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PALLADIUM AND NICKEL-CATALYZED PERFLUOROALKYLATION OF ALDEHYDES USING ZINC AND PERFLUOROALKYL HALIDES

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A room temperature method for the conversion of perfluoroalkyl iodides to α-perfluoroalkyl carbinols under Pd or Ni catalysis is reported. The use of trifluoromethyl bromide provides an economical procedure for trifluoromethyl substituted carbinols.

Perfluoroalkyl substitution often confers unique biological properties on organic molecules and as such their introduction has been the subject of much research. There are two possible approaches, namely, fluorination of a suitable functional group or direct introduction of the perfluoroalkyl group. In the former class halogen exchange of $-CCl_3$ with $HF-SbCl_5$^1) and fluorination of $-CO_2H$ by SF_4^2) provide practical methods. Direct introduction has been carried out at elevated temperatures in an Ullmann-type reaction between the perfluoroalkyl iodide and an aromatic, aliphatic or heterocyclic iodide using copper powder.^3-5) Copper (I) iodide has been used in the treatment of aromatic iodides with an excess of sodium trifluoroacetate at 160 °C to give the trifluoromethyl substituted compounds in fair to good yields.^6) In a search for more versatile perfluoroalkyl organometallic species we have previously developed a procedure in which alkynes, aryl iodides, allyl bromides, dienes, ketones and aldehydes are perfluoroalkylated using perfluoroalkyl iodides and zinc with the aid of ultrasound at room temperature.^7-9) Whilst these are excellent procedures for laboratory preparations, the ultrasonic irradiation of larger scale reactions is impractical. With a view to overcoming these problems we have developed a method for the perfluoroalkylation of aldehydes with perfluoroalkyl halides and zinc in a catalytic cycle using palladium or nickel catalysts, the use of ultrasound being unnecessary.

In a typical experiment commercial zinc powder (*ca.* 90%) together with the catalyst (0.1 to 0.4 molar %) was added to a solution of the perfluoroalkyl iodide (CF_3I, C_2F_5I, $i\text{-}C_3F_7I$, C_4F_9I, $C_6F_{13}I$, or $C_8F_{17}I$) and the aldehyde in DMF. This was then stirred at room temperature and stirring was continued overnight for convenience, though the reaction was usually found to be complete in 3 - 4 h. Acid workup (2M HCl) with ethereal extraction, drying ($MgSO_4$) and evaporation gave the crude carbinol, the yield of which was determined by addition of a known amount of benzotrifluoride as an internal ^{19}F NMR calibrant. These results are summarized in Table 1.

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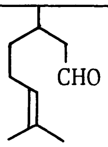
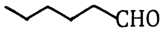
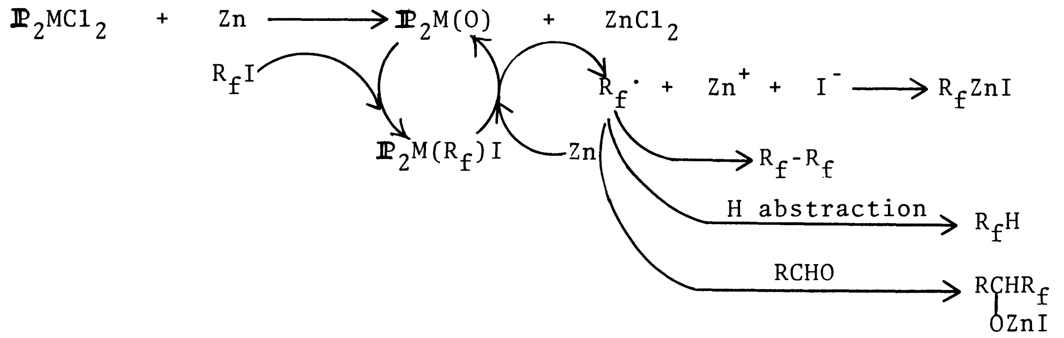
Table 1. Preparation of Perfluoroalkylated α-Carbinols:

$$R_fI + Zn + RCHO \xrightarrow[DMF]{[cat.]} R_fCH(OH)R$$

Aldehyde	R_fI	Ratio RCHO : R_fI	Catalyst[a)]	Yield/% NMR	Yield/% isolated	Bp(°C/mmHg) [Mp °C]
PhCHO	CF_3I	2.1 : 1	B	44	44	52/13
	C_2F_5I	1.8 : 1	A	57	41	84 - 85/10
	i-C_3F_7I	1.1 : 1	A	78	78	68 - 70/4
	C_4F_9I	1.7 : 1	B[b)]	63	33	74.5/5
	$C_6F_{13}I$	1.7 : 1	B[b)]	79	14	[49 - 51]
	$C_8F_{17}I$	1.7 : 1	B[b)]	82	18	[70.5 - 72.5]
PhCH=CHCHO	CF_3I	2.0 : 1	B	21	19	
	C_2F_5I	2.2 : 1	B	49	42	100/5
	i-C_3F_7I	1.01 : 1	A	68	62	88 - 91/4[d)]
	CF_3I	2.2 : 1	B	24	24	88 - 94/5[d)]
	C_2F_5I	2.0 : 1	B	54	21	92 - 94/6
	i-C_3F_7I	1.2 : 1	B	-	78	69 - 70/4
	i-C_3F_7I	1.2 : 1	B	26	18	55 - 60/4[d)]
	CF_3I	1.8 : 1	B	15	-	

a) A = $(Ph_3P)_2PdCl_2$, B = $(Ph_3P)_2NiCl_2$. b) 1-1.6% Ph_3P added as co-catalyst. c) All products were identified by NMR (^{19}F and ^1H), IR, and MS. d) As it was carried out in small scale, the bp was not determined precisely.

Perfluoroalkyl iodides have been reported to add oxidatively to zero valent palladium and platinum complexes.[10)] Thus the catalytic cycle may presumably be shown as follows:



In the case of i-C_3F_7I the reaction is considered to proceed through the carbanion and not the radical. The basis for this is that no coupled material has been observed, furthermore a preformed zinc reagent (i-C_3F_7ZnI), observable on the ^{19}F NMR, also reacts with aldehydes to give carbinols. It is the anionic character of the i-C_3F_7 group which confers this reactivity on the zinc reagent. In the case of CF_3I, CF_3Br and C_2F_5I the zinc reagents are formed as non-reactive by-products.

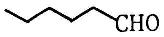
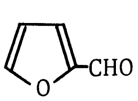
Whereas the palladium catalyst gave good yields for *i*-C_3F_7I it did not promote the reaction with CF_3I. The corresponding nickel catalyst was successful and has the advantage of being cheap. It is easily prepared by stirring $NiCl_2$ with an excess of Ph_3P in methanol either at room temperature overnight, or under reflux for a few hours. Divalent palladium and nickel complexes were used for their stability and ease of handling and should be readily reduced to the active zero valent species by zinc in the reaction media. Other solvents, such as THF, ether, methylene dichloride, and dioxane were tried, but their use resulted in greatly reduced yields. Similar reactions with ketones, epoxides, acetals and acid chlorides were unsuccessful. In the absence of any catalyst either no reaction occurred at all or a low yield of the carbinol was observed together with darkening of the reaction mixture.

In the cases of CF_3 and C_2F_5 the intermediates seem to be more reactive and rapidly give a mixture of products ($R_fCH(OH)R$, R_fH, R_f-R_f and R_fZnI). This is partially overcome by employing an excess of the aldehyde, the remainder of which can be readily separated from the crude product by washing with aqueous $NaHSO_3$. Traces of DMF are removed from the product by washing twice with very dilute aq HCl. In many cases, these washings left the product in a pure state without the necessity of further treatment.

It seemed desirable to make use of the exceedingly cheap reagent CF_3Br (marketed as a fire extinguishing agent with molar cost *ca.*1500 times less than that of CF_3I !) for the trifluoromethylation. The above method was successful and using a 2.8 molar excess of benzaldehyde, a yield of 37.7% was achieved. Using a 1.6 molar excess gave a lowered yield of 34%. Following the observation by Trost et al.,[11)] that addition of a neutral Π-acceptor ligand, such as Ph_3P, accelerates the attack of nucleophiles on Π-allyl palladium complexes, we found that addition of a small amount of Ph_3P (1 - 3 molar % to the reaction mixture) gave a higher yield of 40% using only a 1.4 molar excess of benzaldehyde. The results of the reactions with CF_3Br are given in Table 2.

As trifluoromethyl bromide has a very low solubility in DMF, reactions were therefore carried out in a sealed tube (*ca.*50 ml). The other reactants were first placed in the tube which was then cooled to -78 °C, evacuated and the required amount of CF_3Br condensed in from a balloon. A small magnetic bar placed in the flask provided sufficient stirring. Experiments with benzaldehyde, in which no catalyst was added, twice resulted in no reaction, and once gave a lowered yield of 24%. With catalyst, however, the reaction proceeded smoothly and reproducibly, essentially the same yield (39% being obtained even when the scale was increased to 0.1 mole). Reactions with other electrophiles such as ketones and esters failed.

Table 2. Trifluoromethylation of Aldehydes with $CF_3Br/Zn/(Ph_3P)_2NiCl_2$

Aldehyde	Molar excess	Ph_3P	Yield / %		Bp
		(mol%)	NMR	isolated	(°C/mmHg)
PhCHO	1.4	3	40	28	84 - 87/14
	1.6	-	34	-	
PhCH=CHCHO	3.2	4.5	13	-	
	2.3	-	28	-	
	1.7	3.4	8	-	
$CH_3CH=CHCHO$	2.5	-	6	-	
	1.1[b]	5.6	13	-	
	1.1[b]	-	0	-	
p-MeC_6H_4CHO	1.4	5.3	18	13	
o-MeC_6H_4CHO	1.4	1.2	38	26	69/4
p-$MeOC_6H_4CHO$	1.3	3.6	13	11	
p-ClC_6H_4CHO	1.5	1.7	51	34	80/4
p-$Me_2NC_6H_4CHO$	1.5	2.3	7	-	

a) All products were identified by NMR (^{19}F and ^{1}H). b) Stirred for 3 h, all others stirred overnight.

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