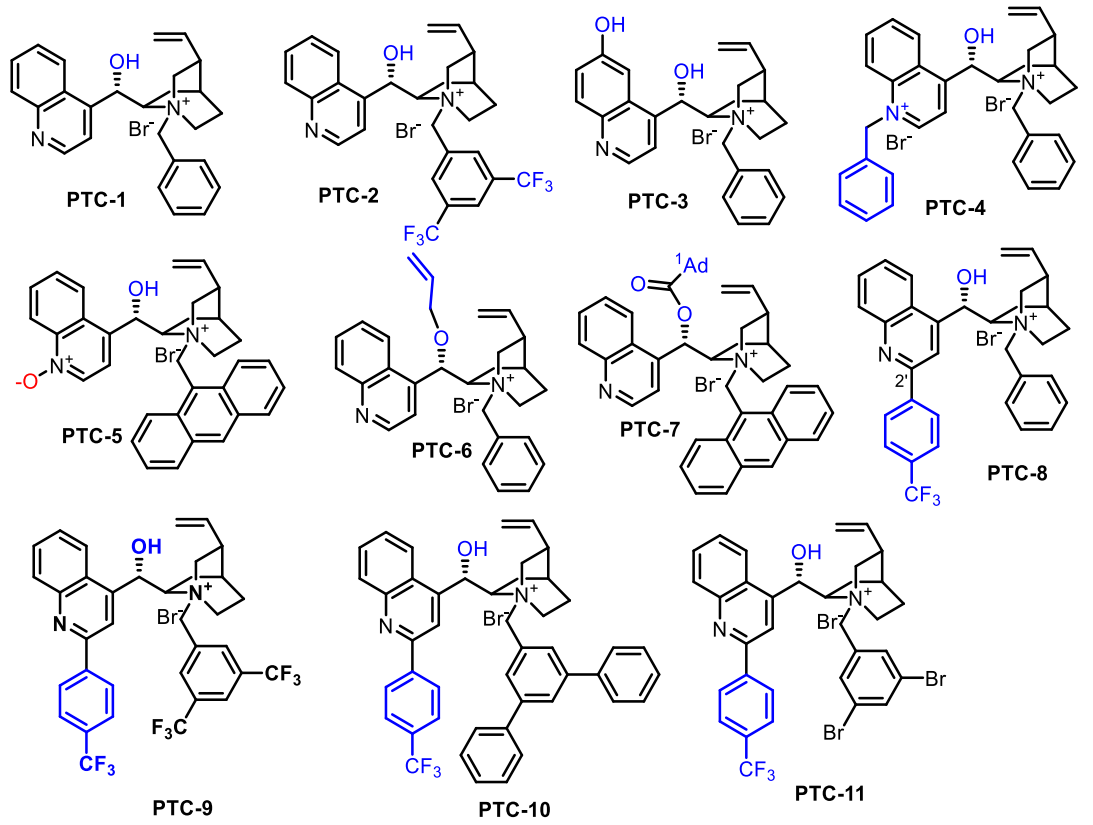


Scheme 7. Proposed mechanism for difluoromethylation of β-keto amides with $TMSCF_2Br$.

Asymmetric phase-transfer catalysis is recognized as an effective and sustainable method, and cinchona alkaloid derived phase-transfer catalysts have been applied to many practical asymmetric synthesis [26]. Considering our interest in the development of efficient and practical enantioselective α-functionalizations of β-dicarbonyl compounds by phase-transfer catalysis [27], we sought to develop a convenient method for asymmetric α-difluoromethylation of β-keto amides. First, we investigated the asymmetric α-difluoromethylation of 1-indanone-derived β-keto amide **1a** using cinchona alkaloid derived phase-transfer catalysts. The simple **PTC-1** and **PTC-2** provided **2a** with 6-8% ee in toluene (Table 2, entries 2-3). **PTC-3**, which has two hydroxy groups at both C-9 and C-6′ positions, showed poor results(Table 2, entry 4). Then we screened the doubly quaternized catalyst **PTC-4**, but the enantioselectivity was poor (Table 2, entry 5). The N-oxide **PTC-5** and the C-9 hydroxy protected **PTC-6** and **PTC-7**, afforded **2a** with 6-11% ee (Table 2, entries 6-8). Then we turned our attention to the C-2′ arylated **PTCs**. **PTC-8** provided **2a** with 24% ee (Table 2, entry 9). **PTC-10** improved the enantioselectivities to 33% ee (Table 2, entry 11). Furthermore, **PTC-11**, containing 3, 5-bromo groups in the benzyl position, worked well and gave enantioselectivity of 37% ee, and the enantioselectivity was improved to 45% when the reaction temperature was decreased to -10°C, but the yield of **2a** was significantly decreased to 61% (Table 2, entries 12-13). Although the result of the asymmetric α-difluoromethylation of β-keto amides was not satisfying, we still developed an enantioselective electrophilic difluoromethylation of β-keto amides by phase-transfer catalysis, and no broadly effective strategy for the construction of enantioenriched tertiary and quaternary centers bearing CF_2H groups has emerged as far as we know [28].

Table 2: Optimization of the reaction conditions for the asymmetric α-difluoromethylation of β-keto amide **1a**.[a]





Entry	Solvent	Base	Cat.	Yield[b] [%]	ee[c] [%]
1	$PhCH_3$	LiOH (3eq)	**PTC-1**	88	0
2	$PhCH_3$	30% K_2CO_3	**PTC-1**	56	6
3	$PhCH_3$	30% K_2CO_3	**PTC-2**	57	8

4	$PhCH_3$	30% K_2CO_3	**PTC-3**	33	0
5	$PhCH_3$	30% K_2CO_3	**PTC-4**	73	10
6	$PhCH_3$	30% K_2CO_3	**PTC-5**	43	6
7	$PhCH_3$	30% K_2CO_3	**PTC-6**	71	8
8	$PhCH_3$	30% K_2CO_3	**PTC-7**	76	11
9	$PhCH_3$	30% K_2CO_3	**PTC-8**	82	24
10	$PhCH_3$	30% K_2CO_3	**PTC-9**	73	23
11	$PhCH_3$	30% K_2CO_3	**PTC-10**	82	33
12	$PhCH_3$	30% K_2CO_3	**PTC-11**	84	34
13	$PhCH_3/CHCl_3$ =1:1	30% K_2CO_3	**PTC-11**	82 (61)[d]	37 (45)[d]

a Unless otherwise specified, the reactions were performed with **1a** (0.1 mmol), TMSCF2Br (0.2 mmol), **PTC** (0.005 mmol), and base (0.5 mL) in solvent (2 mL).[b] Yields shown are of isolated products. [c] Determined by chiral HPLC (Chiralcel AD-H). [d] The reactions were performed with **1a** (0.1 mmol), $TMSCF_2Br$ (0.2 mmol), **PTC-11** (0.005 mmol), and 30% K_2CO_3 (0.5 mL) in $PhCH_3/CHCl_3$ =1:1 (2 mL) at -10℃ for 36 h.

Conclusion

In conclusion, we have developed selective difluoromethylations of of β-keto amides with $TMSCF_2Br$. A variety of β-keto amides could be efficiently and

selectively transformed to the corresponding C-difluoromethylated products under mild conditions. Moreover, the C/O selectivity of β-keto amides could be easily controlled by simply changing the reaction conditions. This protocol can be easily scaled up and the C-difluoromethylation product could be reduced into amino-alcohol derivatives. Plausibles mechanisms and transition state showed that $TMSCF_2Br$ could be activated by LiOH or KHF_2 to form difluorocarbene, and the addition of LiOH (which not only served as a difluorocarbene activator, but also served as the O-steric blocking site) was crucial in the control of high C/O regioselectivity. Moreover, the first enantioselective electrophilic difluoromethylation of β-keto amides under phase-transfer catalysis was investigated. Further work on the application of this useful difluoromethylation for the asymmetric synthesis of natural products and pharmaceuticals are currently underway in our laboratory.

Experimental

General proceduce for the C-difluoromethylation of β-keto amides. The reactions were performed with β-keto amide **1a-1v** (0.1 mmol), LiOH (7.2 mg, 0.3 mmol) in 2.5 mL toluene. The reaction mixture was was stirred at 15℃ for 5 min. Then $TMSCF_2Br$ (0.15 mmol) was added slowly, and the reaction was stirred at this temperature for 24 h. After the reaction was completed, the mixture was diluted with EtOAc (20 mL), washed with water (2 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was subject to crude ^{19}F-NMR to give the C/O isomer ratio (trifluoromethyl benzene 8 μL as internal standard). Subsequently, the residue was purified by flash chromatography (silica gel; petroleum ether/ethyl acetate=25:1–2:1) to afford the α-difluoromethylation products (**2a-2v**).

Supporting Information

Supporting Information File 1

Experimental procedures, compound characterization, NMR spectra of all new compounds, and HPLC traces.

Funding

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