Tetrahedron Letters, Vol. 34, No. 20, pp. 3239-3242, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

# A General Route to α,α-Difluoroketones

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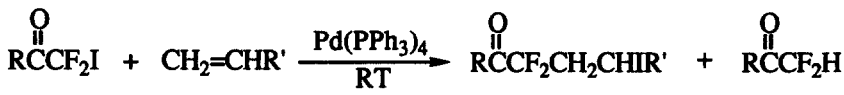
*Abstract:* The reaction of iododifluoromethyl ketones with alkenes catalyzed by $Pd(PPh_3)_4$ in the absence of solvent at room temperature gives high yields of the corresponding 1:1 addition products. Treatment of the adducts with $Zn/NiCl_2 \cdot 6H_2O/THF$ affords α,α-difluoroketones. A variety of functional groups in the olefins are tolerated under the reaction conditions, including alkyl, trimethylsilyl, hydroxy, epoxy, carbonyl and ester groups.

The synthesis of selectively fluorinated compounds has attracted much attention in recent years because the presence of fluorine in a molecule results in many unique physical and chemical properties.[1] Many selectively fluorinated analogues of biologically important compounds have demonstrated dramatic enhancement in their biological activity.[2] α,α-Difluoroketones have been successfully used as inhibitors of hydrolytic enzymes, and greatly enhanced biological activity has been reported compared with their nonfluorinated analogs.[3]

Although efforts have been made toward the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group,[4] only limited methods have been available for the direct synthesis of α,α-difluoroketones. Some fluorinating agents, such as elemental fluorine, perchloryl fluoride, xenon difluoride, acetyl hypofluorite and cesium fluoroxysulfate have been used for this purpose.[5] Recently, α,α-difluoro-β-hydroxy ketones have been prepared *via* treatment of chlorodifluoromethyl ketone with zinc and carbonyl compounds by the Reformatsky reaction.[6] Seyferth reported the reaction of the gem-difluoroallyl anion with esters to give the corresponding α,α-difluoroallyl ketones.[7] More recently, N-F compounds have been applied as fluorinating agents for the reaction with enolate anions or highly acidic methylene compounds to afford α,α-difluoroketones.[8] Although some of the N-F reagents exhibit some generality and specificity, most of the previously described methods use expensive or hazardous reagents, do not tolerate a variety of functionalities or give low yields. Herein, we wish to report a novel and practical method for the general synthesis of α,α-difluoroketones which tolerates a variety of substituents.

The addition of fluoroalkyl iodides to olefins is one of the most important methods for the synthesis of fluorinated compounds.[9] Many initiators have been available for this reaction since the pioneering work of Haszeldine and Brace.[10] However, the discovery of new and more efficient initiator systems and the expansion of their application in organic synthesis is ongoing.[11-13] Recently, this method has been applied to the synthesis of selectively fluorinated compounds. Palladium(0) was found to be a highly efficient initiator for the addition of diethyl iododifluoromethyl phosphonate with alkenes.[12] Similarly, we found that α,α-difluoro-γ-iodoketones (3) could be obtained in high yields by the reaction of iododifluoromethyl ketones (1) with olefins in the presence of a catalytic amount of tetrakis(triphenyl-phosphine)palladium in the absence of a solvent at room temperature. The results are summarized in Table I.

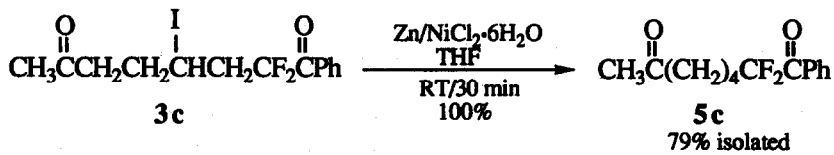


1 2 3 4

R: Ph R': *n*-$C_6H_{13}$(a), $CH_2CH_2\overset{O}{\overset{/\backslash}{C}}H\text{-}CH_2$(b), $CH_2CH_2COCH_3$(c), $CH_2C(CO_2Et)_2CH_2CH{=}CH_2$(d), $Me_3CCH_2$(e)
R: *n*-$C_4H_9$ R': *n*-$C_4H_9$(f)
R: *n*-$C_6H_{13}$ R': $CH_2CH_2OH$(g), $CH_2OCOCH_3$(h), $Me_3Si$(i)

Both phenyl- and alkyl- substituted ketones reacted with olefins to give high yields of adducts under mild conditions. By using iodine-free ketones,[14] 1.5-3 mol% Pd(0) was sufficient to initiate the reaction. More importantly, many organic functional groups, such as alkyl, trimethylsilyl, hydroxy, epoxy, carbonyl and ester in the alkenes were tolerated under the reaction conditions. Thus, a variety of α,α-difluoro-γ-iodoketones (3) bearing different functional groups were produced by this method.

α,α-Difluoro-γ-iodoketones were easily reduced by treatment with $Zn/NiCl_2{\cdot}6H_2O$ ( Zn : $NiCl_2{\cdot}6H_2O$ = 1.5% : 10% based on 1 ) in THF at room temperature and gave excellent yields of α,α-difluoroketones (5).[12]



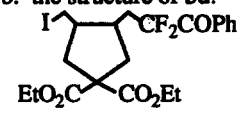
3c 5c
RT/30 min
100%
79% isolated

**Table I: The Reaction of Iododifluoromethyl Ketones with Alkenes Catalyzed by $Pd(PPh_3)_4$[a]**

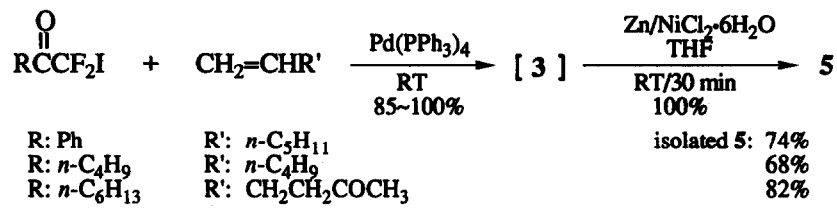
| Entry | R | 2 | Conversion(%) | 3(%) | 4(%) |
|---|---|---|---|---|---|
| 1 | Ph | a | 94 | 93(81) | <3 |
| 2 | Ph | b | 100 | 99(68) | <2 |
| 3 | Ph | c | 100 | 100(84) | – |
| 4 | Ph | d | 100 | 95(66)[b] | <3 |
| 5 | Ph | e | 100 | 100(88) | – |
| 6 | $n$-$C_4H_9$ | f | 95 | 85(62) | 10 |
| 7 | $n$-$C_6H_{13}$ | g | 71 | 76(50) | 24 |
| 8 | $n$-$C_6H_{13}$ | h | 100 | 93(87) | 7 |
| 9 | $n$-$C_6H_{13}$ | i | 100 | 98(90) | <2 |

a: Reaction conditions: RT/~30 min.; the ratio of 1:2:Pd(0) = 1:1.5~3:1.5~3%; conversion and yields were determined by $^{19}F$ NMR analysis except the yields in parenthesis (isolated); all products gave satisfactory $^1H$, $^{19}F$, $^{13}C$ NMR, GC-MS and FT-IR data.

b: the structure of 3d:




Also, high yields of α,α-difluoroketones (5) were obtained by a one-pot addition-reduction procedure without the isolation of α,α-difluoro-γ-iodoketones (3) [the mole ratio of reactants: 1:2:Pd(0):Zn:$NiCl_2$·$6H_2O$ =1:1.3~2.3:1.5~3%:1.2~2:10~20%].[15]




In conclusion, this reaction provides a simple, efficient, and general method for the direct synthesis of a variety of substituted α,α-difluoroketones.

## Acknowledgement:

We would like to thank the National Science Foundation for financial support of this work.

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14. The iodine in the ketones could be easily removed by shaking with metal Hg for several minutes at room temperature.
15. A typical procedure is as follows: a two-neck flask fitted with a magnetic stir bar and a condenser topped with a nitrogen inlet was charged with 0.11 g (0.10 mmol, 1.3%) of $Pd(PPh_3)_4$ and 1.1 g (11.2 mmol) of 1-heptene. 2.1 g (7.4 mmol) of iododifluoromethyl phenyl ketone was added *via* syringe under nitrogen at room temperature. The reaction was initiated in 5~10 seconds and the mixture became exothermic. After the reaction mixture was stirred for ~30 min. and cooled to room temperature, 10 mL of hexane was added and the solids were removed by filtration. After evaporation of the solvent, the residue was added to a flask charged with 0.18 g (0.75 mmol) of $NiCl_2 \cdot 6H_2O$ and 0.75 g (11.5 mmol) of zinc in 10 mL of moist THF. The reaction mixture was stirred for 30 minutes at room temperature, and then poured into a beaker containing 50 mL of aq. $NH_4Cl$ solution and 40 mL of ether. The solid was removed by filtration and washed with ether. The combined organic layers were washed with water and dried over $MgSO_4$. After evaporation of the ether, the residue was distilled to give 1.4 g of α,α-difluorooctyl phenyl ketone (isolated yield 74%; GLPC purity >96%), b.p. 117-119 °C / 0.4 mmHg. $^{19}F$ NMR ($CDCl_3$, $CFCl_3$): δ = -100.2 (t, $J$ = 0.75 Hz) ppm; $^1H$ NMR ($CDCl_3$, TMS): δ = 8.08 (d, $J$ = 7.53 Hz, 2H), 7.49 (t, $J$ = 7.41 Hz. 1H), 7.37 (t, $J$ = 7.66 Hz, 2H), 2.14 (m, 2H), 1.52 (m, 2H), 1.27-1.24 (m, 8H), 0.86 (t, $J$ = 6.75 Hz, 3H) ppm; $^{13}C$ NMR ($CDCl_3$, TMS): δ = 189.2 (t, $J$ = 31.71 Hz), 134.1, 132.4, 130.3, 128.7, 120.1 (t, $J$ = 252.6Hz), 34.2 (t, $J$ = 22.7Hz), 32.0 (s), 29.6, 29.3, 22.9, 21.7, 14.2 ppm; FT-IR ($CCl_4$): 2958, 2930, 2929, 2873, 1705, 1599, 1178 $cm^{-1}$; GC-MS: 254 ($M^+$), 105 ($PhCO^+$, 100).


(Received in USA 28 January 1993; accepted 16 March 1993)