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Radical difunctionalization of alkenes with iododifluoromethyl ketones under Nicatalysis

Tianyu Zhang,^[a] Jun Pan,^[a] Jin Duan,^[a] Jingjing Wu,^{*[a]} Wei Zhang,^[b] Fanhong Wu^{*[a]}

Abstract: Ni-catalyzed radical difunctionalization of alkenes with iododifluoromethyl ketones was realized for the synthesis of α , α -difluoroketones. This reaction can also be used for the construction of analogs containing 5-membered heterocycles through radical addition and sequenced cyclization reactions.

Introduction

Due to an increased number of compounds containing α, α -difluoroketo motif found to have biological activities,^[1] the development of synthetic methods for making α, α -difluoroketone molecules have received much recent attention.^[2] Addition of perfluoroalkyl (R_f) radicals derived from R_fI to alkenes is an established method by using AIBN^[3] and Na₂S₂O₄^[4] as radical initiators, and under photoredox^[5] or transition-metal catalysis^[6]. However, the addition reactions of difluoroalkyl (RCF₂) radicals are not fully explored yet,^[7] especially those derivatived from difluoroacyl iodides (RCOCF₂I).^[8]

We have recently reported a 2-iodo-2,2series of radical difluoroketone-based reactions for benzoyldifluoromethylation with alkynes using AIBN as initiator or under Pd-catalyzed conditions,^[9] as well as aldol reactions with aldehydes.^[10] Since Ni-catalyzed radical fluoroalkylation reactions has been emerged as a powerful tool for the synthesis of fluorinated molecules,^[11] we envisoned that RCOCF₂ radicals generated from RCOCF₂I could be used in addition reactions with alkenes. Hence, report here is our effort on the development of Ni-catalyzed radical addition of 2-iodo-2,2difluoroketones with alkenes for the synthesis of different gemdifluromethylene-containing scaffolds (Scheme 1). It is worth noting that these scaffolds are prepared by catalyst-promoted difunctionalization reactions, which is an efficinet and green synthetic technique. Other than the desired difluromethylene, the second group could be readily used for further transformations.

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Scheme 1. Ni-catalyzed reaction of iododifluoromethyl ketones and alkenes

Results and Discussion

Optimization of reaction and substrate scope screening

In our initial investigation, 2,2-difluoro-2-iodo-1-phenylethanone 1a was used as the difluoromethylation agent and 1-octene 2a as the substrate for the NiCl₂ (5 mol%)-catalyzed reaction in 1,4dioxane at 100 °C under nitrogen. The desired product 2,2difluoro-4-iodo-1-phenyldecan-1-one 3a was obtained in 24% yield when 1,10-phen (6mol%) was used as a ligand in the of KOAc (Table1, entry 1). Exploring other Ni presence catalysts (Table1, entries 1-7) indicated that Ni(acac)₂ was the best one (Table1, entry 7). Screening of ligands and bases (Table1, entries 8-16) showed that 1,10-phen and K₂CO₃ were the most suitable ligand and base respectively (Table1, entry 12). Then, the solvent investigation (Table1, entries 17-20) showed that cyclopentyl methyl ether (CPME) is also a suitable solvent for this reaction. Since CPME is more environmental friendly than 1,4-dioxane, we chose CPME as the reaction solvent (Table 1, entry 17). Further examination showed that Ni(0) and Raney Ni were not suitable catalysts for the reaction which gave lower yields of 3a (Table 1, entries 21 and 22). Thus, the optimized reaction condition was to use Ni(acac)₂ as catalyst in the presence of 1,10-phen and K_2CO_3 in CPME at 100 °C under nitrogen (Table 1, entry 16). Two control reactions showed that the reaction could proceeded without base or ligand and gave the product 3a in lower yield accompanied with unreacted starting material 1a respectively (Table 1, entries 23 and 24). It's worth noting that the product 3a could be obtained in 48% yield just in the presence of base without Ni catalyst and ligand when the reaction time was extended to 24 h (Table 1, entry 25).

Table 1. Optimization of Reaction Conditions^[a]

			cat/linand		_C ₆ H ₁₃
		C ₆ H ₁₃ b	ase, solvent	F F	
	1a	2a		3a	
Entry	Catalyst	Ligand	Base	Solvent	Yield [%] ^[b]
1	NiCl ₂	1,10-phen	KOAc	1,4-dioxane	24
2	NiCl ₂ (dppf)	1,10-phen	KOAc	1,4-dioxane	16
3	NiCl ₂ (dppp)	1,10-phen	KOAc	1,4-dioxane	9
4	NiBr ₂ (DME)	1,10-phen	KOAc	1,4-dioxane	44
5	$NiCl_2(PPh_3)_2$	1,10-phen	KOAc	1,4-dioxane	67
6	NiCl ₂ glyme	1,10-phen	KOAc	1,4-dioxane	71
7	Ni(acac) ₂	1,10-phen	KOAc	1,4-dioxane	83
8	Ni(acac) ₂	xantphos	KOAc	1,4-dioxane	75
9	Ni(acac) ₂	dppf	KOAc	1,4-dioxane	20
10	Ni(acac) ₂	bpy	KOAc	1,4-dioxane	63
11	Ni(acac) ₂	TCHP	KOAc	1,4-dioxane	0
12	Ni(acac) ₂	1,10-phen	K ₂ CO ₃	1,4-dioxane	92
13	Ni(acac) ₂	1,10-phen	K_3PO_4	1,4-dioxane	72
14	Ni(acac) ₂	1,10-phen	Et ₃ N	1,4-dioxane	60
15	Ni(acac) ₂	1,10-phen	TMEDA	1,4-dioxane	56
16	Ni(acac) ₂	1,10-phen	DBU	1,4-dioxane	0
17	Ni(acac)₂	1,10-phen	K ₂ CO ₃	CPME	90
18	Ni(acac) ₂	1,10-phen	K_2CO_3	DMF	45
19	Ni(acac) ₂	1,10-phen	K_2CO_3	DMA	31
20	Ni(acac) ₂	1,10-phen	K_2CO_3	NMP	11
21	Ni(COD) ₂	1,10-phen	K_2CO_3	CPME	trace
22	Raney Ni	1,10-phen	K_2CO_3	СРМЕ	13
23	Ni(acac) ₂	1,10-phen	-	CPME	38
24	Ni(acac) ₂	-	K_2CO_3	CPME	55
25 ^[c]	-	-	K ₂ CO ₃	CPME	48

^[a] Reaction conditions: **1a** (1 mol), **2a** (1.2 mmol), base (2 mmol), catalyst (5 mol%), ligand (6 mol%), and solvent (4 mL) in a sealed Schlenk tube, 100 °C for 5-8 h under N₂. ^[b] Yields were determined by ¹⁹F NMR analysis using trifluorotoluene as an internal standard. ^[c] Reaction for 24 h.

explore the substrate scope, different 2-iodo-2,2-То difluoroketones 1 were investigated in combination with several unactivated alkenes 2 under the optimized reaction conditions (Table 2). Aryl 2-iodo-2,2-difluoroketones bearing electrondonating or -withdrawing groups were tested to give diverse difluoroalkyl ketones (3a-k) in excellent yields except 3j (42% yield). The product 3j was formed along with several unknown byproducts. It was observed that 2,2-difluoro-2-iodo-1-(ptolyl)ethan-1-one reacted with 2a affording 2,2-difluoro-4-iodo-1-(p-tolyl)decan-1-one 3g with a high yield of 91%. The aliphatic and heterocyclic 2-iodo-2,2-difluoroketones were also suitable fluorinated agents to give desired products 31-3n in good yields. Furthermore, various unactivated alkenes were used in the reactions under the optimized conditions giving products in good yields (3o-r). 2,5-Dihydrofuran was found to be a good substrate and produced the product 3q in 65% yield. Moreover, the

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internal alkene cyclohexene could be employed in the reaction to give the compound **3r** in moderate yield. However, the reaction of phenylethylenes only gave a trace amount of product and most starting material was unreacted. When naphthalenyl iododifluoromethyl ketone was reacted with 1octene, both the addition product **3s** and cyclization product **3t** were obtained in almost 1:1 ratio. A gram-scale reaction of **1a** and **2a** was carried out under the optimized conditions to afford **3a** in 80% yield by using decreased amount of Ni catalyst (1 mol%) (Scheme 2).

Table 2. Scope of the radical addition fluoroalkylation^{[a],[b]}



 $^{[a]}$ Reaction conditions: 1 (1.0 mmol), 2 (1.2 mmol), Ni(acac)₂ (0.05 mmol), 1,10-phen (0.06 mmol), K₂CO₃ (2 mmol), CPME (4 mL), 100°C for 5-8 h under N₂. $^{[b]}$ Isolated yield.



Post-modifications for cyclization- difunctionalization

We have previously reported the AIBN-initiated radical reactions 2-iodo-2,2-difluoroacetophenones with of unsaturated acids/alcohols for preparing cyclic esters and ethers.^[12] We wonder if the Ni-catalyzed radical reaction of similar substrates could also yield the cyclization products. Gratifyingly, lactone 7 and cyclic ether 8 were obtained in good yields when 1a was reacted with 2,2-dimethylpent-4-enoic acid 4 or pent-4-en-1-ol 5, respectively (Table 3). N-Methyl-N-phenylmethacrylamide 6 was also used in the reaction, which provided PhOCF2-containing indolinone 9 in 71% yield. Since indolinone is a privileged heterocyclic scaffold found in bioactive natural products and synthetic compounds,^[13] this reaction provides an alternative route to acesss fluorinated indolinons.

Table 3. Synthesis of PhCOCF2-containing heterocyclic compounds^[a]



 $^{[a]}$ Reaction conditions: **1a** (1.0 mmol), alkene (1.2 mmol), Ni(acac)₂ (0.05 mmol), 1,10-phen (0.06 mmol), K₂CO₃ (2 mmol), CPME (4 mL), 100 °C, under N₂ for 8 h. ^[b] Reaction for 20 h.

The Wu and Jiang groups recently reported a Pd-catalyzed reaction of R_fI with olefins through radical addition and then cyclization to afford the fluoroalkylated 2,3-dihydrobenzofuran.^[14] Since Ni-catalyst is more affordable than Pd-catalyst, we would like to explore the possibility of using a Ni-catalyst to replace the Pd-catalyst. Fortunately, our effort to construct C_{sp}^3 -CF₂ and C-O bonds through radical bifuctionalization was successful and gave difluoroalkylated 2,3-dihydrobenzofurans **11a-c** in good yields (Table 4). In this reaction, TMEDA insead of K₂CO₃ was used as the base.



Table 4. Synthesis of difluoromethylated 2,3-dihydrobenzofuran [a].

 $^{[a]}$ Reaction conditions: 1a (1.0 mmol), alkene (1.2 mmol), Ni(acac)_2 (0.05 mmol), 1,10-phen (0.06 mmol), TMEDA (2 mmol), CPME (4 mL), 100 °C, under N_2 for 5-8 h.

Control reactions and proposed reaction mechanism

Several control reactions were carried out to understand the mechanism of the Ni-catalyzed difluoroalkylation reaction (Scheme 3). When the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction, the radical difluorination process was inhibited, and the TEMPO-CF₂COPh adduct **13** was detected (δ -71.85 for compound **13**, see the Supporting Information) (Scheme 3a). A radical clock reaction using (1S)-(-)- β -Pinene **14** as the radical probe was also conducted, thus giving the ring-opened diene **15** in 72% yield (Scheme 3b). The two reactions indicated that the generation of the PhCOCF₂· radical might be involved in the reaction process.



On the basis of the above control experiments and previous reports, ^[15] we proposed a plausible reaction mechanism for the radical addition of alkenes with 2-iodo-2,2-difluoroketone 1 (Scheme 4). Both of Hu's group and Studer's group disclosed that base could initiate the radical reaction in an unknown way. ^[15] We also found that the radical adduct could be formed only in the presence of K₂CO₃ (Table 1, entry 25). In the presence of Ni(acac)₂, the Ni catalyst might somehow act in concert with K₂CO₃ to accelerate the generation of the benzoyldifluoroalkyl radical from 1 (Table 1, entry 24), which is similar to both Hu's and Studer's reports.^[15] Moreover, the addition of ligand could further active the 2-iodo-2,2-difluoroketone 1 and give higher yield of 3a (Table 1, entry 17). Accordingly, we proposed that benzoyldifluoroalkyl (RCOCF₂) radical A is generated from benzoyldifluoroalkylation agent 1 in the presence of Ni catalyst, ligand and base (step 1). The RCOCF₂ radical A adds to the alkene to generate alkyl radical B (step 2), which can react with another molecule of benzoyldifluoroalkylation agent 1 to produce the addition product 3 and regenerate RCOCF₂ radical A (step 3).

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Scheme 4. A proposed reaction mechanism

Conclusions

In summary, we have developed an operationally simple and higly efficient Ni-catalyzed radical difunctionaliztion reaction of alkenes and 2-iodo-2,2-difluoroketones. The reaction is not only good for the synthesis of 1,2-difluroalkylated and iodinated products, it also can be used for the construction of difluoroalkylated tetrahydrofuran, dihydrobenzofuran, and indolinone compounds through a radical addition and cyclization process. Preliminary mechanistic investigation demonstrated the possibility of formation of RCOCF₂ radical by Ni-catalysis. Further synthetic applications of the Ni-catalyzed radical reaction for the construction of diversity difluorinated compounds are currently underway in our laboratory and will be reported in due course.

Experimental Section

General catalytic reaction procedures: An oven-dried Schlenk tube was charged with Ni(acac)₂ (0.05 mmol), 1,10-phen (0.06 mmol) and K₂CO₃ or TMEDA (2 mmol). The tube was evacuated and backfilled with nitrogen (repeated three times). Then a 2-iodo-2,2-difluoroacetophenone **1** (1.0 mmol) and an alkene **2** (1.2 mmol) in CPME (4.0 mL) were added into the tube. The reaction mixture was stirring at 100 °C for 5-8 h. After completion of the reaction as indicated by TLC, the reaction was quenched with an appropriate amount of water, and the reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with saturated brine, dried over Na₂SO₄, and concentrated in *vacuum* to give the crude product **3**. It was purified by silica-gel column chromatography (100:1 petroleum ether/EtOAc) to afford the desired product .

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Keywords: Ni-catalyst • 2-iodo-2,2-difluoroketones • alkenes • radical • difunctionalization

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Radical difunctionalization of alkenes with iododifluoromethyl ketones under Ni-catalysis



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Nickel-catalyzed radical difucntionalization of alkenes with iododifluoromethyl ketones through 1,2-addition or addition and cyclization sequences