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Highly Enantioselective Addition of Dimethylzinc to Fluorinated Alkyl Ketones, and the Mechanism Behind It †

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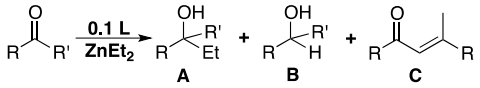
Chiral-diamine catalyzed addition of $ZnMe_2$ to $PhC(O)CF_2X$ (in dichloromethane at –30 °C affords fluorinated alkyl tertiary alcohols in high yield (quantitative for X = H, F, Cl; 84% for X = CF_3) and up to 99% ee. These conditions are similarly efficient for other various $ArC(O)CF_3$ molecules. A fine analysis of the results can be made based on a double-cycle mechanism.

The ligand catalyzed addition of diorganozinc reagents to aldehydes and ketones is a most useful C–C bond formation reaction that allows, in its enantioselective version, to prepare enantiomerically enriched chiral alcohols.[1] It works in mild conditions and the good tolerance of the organozinc compounds to many functionalities, such as ester, amide, nitrile or nitro groups, increases its versatility. Chiral alcohols are structural components of many compounds with biological activity.[2]

Compared to aldehydes, the application of the asymmetric addition reaction to ketones has been a major challenge. Ketones are less reactive than aldehydes, and they have less steric and electronic differences between the two substituents of the carbonyl group, which makes the face enantiodiscrimination for the attack less efficient. In spite of that and the possibility of other reactions products competing with the addition product (**A**, Eq. 1), such as reduction products (**B**, Eq. 1, for alkyls with β hydrogen atoms) or aldol condensation products (**C**, Eq. 1, for R' = Me),[3] some methods to synthesize chiral tertiary alcohols have been published including one of the following processes: *i)* activation of the ketone with a Lewis acid catalyst; *ii)* activation the organozinc reagent with a Lewis base catalyst; *iii)* double activation of the ketone and the organozinc with a bifunctional catalyst (acid and Lewis base).[1j,4]



(1)

Trifluoromethylketones (TFMKs) are particularly interesting reagents because they can be used for the synthesis of chiral organofluorine compounds.[5] These are important synthetic targets because of the unique bioactivity of fluorinated biochemicals compared to their non-fluorinated congeners. Diamines and bisoxazolines can catalyse the addition of $ZnEt_2$ to TFMKs, as reported by our group and others.[6-10] In the absence of these ligands, the undesired reduction of the TFMKs (a background slower reaction) is the only process observed.[8,11]

Using the chiral diamines **L*** (Figure 1) or *ent*-**L***,[12] derived from (*R*,*R*)-1,2-diphenylethylenediamine and (S)-2,2'-bis(bromomethyl)-1,1'-binaphthalene, we achieved very high yields and the best enantioselectivity reported so far for the addition to $PhC(O)CF_3$ of $ZnEt_2$ (99% yield, and 93% ee at 244 K),[13] or the less reactive $ZnMe_2$ (98% yield, and 83% ee at 236 K/rt).[8] The reactions were carried out in hexane/toluene for $ZnEt_2$, and in toluene for $ZnMe_2$.

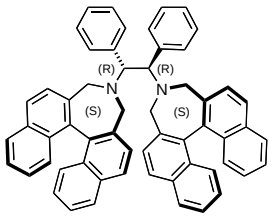


Fig. 1 Diamine **L*** used for the addition of ZnR_2 (R = Me, Et) to TFMKs.

Recently, other fluorinated alkyl ketones (FAKs) have been made commercially available or, alternatively, suitable synthetic methods have been reported for them.[14,15] Their Rh-catalysed arylation to alcohols with arylboronic acids has been reported, but in a non-enantioselective approach.[16a] Enantioselective Rh-catalysed arylations of aryltrifluoromethyl ketones with arylboronic acids have been reported, with variable success from bad to very good depending on the chiral ligand,[16b-f] but alkylations are not accessible in this way.

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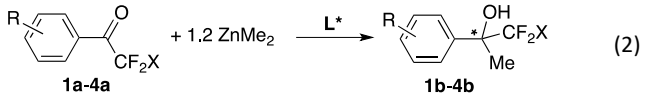
Electronic Supplementary Information (ESI) available: Experimental details, NMR spectra, and GC and HPLC chromatograms of the compounds. See DOI: 10.1039/x0xx00000x

In this study we extend our enantioselective alkylation studies with **L*** to these new fluorinated alkyl ketones. Moreover, in view of the significant ee improvement achieved for these FAKs upon changing the solvent, we revisit also successfully our previous results with CF_3-FAKs.

The FAKs PhC(O)CF_2X (X = H, **1a**; F, **2a**; Cl, **3a**; CF_3, **4a**) were tested in the nucleophilic addition reaction of $ZnMe_2$ using $ZnMe_2$/ketone/**L*** = 1.2/1/0.1 ratio (Eq. 2). $ZnMe_2$ was chosen because of its lower reactivity, as the more challenging reaction test. The reactions were carried out at –30 °C for 24 h using toluene or dichloromethane (DCM) as solvents. The conversions and enantiomeric excesses of the products PhC(CF_2X)(Me)OH (**1b**-**4b**) were obtained by ^{19}F NMR integration of the reaction mixtures after hydrolisis,[17] and by chiral GC or HPLC analysis. The *S*-configuration of the major enantiomer of **1b** was confirmed by comparison with literature data.[18]



(2)

X = H, F, Cl, CF_3 (in 1-4 order)

The results collected in Table 1 show total conversion to the alcohol in both solvents, except for **4a**, and a remarkable increase in conversion and, more important, in enantioselectivity when DCM is used as solvent instead of toluene. For **4b** an unprecedented alkylation of a fluorinated ketone to a single enantiomer is achieved.

Table 1. Screening of Enantioselective Addition of $ZnMe_2$ to Fluorinated Alkyl Ketones PhC(O)CF_2X.

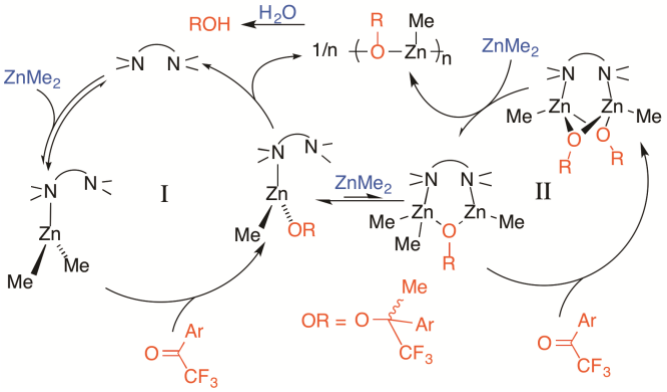
		toluene		DCM	
FAK	**X**	**conv.%**	**ee%**	**conv.%**	**ee%**
1a	H	> 99	68	> 99	78
2a	F	> 99	86	> 99	92
3a	Cl	> 99	88	> 99	98
4a	CF_3	59	58	84	> 99

The ketone was added to a $ZnMe_2$/**L*** = 1.2/0.1 solution at –30 °C and the mixture stirred at this temperature for 24 h.

Solvent effects were recently reported by Sasaki using as model reaction the addition of $ZnEt_2$ to $PhCOCF_3$ at –50 °C for 20 h, in the presence of (Me_2PhC)BOX as ligand.[10] In these conditions, the use of THF or DMF as solvent prevented the reaction to occur, probably because their coordinating ability to $ZnEt_2$ prevents the coordination of the catalytic chiral ligand. In contrast, in hexane, toluene, diethyl ether or DCM the reactions proceed smoothly, with DCM providing the best performance and enantioselectivity. This interpretation is strongly supported by our recent experimental and calculated evidence on the speciation of $ZnMe_2$ in THF, which confirms unambiguously the formation of $ZnMe_2(THF)_2$ species and evaluates the coordination free energy involved.[19] $ZnMe_2(DMF)_2$ analogues should be even more stable. On the other hand, modest coordinating ability of toluene to $Zn(C_6F_5)_2$ has been reported,[20] whereas the coordination ability of hexane or DCM must be negligible.

Monitoring of conversions for the reactions in equation 2 showed that the reactions in DCM corresponding to ketones **1a**-**3a** at –30 °C were complete in 3 h, which prompted us to carry out these reactions at a lower temperature in order to increase their ees, which obviously is detrimental for the conversion time. The reactions with **1a**-**3a** at –50 °C showed complete conversion in 24 h, but only similar ees, although **3b** was obtained as a single enantiomer. On the other hand, for **4a** only 11% conversion was achieved in 24 h at –50 °C; fortunately the reaction at 0 °C was complete in 24 h giving **4b** in 90% ee. As it is usually the case, optimizing the results requires some trade off between best reaction rate and best enantioselectivity for each case. The comparative low reactivity of ketone **4** was not predicted from its expectedly more stabilized LUMO, which, on the contrary, should favour the nucleophilic attack. The higher bulkiness of the perfluoroethyl group can be responsible for this behaviour.

In order to discuss these catalytic results we need to remind the singular double cycle mechanism that we proposed for the actuation of **L***.[13] Our mechanistic studies for $ZnEt_2$ addition reactions revealed that the reasons for the outstanding singular efficiency of **L*** compared to other related ligands are: *i)* in contrast to other chelating ligands, due to its very high steric congestion the potentially chelating **L*** coordinates initially as monodentate only, producing 3-coordinated Et_2Zn**L***, and cycle **I** is not very efficient; *ii)* at variance with other ligands, **L*** triggers a second much more efficient catalytic cycle **II**, in which **L*** acts as bidentate chelate, which leads to autocatalytic asymmetric enhancement through dinuclear intermediates with **L*** bridging the two Zn centers. We assume that the same double cycle mechanism operates for $ZnMe_2$.



Scheme 1. Double catalytic cycle for the addition reaction of $ArCOCF_3$ with $ZnEt_2$ (N–N = L*).

Since the catalysis operates via two competing catalytic cycles, one of mononuclear species and another of bridged binuclear species, any molecular or solvent changes should be expected to induce non linear changes on conversion and ee, and the effects can have some complexity. A prior equilibrium exists between mononuclear species in cycle **I**, and binuclear species in cycle **II**. Thus, the formation of binuclear versus mononuclear species can be seriously conditioned by the coordinating ability of the solvent (toluene > DCM) or other

coordinating molecules in solution, and by the electronic and steric effects of the aryl substituents. All these effects are particularly harmful for the formation of dimers operating in cycle **II**.

In order to examine these effects, the reaction of $PhC(O)CF_3$ (**2a**) and $ZnMe_2$ was carried out, in toluene and in DCM at –30 °C, for three different percentages of **L*** respect to **2a**: 2.5, 5, and 10%. These experiments showed higher reaction rates in DCM compared to toluene, and they showed also that increasing the **L***/**2a** ratio causes an increase in the reaction rate. This is in agreement with the higher coordinating ability of toluene to $ZnMe_2$, compared to DCM, which makes the **L*** coordination equilibrium in neat toluene less efficient than in DCM. In spite of the modest coordinating ability of toluene to Zn, its use as neat solvent is detrimental for the formation of dimers, and the participation cycle **II** (fast) decreases, making the reaction slower and less enantiomerically efficient. This justifies very well why the enantioselectivity is higher in DCM than in toluene.

Obviously, the percentage of active Me_2ZnL^* increases with the percentage of **L*** added and, since L is always in catalytic concentration only, it is positive for the formation of the dimeric active species also. On the other hand, since the ees remain almost constant regardless of the **L***/**2a** ratio, this suggests that the most ee efficient cycle **II** in Scheme 1 is in all cases the pathway providing most of the product.

The excellent results in DCM moved us to revisit our previous studies on $(R\text{-}C_6H_4)C(O)CF_3$ ketones,[8,9] applying the new methodology for less stringent conditions (–30 °C, 24 h, DCM as solvent). The $(R\text{-}C_6H_4)C(O)CF_3$ ketones (**na**, **n** = **2**, **5**-**15**) used in the study are listed in the first column of Table 2, and give rise to the corresponding **nb** alcohols. Alcohols **5b**-**8b** and **13b** have been obtained previously by enantioselective trifluoromethylation of aryl ketones,[21] but with noticeably lower yields and ees. The *R* configuration was dominant in the reported cases, whereas the *S* configuration for the major enantiomers is obtained in our case using **L***. Obviously the availability of *ent*-**L*** would allow us to obtain the *R* isomers if desired with the same good conversions and ees. For comparative purposes the reactions were also carried out in toluene in the same conditions. The reactions made in toluene at –30 °C afford higher enantioselectivity than the ones published before by our group (carried out starting at –37 °C and leaving to raise to room temperature), confirming the positive influence on enantioselectivity of keeping the temperature low during the addition reaction.

The experimental results in Table 2 show very good conversions (except for **10a** and **12a**) and excellent enantioselectivity in DCM as solvent, improving very significantly the results in toluene in the same conditions. As expected, ketones with EWG on the aromatic ring show very fast reactions and after 2 h they are almost complete. On the other hand, substrates bearing EDG, namely MeO, MeS, and EtS, show low rates and relatively long induction periods when the evolution of the reaction is checked by ^{19}F NMR. These TFMKs have a potentially coordinating heteroatom that can contribute, similar to a coordinating solvent, to make cycle **II** less- or non-operative. The effect should be more important for OMe, with a harder donor atom, than for SR. The expected result if the percentage of catalysis via cycle **I** increases in detriment of cycle **II** is somewhat slower rates and, more important, lower ees, as observed. Interestingly, the bulkiness of the phenyl substituent 4-Pr^i seems to influence very negatively the yield of the addition product regardless of the solvent. In this case it is necessary to increase the temperature in order to get **10b** (71% yield and 46% ee, 24 h at 25 °C).

Table 2. Enantioselective Addition of $ZnMe_2$ to various TFMKs $(R\text{-}C_6H_4)C(O)CF_3$ in toluene and DCM.

		toluene		DCM	
TFMK	**R**	**conv.%**	**ee%**	**conv.%**	**ee%**
2a	H	> 99	86	> 99	92
5a	4-F	> 99	90	> 99	92
6a	4-Cl	> 99	82	> 99	90
7a	4-Br	> 99	82	> 99	88
8a	4-Me	> 99	88	> 99	92
9a	4-Et	> 99	57	> 99	88
10a	4-Pr^i	< 1	-	< 2	-
11a	3,5-Me_2	> 99	94	> 99	96
12a	2-OMe	17	50	64	16
13a	4-OMe	> 99	76	> 99	84
14a	4-SMe	> 99	76	> 99	90
15a	4-SEt	> 99	72	> 99	86

The ketone was added to a $ZnMe_2$/**L*** = 1.2/0.1 solution at –30 °C and this temperature was maintained for 24 h.

Finally, the most curious result in DCM is observed for **12a** with the phenyl substituent 2-OMe. The reactions of **12a** are slow in both solvents, with much lower enantioselectivity in DCM compared to toluene. Certainly OMe is the substituent with higher affinity for Zn, as commented above, but the contrast between 2-OMe in **12a** and 4-OMe in **13a** is striking. Our interpretation is based on the fact that 2-OMe is also the one structurally appropriate to chelate the Zn atoms shown in Figure 2. Not only this structure is incompatible with operation of cycle **II** as conceived, but it probably requires also higher energy to proceed via cycle **I** in order to split the chelating structure. Consequently the results observed cannot be reasoned on the basis of the mechanism in Scheme 1, operating for all the other ketones.

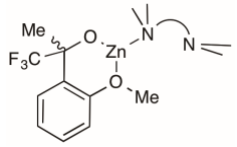


Fig. 2 Possible chelated intermediate from **12a** diverting the reaction to less efficient pathways.

In summary, the crucial effect of the solvent in the enantioselectivity of the addition reaction of $ZnMe_2$ to different FAKs has allowed us to prepare almost pure enantiomers of the fluorinated tertiary alcohols derived from $PhC(O)CF_2X$ (X = Cl, CF_3) for the first time. In other cases, the same reaction affords synthetic valuable fluorine-containing tertiary alcohols with very good yields and enantioselectivities. They can be obtained in any configuration thanks to the

availability of the ligands **L*** and *ent*-**L***. The influence of the solvents and the aryl substituents in reactions with (R-C_6H_4)C(O)CF_3 ketones is easy to understand in the context of the two-cycle mechanism of catalysis with **L***, which in turn reinforces the mechanistic proposal. As an exception, R = 2-OMe seems to be the only exception to this mechanism.

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17 The reaction in DCM has only advantages both in conversion and in enantioselectivity. Furthermore, the volatility of the solvent makes the final isolation of the chiral alcohol easier. All the syntheses are reported in the ESI. A typical preparative procedure using higher amount of starting ketone is reported here: Ketone **3a** (500 mg, 2.6 mmol, 1 eq) was added to a previously prepared solution containing $ZnMe_2$ (6.3 mL of a 0.5 M solution in DCM, 3.1 mmol, 1.2 eq) and L* (201.7 mg, 0.26 mmol, 0.1 eq) in a 100 mL screw tap Schlenk, immersed in a –85 °C bath of isopropanol. After addition of the ketone, the reaction was placed during 24 h in an isopropanol bath with the temperature regulated at –30 °C by a cryoprobe. Then the mixture was carefully hydrolysed by dropwise addition of 2 M HCl (15 mL). The aqueous layer was separated from the DCM layer, and extracted with Et_2O (2 × 15 mL). Addition of the Et_2O extracts over the DCM layer produced a white precipitate essentially corresponding to a salt derivate from the ligand, which was not separated. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under airflow until *ca*. 4 mL. The solution was then passed through a short silica gel column to filter off the insolubles. The resulting solution afforded alcohol **3b** as a colourless oil upon evaporation of the solvent by airflow. Yield: 525.7 mg, 2.5 mmol, 97%. **Warning**: all these alcohols are fairly volatile and attention must be paid to the moment when all the DCM has been removed, in order to minimize loses of the desired product.

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