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Difluoroalkylative carbonylation of alkenes to access carbonyl difluoro-containing heterocycles: convenient synthesis of gemigliptin

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Fluorinated heterocycles play a vital role in pharmaceutical and agrochemical industries. Hence, rapid and efficient construction of fluorinated heterocycles remains highly demanded. Herein, a difluoroalkylative carbonylative cyclization of unactivated alkenes and ethylene gas enabled by palladium catalysis has been developed for the first time toward the synthesis of α-carbonyl difluoro-modified glutarimides. This procedure can also be applied to the synthesis of GeMigliptin which is a medicine approved for the treatment of type 2 diabetes mellitus.

difluoroalkylative, carbonylative, unactivated alkenes, ethylene gas, heterocycles

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1 Introduction

The efficient assembly of complex compounds from simple starting materials is one of the challenging and long-lasting goals in organic synthesis [1]. The direct difunctionalization of alkene can efficiently introduce two new functional groups across the C=C double bond to form two new chemical bonds in one step, which is an elegant way to construct complex structures and has attracted much attention from organic chemists [2,3]. On one hand, due to the small radius and unique electronic properties of fluorine atom, introducing fluorine atoms into a molecule often significantly influences the potency, conformation, metabolism, membrane permeability, and so on [4–7]. On the other hand, the carbonyl group in small molecules enables flexible enhancement of the molecular complexity *via* a myriad of conversions [8–12]. Recently, Chu and co-workers [13] reported a robust chelation-assisted strategy for fluoroalkylative carboacylation of alkyl olefins to obtain important *β*-fluoroalkyl ketones. In 2020, Zhang and co-workers [14] developed a novel procedure on nickel-catalyzed four-component reaction of alkenes, arylboronic acids, and difluoroalkyl electrophiles under 1 bar of CO (Scheme 1a). Inspired by these novel studies, we were able to estabilish a new methodology on this topic (Scheme 1b). While we employed cheap and abundant carbon monoxide (CO) as a carbonyl group source, 1-bromo-1,1-difluoroacetamides as readily available difluoride reagents, ethylene gas, and unactivated inert terminal and internal alkenes were transformed into the corresponding α-carbonyl difluoro-modified glutarimides in good to excellent yields.

Glutarimide moieties are key heterocyclic skeletons present in many significant pharmaceuticals and bioactive compounds [15–17]. For example, Revlimid and Pomalyst are popular antitumor drugs that ranked 6th and 47th in the top 200 pharmaceuticals by retail sales in 2021 (Scheme 2a)

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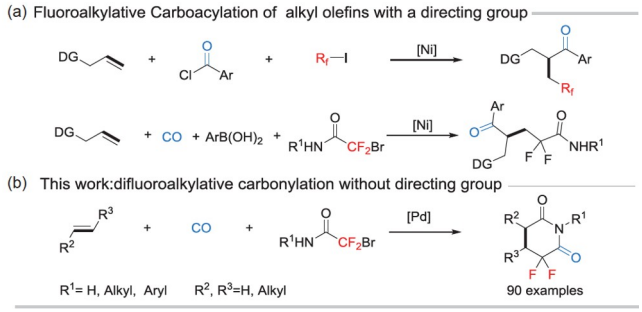


Scheme 1 (a) Fluoroalkylative carboacylation of alkyl olefins with a directing group; (b) this work: difluoroalkylative carbonylative cyclization of alkenes to synthesize α-carbonyl difluoro-modified glutarimides (color online).

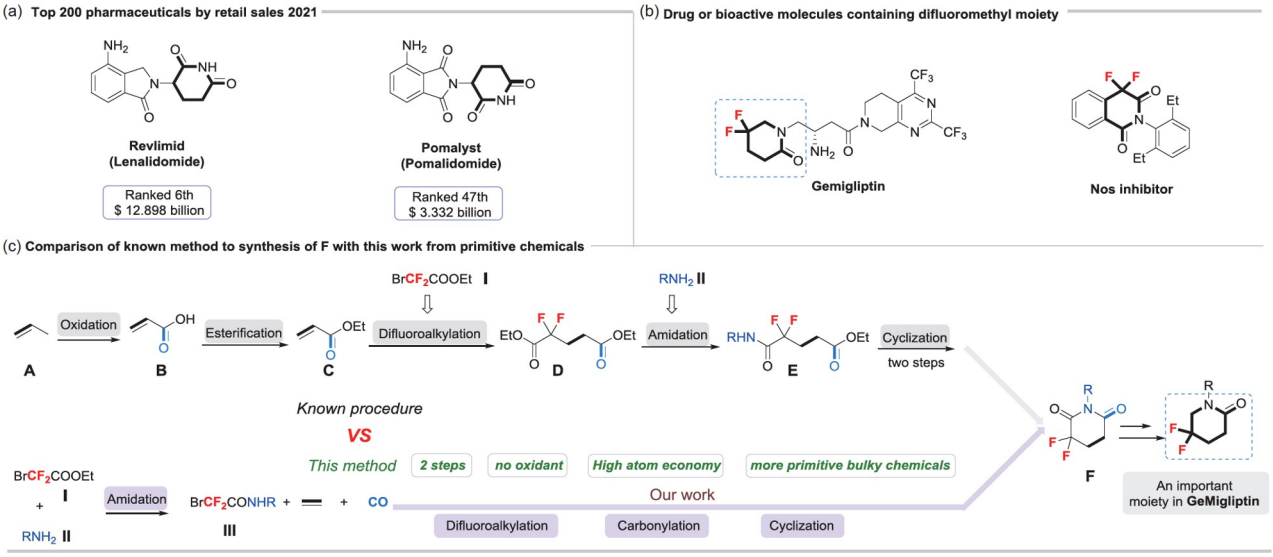
[18]. GeMigliptin is a prolyl-specific dipeptidyl aminopeptidase IV (DPP IV, CD26) inhibitor approved for the treatment of type 2 diabetes mellitus by the Korean Food and Drug Administration in 2012, which is now the sixth DPP-4 inhibitor approved for the treatment of diabetes. 5,5-Difluoropiperidin-2-one is an intriguing scaffold in GeMigliptin as shown in Scheme 2b, which can be prepared from α-carbonyl difluoro-modified glutarimide. The construction of fluorinated heterocycles is a topic of ongoing interest and attracts the attention of synthetic chemists [19–21]. The synthesis of similar building blocks is one of the most exciting topics; however, daunting challenges remain, and the limited known approaches suffer from the necessity of using highly functionalized substrates, lengthy synthetic procedures, harsh reaction conditions, and so on [22–32]. Thus, developing a novel direct synthetic strategy featuring high efficiency, convenient and flexibility is extremely necessary.

It is a simple and efficient strategy to construct difluorine-containing complex compounds if carbonyl group and CF_2 moiety are introduced in a transformation simultaneously [33–36], and transition-metal-catalyzed difluoroalkylative carbonylation has emerged as one of the most straightforward strategies [37–40]. However, employing this strategy to construct difluoro-modified heterocyclic compounds is still challenging and has not been explored yet. Additionally, α-carbonyl difluoro-modified glutarimide was synthesized and used against dipeptidyl peptidase-IV (DPP-IV) (Scheme 2c) [41,42]. In the known procedure, ethyl acrylate **C** was used as the starting material which was mainly obtained *via* oxidation and esterification of propylene, after difluoroalkylation, amidation and cyclization steps to give α-carbonyl difluoro-modified glutarimide **F**. In our designed procedure, we can utilize ethylene and carbon monoxide to replace oxidant and propylene, and this methodology has advantages including short steps, high atomic economy, more primitive raw materials.

2 Experimental

2.1 General information

Unless otherwise noted, all reactions were carried out under a carbon monoxide or nitrogen atmosphere. All reagents were from commercial sources, and all solvents are extra dry solvents and used as received without further purification. Column chromatography was performed on silica gel (200–300 meshes) using petroleum ether (b.p. 60–90 °C) and ethyl acetate as the eluents. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were taken on Bruker AVANCE III 400 MHz or 700 MHz spectrometers and spectral data were reported in ppm relative to tetramethylsilane (TMS) as the internal



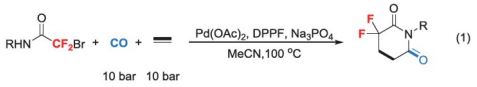
Scheme 2 (a) The structures of Revlimid and Pomalyst that ranked 6th and 47th in the top 200 pharmaceuticals by retail sales in 2021 from the Njardarson research team. (b) Selected drug or bioactive molecules containing difluoromethyl moiety. (c) Comparison of known method to synthesize α-carbonyl difluoro-modified glutarimide with this work from primitive chemicals (color online).

standard and $CDCl_3$ or DMSO-d_6 as solvent. All coupling constants (*J*) are reported in Hz with the following abbreviations: s=singlet, d=doublet, dd=double doublet, t=triplet, dt=double triplet, q=quatriplet, m=multiplet, br=broad. Gas chromatography (GC) analyses were performed on an Agilent HP-7890A instrument (USA) with a FID detector and HP-5 capillary column (polydimethylsiloxane with 5% phenyl groups, 30 m, 0.32 mm i.d. 0.25 μm film thickness) using argon as carrier gas. Gas chromatography mass spectrometer (GC-MS) analyses were performed on a Shimadzu QP2020 NX instrument (Japan). High resolution mass spectra (HRMS) were recorded on Agilent 8890-7250 and Agilent Q-TOF 6540. Because of the high toxicity of carbon monoxide, all of the reactions should be performed in an autoclave. The laboratory should well-equipped with a CO detector and alarm system.

2.2 General procedures

2.2.1 General procedure I

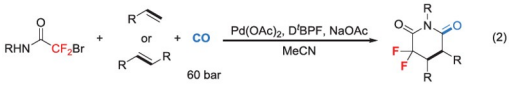
A 4 mL screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %,6.7 mg), 1,1′-ferrocenediyl-bis(diphenylphosphine) (DPPF, 10 mol%, 16.6 mg), Na_3PO_4 (0.45 mmol, 73.8 mg) and an oven-dried stirring bar. The vial was closed with a Teflon septum and cap and connected to the atmosphere *via* a needle. Then bromodifluoroamides (0.3 mmol), MeCN (2 mL) was added with a syringe under N_2 atmosphere, and then the vial was moved to an alloy plate and put into a Parr 4560 series autoclave (300 mL) under N_2 atmosphere. At room temperature, the autoclave was flushed with CO three times and charged with 10 bar CO and 10 bar ethylene gas. The autoclave was placed on a heating plate equipped with a magnetic stirrer. The reaction mixture was heated to 100 °C for 18 h. After the reaction was completed, the crude mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography (PE/EA =10/1 to 3/1) on silica gel to afford the corresponding products.



(1)

2.2.2 General procedure II

A 4 mL screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %,6.7 mg), 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D^{t}BPF, 10 mol%, 14.2 mg), NaOAc (0.45 mmol, 36.9 mg) and an oven-dried stirring bar. The vial was closed with a Teflon septum and cap and connected to the atmosphere *via* a needle. Then bromodifluoroamides (0.3 mmol), unactivated alkene (0.45 mmol), and MeCN (2 mL) was added with a syringe under N_2 atmosphere, and then the vial was moved to an alloy plate and put into a Parr 4560 series autoclave (300 mL) under N_2 atmosphere. At room temperature, the autoclave was flushed with CO three times and charged with 60 bar CO. The autoclave was placed on a heating plate equipped with a magnetic stirrer. The reaction mixture was heated to 85 °C (terminal olefins) or 100 °C (internal olefins) for 24 h. After the reaction was completed, the crude mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography (PE/EA =10/1 to 3/1) on silica gel to afford the products.



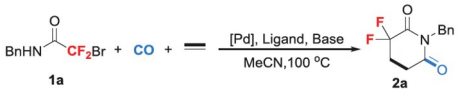
(2)

3 Results and discussion

Ethylene is the simplest C2 synthon which is readily available on an industrial scale *via* cracking of petroleum. For testing our hypothesis, ethylene gas (5 bar) was selected as the substrate to value this difluoroalkylative carbonylative cyclization and with carbon monoxide (5 bar) as a C1 source together with *N*-benzyl-2-bromo-2,2-difluoroacetamide. To our delight, with Na_3PO_4 as the base at 100 °C, the desired product **2a** was obtained in 31% yield in the presence of $Pd(OAc)_2$ and Xantphos (Table 1, entry 1). Subsequently, the different pressure ratio of ethylene gas and carbon monoxide was studied (Table 1, entries 1–3), and **2a** was obtained in 71% yield under ethylene gas (10 bar) and carbon monoxide (10 bar). Then we investigated the effect of palladium catalysts, but unfortunately, reduced yields were obtained with $Pd(TFA)_2$, $PdCl_2$, or $Pd(acac)_2$ as the catalyst precursor (Table 1, entries 4–6). Various bases were studied, and the desired product **2a** could not be detected when employing Na_2HPO_4 or Li_3PO_4 as the bases, while a lower yield was observed in the presence of K_3PO_4 (Table 1, entries 7–9). Further ligand screening showed that DPPF seemed to be the best ligand for this transformation while **2a** was obtained in 89% yield with 84% isolated yield (Table 1, entries 10–12). Finally, we attempted to reduce the loading of palladium catalyst to 5 mol% and the yield of **2a** dropped to 78% (Table 1, entry 13). Besides the above discussed palladium catalysts, nickel and copper catalysts were also tested but no desired product could be detected.

With the best reaction conditions in hand, we started to probe various 1-bromo-1,1-difluoroacetamides for this difluoroalkylative carbonylative cyclization (Scheme 3). *N*-Benzyl-2-bromo-2,2-difluoroacetamides with electron-donating groups, such as methyl, *tert*-butyl, phenyl, methoxy, benzeneoxy, were tolerated well to give the corresponding α-carbonyl difluoro-modified glutarimide products with moderate to high yields (**2b**–**2f**). The substrates with halogen groups, including fluoro, chloro, and bromo substituents, can

Table 1 Optimization of reaction conditions[a)]



Entry	Ethylene/CO (bar)	[Pd]/Ligand	Base	Yield (%)[b)]
1	5/5	$Pd(OAc)_2$/Xantphos	Na_3PO_4	31
2	10/10	$Pd(OAc)_2$/Xantphos	Na_3PO_4	71
3	20/20	$Pd(OAc)_2$/Xantphos	Na_3PO_4	68
4	10/10	$Pd(TFA)_2$/Xantphos	Na_3PO_4	57
5	10/10	$PdCl_2$/Xantphos	Na_3PO_4	58
6	10/10	$Pd(acac)_2$/Xantphos	Na_3PO_4	54
7	10/10	$Pd(OAc)_2$/Xantphos	Na_2HPO_4	N.D.
8	10/10	$Pd(OAc)_2$/Xantphos	Li_3PO_4	N.D.
9	10/10	$Pd(OAc)_2$/Xantphos	K_3PO_4	67
10	10/10	$Pd(OAc)_2$/DPEphos	Na_3PO_4	62
11	10/10	$Pd(OAc)_2$/PPh_3	Na_3PO_4	72
12	10/10	$Pd(OAc)_2$/DPPF	Na_3PO_4	89(84)[c)]
13	10/10	$Pd(OAc)_2$/DPPF	Na_3PO_4	78[d)]

a) Reaction conditions: **1a**(0.3 mmol), ethylene (*x* bar), CO (*y* bar), [Pd] (10 mol%), monodentate ligand (20 mol%) or bidentate ligand (10 mol%), base (0.45 mmol) in MeCN (2 mL) at 100 °C for 18 h. b) Yields were determined by GC-FID analysis using *n*-hexadecane as internal standard. c) Yield of isolated product. d) $Pd(OAc)_2$ (5 mol%), DPPF (5 mol%).

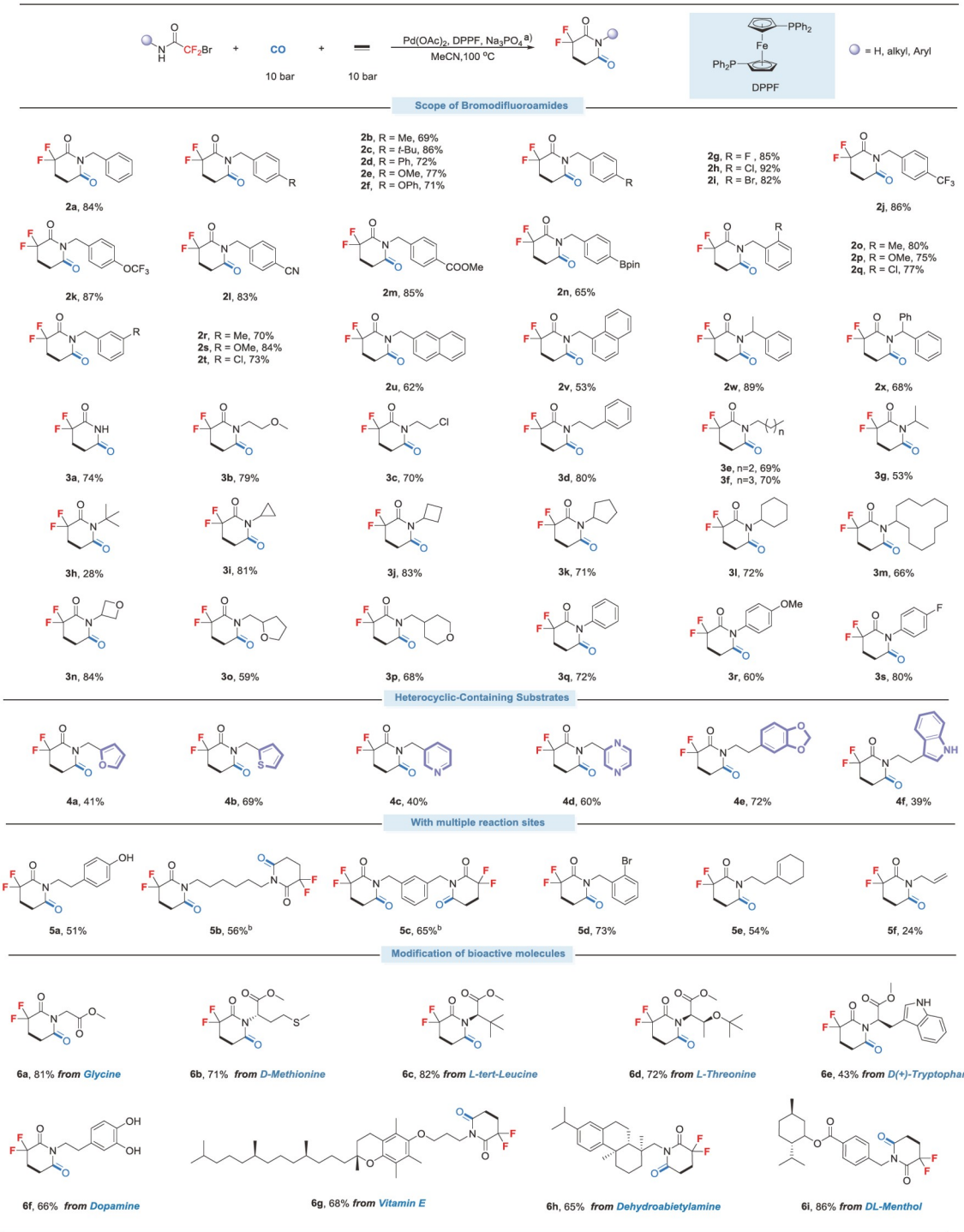
be transformed well and the targeted products were isolated in high to excellent yields (**2g**–**2i**), It is worth noting that up to 92% yield of the desired product can be obtained with 2-bromo-*N*-(4-chlorobenzyl)-2,2-difluoroacetamide as the substrate under our standard conditions. *N*-Benzyl-2-bromo-2,2-difluoroacetamides bearing electron-withdrawing groups, such as trifluoromethyl, trifluoromethoxy, cyano, and ester can afford the desired products in 83%–87% yields (**3j**–**3l**). To our pleasure, sensitive moiety like boronic acid ester can also be tolerated in this reaction. Reduced yields were obtained when ortho-substituted *N*-benzyl-2-bromo-2,2-difluoroacetamides were tested (**2o**–**2q**). The yields of the desired products were also decreased when methyl, methoxy, or chloro meta-substituted *N*-benzyl-2-bromo-2,2-difluoroacetamides were tested (**2r**–**2t**). Inferior results were obtained for substrates with steric hindrance (**2u** and **2v**). Likewise, in comparation with the experimental results of **2w** and **2x**, we can infer that the steric hindrance factor has a great influence on this transformation. Notably, the interesting product α-carbonyl difluoro-modified glutarimide was obtained with a 74% yield (**3a**). For the substrates of some alkyl bromodifluoroamides, moderate to good yields of the corresponding products were obtained (**3b**–**3g**). It should be mentioned that **3h** was only obtained in 28% yield because of the huge steric hindrance of 2-bromo-*N*-(*tert*-butyl)-2,2-difluoroacetamide. Subsequently, various cyclic substrates underwent this conversion very smoothly to give the aimed products in good yields (**3i**–**3p**). Moreover, some aryl bromodifluoroamides were also investigated and the corresponding products with good yield were isolated (**3q**–**3s**).

The electron pairs of heteroatoms in heterocycles tend to coordinate with palladium catalysts and reduce or even inhibit their catalytic activity. In some carbonylative transformations, substrates containing heterocycles were often restricted [43]. Remarkably, various heterocycles such as furan, thiophene, pyridine, pyrazine, and unprotected indole, are compatible in this reaction (**4a**–**4f**). To explore the specificity of this reaction, we chose to examine it with substrates containing multiple reaction sites. For example, our reaction proceeds smoothly without any influence when there is a hydroxyl group in the substrate (**5a**). The reaction can be carried out in an orderly manner if there are two identical reaction sites in the substrate (**5b**–**5c**). When 2-bromo-*N*-(2-bromobenzyl)-2,2-difluoroacetamide was selected as the substrate, the difluoroalkylative carbonylative cyclization was well implemented (**5d**). Alkene group can be tolerated as well, giving the corresponding products in moderate to good yields (**5e**–**5f**). Notably, the decreased yields here are due to the presence of the alkene group in the substrates which can compete with ethylene to give non-desired products.

Subsequnently, to testify the practicality of this method, several drug molecules, natural products, as well as amino acid derivatives modified bromodifluoroamides were also investigated (Scheme 3). Delightly, amino acid derivatives, including glycine, D-methionine, L-*tert*-leucine, L-threonine, and D(+)-tryptophan were all reacted smoothly and furnished the expected products **6a**–**6e** in 43%–82% yields. Moreover, bromodifluoroamides bearing dopamine, vitamin E, dehydroabietylamine, and DL-menthol moieties showed high reactivity as well, affording the corresponding difluoroalkylative carbonylative cyclization products in 65%–86% yields. Various bioactive molecules were also successfully prepared *via* late-stage difluoroalkylative carbonylative cyclization under the current procedure.

Besides ethylene gas, unactivated alkenes can also be applied in this difluoroalkylative carbonylative cyclization (Scheme 4). By slightly modify the reaction conditions, various olefins with functional groups including methoxy, bromo, ester, and chloro, were tolerated well to give the desired products in moderate to good yields (**7a**–**7j**). In this transformation, trimethylsilyl (TMS) group seems to be less compatible under this catalytic system (**7k**). Unfortunately, only a trace amount of the corresponding product was detected when using styrene as the starting material (**7l**). Notablly, internal alkenes underwent this procedure smoothly and the desired products were obtained in moderate yields (**8a**–**8e**).

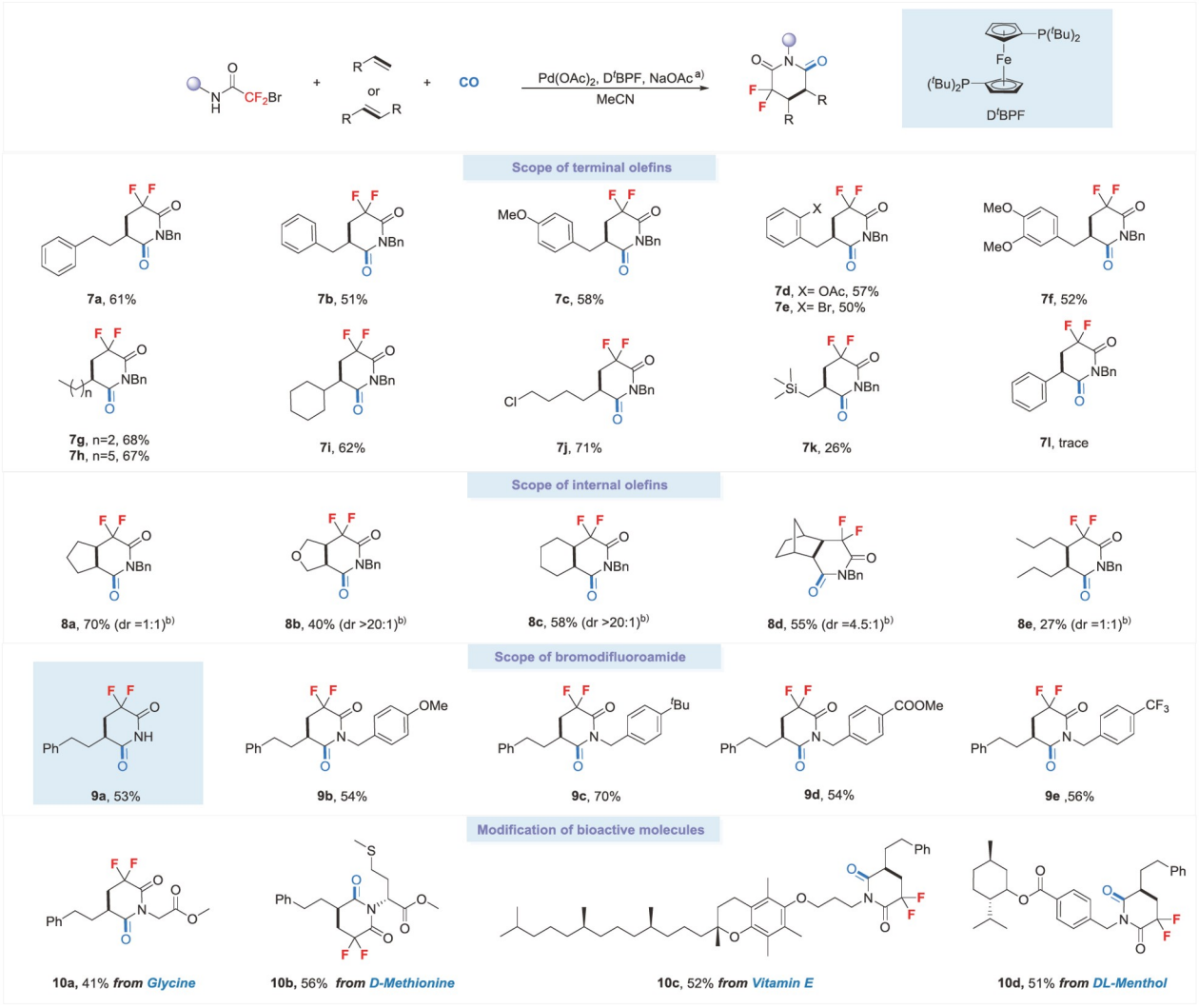
An intriguing structure **9a** was obtained from 4-phenyl-1-butene and 1-bromo-1,1-difluoroacetamide. *N*-Benzyl-2-



Scheme 3 Scope of 1-bromo-1,1-difluoroacetamides. (a) Reaction conditions: **1a** (0.3 mmol), ethylene (10 bar), CO (10 bar), $Pd(OAc)_2$ (10 mol%), DPPF (10 mol%), Na_3PO_4 (0.45 mmol), MeCN (2 mL), 100 °C, 18 h, isolated yields. (b) Bromodifluoroacetamides (0.15 mmol) (color online).

bromo-2,2-difluoroacetamides with electron-donating groups or electron-withdrawing groups, like methoxy, *tert*-butyl, phenyl, trifluoromethyl and ester were all well tolerated to give the targeted products in 54%–70% isolated yields (**9b**–**9e**). Finally, we explored some bioactive molecule related bromodifluoroamides for this transformation with 4-phenyl-1-butene, such as glycine, D-methionine, vitamin E, and DL-menthol, the corresponding products were obtained in moderate yields (**10a**–**10d**).

As valuable synthetic intermediates, the obtained α-carbonyl difluoro-modified glutarimide products can be smoothly converted into other difluoro-modified heterocyclic compounds. In the presence of borane tetrahydrofuran complex solution, product **3d** can be converted into 3,3-di-

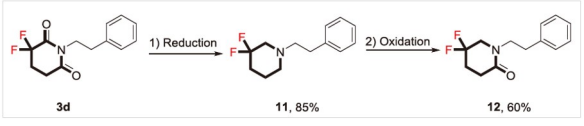


Scheme 4 Scope of different alkenes and 1-bromo-1,1-difluoroacetamides. (a) Reaction conditions: bromodifluoroamides (0.3 mmol), alkenes (0.45 mmol), $Pd(OAc)_2$ (10 mol%), D^{t}BPF (10 mol%), NaOAc (0.45 mmol), MeCN (2 mL), CO (60 bar), 85 °C, 24 h, isolated yields. (b) 100 °C (color online).

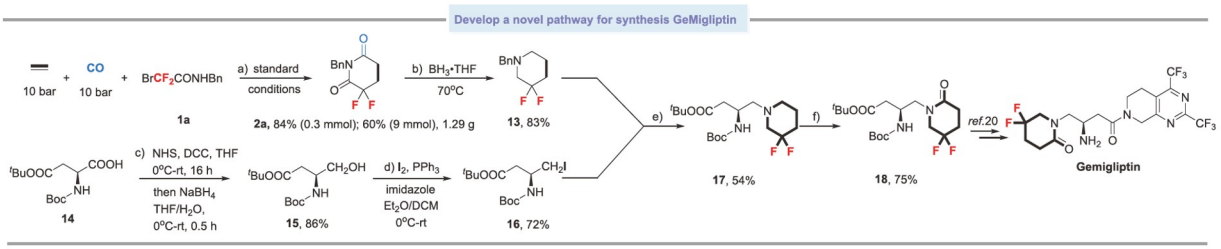
fluoropiperidine derivative **11** in 85% yield, and **11** can be selectively oxidized into 5,5-difluoropiperidin-2-one derivative **12** in 60% yield, which is an important building block in GeMigliptin (Scheme 5).

GeMigliptin is now the sixth DPP-4 inhibitor approved for the treatment of diabetes, which was designed and synthesized by LG Life Sciences Ltd. [44], and the corresponding synthetic route can be viewed in Supporting information. Herein, our developed new procedure can be applied to the synthesis of GeMigliptin with minimal steps (Scheme 6). Our strategy exploits difluoroalkylative carbonylative cyclization to construct difluoro-modified six-membered ring **2a** in one step, then experiencing reduction, coupling with **16** to obtain **17**, and finally oxidization of **17** in the presence of ruthenium(IV) oxide hydrate and sodium periodate afforded **18**.

To gain more insight into the mechanism of this difluoroalkylative carbonylative cyclization, a series of control experiments were performed. First, a radical clock experiment was performed and the ring expanded product **20** was obtained in 42% yield under the standard reaction conditions from α-cyclopropylstyrene **19** (Scheme 7a). However, the yield of product **2a** only slightly decreased when free radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol, a radical scavenger, 1–3 equiv.) was added to under standard conditions. In the case with TEMPO (2,2,6,6-tetramethyl-1-piperinedinyloxy, a radical scavenger, 2 equiv.), **2a** could not be detected (Scheme 7b). When 1,1-diphenylethylene was



Scheme 5 Synthetic transformations. 1) **3d** (1 mmol, 1 equiv.), BH_3·THF (4 mmol, 4 equiv.), THF (5 mL), 70 °C, 3 h; 2) **11** (0.6 mmol, 1 equiv.), $RuO_2 \cdot nH_2O$ (20 mol%), $NaIO_4$ (4 equiv.), H_2O (2 mL), EA (2 mL), rt, 2.5 h (color online).



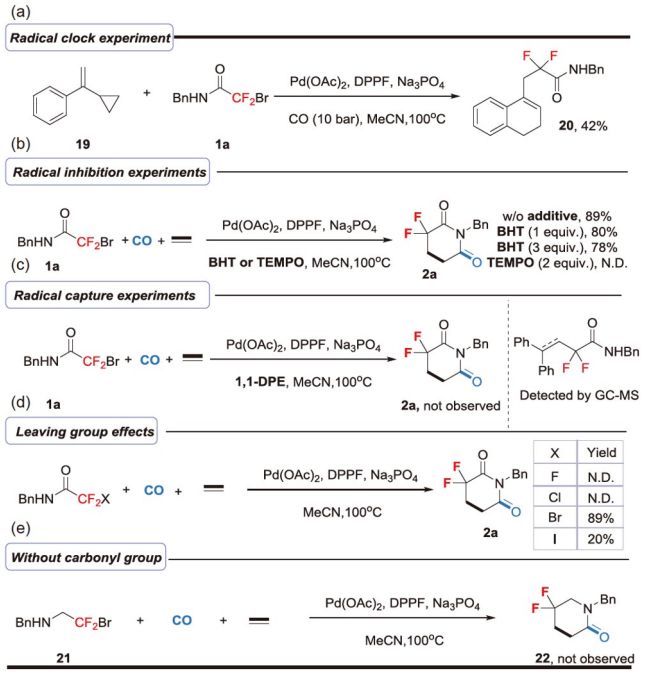
Scheme 6 New producedure for GeMigliptin synthesis. a) **1a** (0.3 mmol), ethylene (10 bar), CO (10 bar), $Pd(OAc)_2$ (10 mol%), DPPF (10 mol%), Na_3PO_4 (0.45 mmol), MeCN (2 mL), 100 °C, 18 h, 84% yield; 9 mmol scale, ethylene (20 bar), CO (20 bar), 60% yield; b) **2a** (1 mmol), BH_3·THF (4 mmol), THF (5 mL), 70 °C, 3 h; c) **14**(10 mmol), NHS (11 mmol), DCC (11 mmol), THF (15 mL), 0 °C-rt, 16 h, then $NaBH_4$ (15 mmol), THF/H_2O, 0 °C-rt, 0.5 h; d) under dark conditions, **15** (10 mmol), I_2 (15 mmol), PPh_3 (15 mmol), imidazole (20 mmol), Et_2O/DCM, 0°C-rt; e) **13** (1.5 mmol), Pd/C, H_2 (10 bar), MeOH (2 mL), 50 °C, 48 h, then **16** (0.3 mmol), DiPEA (0.45 mmol), NaI (0.6 mmol), DMF (2 mL), 70 °C, 30 h; f) **17** (0.1 mmol), $RuO_2 \cdot nH_2O$ (20 mol%), $NaIO_4$ (0.4 mmol), H_2O (0.5 mL), EA (0.5 mL), rt, 2.5 h. NHS= *N*-hydroxysuccinimide, DCC= *N*,*N*′-dicyclohexylcarbodiimide (color online).

added to the reaction under the standard conditions, no product was observed and the difluoroamide radical was captured by 1,1-diphenylethylene (Scheme 7c), which indicates that the radical intermediates were involved in this process. Besides bromine atom, the leaving group in this difluoroalkylative carbonylative cyclization, we explored other possible leaving groups, such as fluorine, chlorine and iodine atoms, and the targeted product **2a** was not observed when using fluorine or chlorine atom as leaving groups in the starting materials. When the iodine atom was used as the leaving group in the substrate, 20% yield of **2a** was obtained and the direct Heck cross-coupling product was detected as the main product (Scheme 7d). Finally, the corresponding product was not detected and the starting material remained unreacted when low activity compound **21** was tested as the substrate (Scheme 7e).

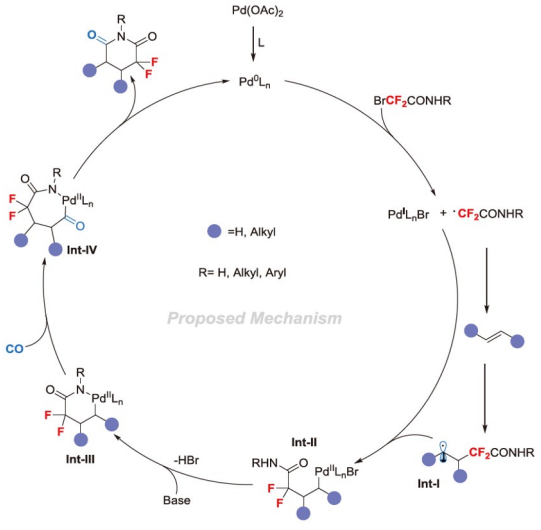
Based on the above results and previous literatures [45–50], a plausible reaction mechanism was proposed (Scheme 8). Initially, the active catalyst Pd^0Ln species was generated from the $Pd(OAc)_2$ pre-catalyst under the reaction conditions. Subsequently, the Pd^0Ln species induced a single-electron transfer reduction of 1-bromo-1,1-difluoroacetamide to get the difluoroamide radical and a Pd^ILnBr species, followed by the addition of the difluoroamide radical to alkene which produces a new carbon radical **Int-I**. Then, **Int-I** reincorporated with the Pd^ILnX species to afford the **Int-II**. Intermediate **Int-III** can be formed after a cyclization process in the presence of base, which produce complex **Int-IV** after the coordination and insertion of CO. Finally, the desired product was formed after reductive elimination step, regenerating Pd^0Ln species to complete the catalytic cycle.

4 Conclusions

In summary, we have developed a new palladium-catalyzed procedure on difluoroalkylative carbonylative cyclization of unactivated alkenes, ethylene gas and 1-bromo-1,1-di-



Scheme 7 Control experiments (color online).



Scheme 8 Proposed mechanism (color online).

fluoroacetamides. A wide range of α-carbonyl difluoro-modified glutarimides were obtained in this transformation with good functional group compatibility under mild conditions. This process provides a potentially valuable strategy for the synthesis of fluorinated heterocycles. Notably, this synthetic method paves a novel pathway for the synthesis of GeMigliptin.

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