The Remarkably High Reactivity of α-Cyano-α-fluorophenylacetyl Chloride (CFPA–Cl) towards Hindered Nucleophiles in Enantiomeric Excess Determination

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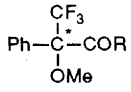
The reaction of PhCF(CN)COCl **2b** with 3,3-dimethylbutan-2-ol **5** was found to proceed more than 500 times faster than that of $PhCCF_3(OMe)COCl$ (MTPA–Cl) **1b**, suggesting that the CFPA method should potentially lead to much less kinetic resolution than the currently much-used MTPA method in enantiometric excess determinations.

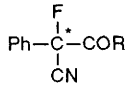
The development of efficient chiral derivatizing reagents is of interest and significance, not only for enantiomeric excess (e.e.) determination but also for structural characterization, absolute configuration estimation, enantiomeric separation, *etc*. To be effective, the derivatizing reagent must be sufficiently reactive† towards various samples of interest and also it must produce a pair of diastereoisomers which have distinctly different physical and chemical properties, in particular, NMR chemical shifts. Although Mosher's method[1] of using α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) **1a** is widely employed for e.e. determinations, kinetic resolution[2] and/or incomplete derivatization[3] may result from this method owing to the low reactivity of the reagent.

We have recently developed a new chiral derivatizing reagent, α-cyano-α-fluorophenylacetic acid (CFPA) **2a**,[4] and have shown that NMR-based e.e. determinations using this reagent are much more definitive than those using analogous MTPA derivatives, especially so in those compounds which have remotely disposed stereogenic centres.[5] Here we report that the surprisingly high reactivity of CFPA chloride (CFPA–Cl) **2b** compared with that of MTPA–Cl **1b** makes the CFPA method more reliable for e.e. determinations. It is possible that essentially no kinetic resolution occurs in the CFPA derivatization.

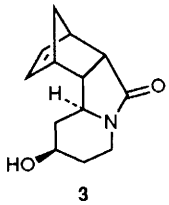
In the course of our e.e. determinations of the key compounds **3** and **4** in asymmetric synthesis,[6] we found that **1b** does not react with these alcohols even with prolonged (2 days) heating, presumably owing to both steric and electronic factors inherent in the MTPA structure. In contrast, the corresponding CFPA esters were easily formed under ambient conditions within 10 min and substantial ^{19}F NMR chemical shift differences were obtained ($\Delta\delta_F$ values for CFPA diastereoisomers of **3** and **4** are 0.14 and 1.01 ppm, respectively). We have now estimated the rate constant of **1b** and **2b** in analogous reactions in order to study more quantitatively the relative reactivity of both reagents.



1a; R = OH (MTPA)
1b; R = Cl (MTPA-Cl)



2a; R = OH (CFPA)
2b; R = Cl (CFPA-Cl)



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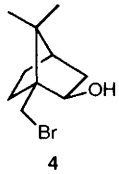

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† In most cases in the literature, the possibility of kinetic resolution of chiral derivatizing reagents during the course of their condensation has been neglected in spite of its critical significance for determining exact e.e. values.

Table 1 Isolated yields after preparative TLC of MTPA and CFPA derivatives of some hindered nucleophiles

			1b (room temp.)		**1b** (reflux)		**2b** (room temp.)	
Entry	Nucleophile		*t*/min	Yield (%)	*t*/min	Yield (%)	*t*/min	Yield (%)
1		**5**	600	34			5	80
2		**6**	300	39			5	73
3		**7**	2400	57	1000	60	5	75
4		**8**	2400	42	1000	61	10	72
5		**9**	30	70			10	89
6		**10**	30	73			10	92
7		**11**	10	57			5	91

To a solution of the alcohol **5** (2.5 mmol) and pyridine (5 mmol) in dry CH_2Cl_2 (50 ml) was added **1b** or **2b** (3 mmol) and the mixture was stirred at 25 °C. Periodically, 3 ml aliquots were taken and quenched with water. The products were analysed by HPLC (stationary phase, Develosil; eluent, hexane–EtOAc, 4:1).‡ The slopes of the graphs of the integrated second-order rate equations *vs.* time for both acid chlorides were calculated by least-squares. k_{2b} (14.5 ± 0.1 l mol^{-1} min^{-1}) was more than 500 times greater than k_{1b} (0.028 ± 0.001 l mol^{-1} min^{-1}).

The large rate constant of **2b** prompted us to determine the actual isolation yields after preparative TLC on silica gel of some derivatives prepared by the condensation of **1b** or **2b** with hindered nucleophiles under conditions§ analogous to those in Moshers' reactions (pyridine–CCl_4, room temp).[1] In the case of compounds **7** and **8**, heating for a prolonged time was not sufficient for completion of MTPA derivatization, whereas the reaction of **2b** with various nucleophiles is usually complete within 20 min at room temperature (Table 1).‡

CFPA had been designed to be highly reactive for both steric and electronic reasons based on considerations of its multifunctionalized structure;[7] *i.e.*, the three substituents surrounding an acetate-derived chiral centre should be quite electronegative and one of them should be as sterically small as possible.¶ Also, all three should have an effective bulkiness significantly different from each other.[5] The high reactivity of **2b** was supported by its spectral data.‖

The high reactivity of **2b** towards nucleophiles has been demonstrated, which implies that the CFPA method should induce essentially no kinetic resolution during the condensation of **2b** even with sterically hindered nucleophiles.

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‡All compounds have been characterized as a 1:1 mixture of two diastereoisomers by IR, NMR and mass spectroscopy.

§ General procedure is as follows. To a solution of the alcohol (0.1 mmol) and pyridine (0.5 mmol) in CCl_4 (5 ml) was added **1b** or **2b** (0.1 mmol). To a solution of the amine (0.4 mmol) and pyridine (2.0 mmol) in CCl_4 (1 ml) was added **1b** or **2b** (0.12 mmol).

¶ In order to reduce the steric bulkiness surrounding the chiral centre, the fluorine atom was chosen in designing the CFPA structure. Only hydrogen is sterically smaller than fluorine.

‖ The carbonyl IR absorptions for **1b** and **2b** were at 1790 and 1796 cm^{-1}. ^{13}C NMR chemical shifts of the chiral and the carbonyl carbon atoms for **1b**: δ −89.1 (s) and −171.1 (s); for **2b**: δ −91.6 (d, *J* 208.6 Hz) and −165.9 (d, *J* 36.6 Hz).