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Asymmetric Catalysis

Diamine Catalyzed Addition of $ZnEt_2$ to $PhC(O)CF_3$: Two Mechanisms and Autocatalytic Asymmetric Enhancement

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Dedicated to Pierre Braunstein for his contribution to make chemistry a European home

Abstract: NMR studies of the catalytic addition reaction of $ZnEt_2$ to $PhC(O)CF_3$ in the presence of three very efficient catalysts (TMEDA, ^{t}BuBOX, and **L**; **L** is a chiral diamine synthesized from optically pure (*R*,*R*)-1,2-diphenylethylenediamine and (*S*)-dibromomethyl-1,1'-binaphthalene) reveal strong differences in their behavior. For the ligands TMEDA and ^{t}BuBOX the catalysis shows no unusual features and goes through [(N–N)Zn(Et){OC(CF_3)(Et)Ph}]. For N–N = **L**, the observation of autocatalytic asymmetric enhancement during the catalysis, and unusual inverse concentration dependence on the reaction rate, support an additional novel catalytic cycle that goes through a dinuclear intermediate containing one $ZnEt_2$ and one ZnEt fragment connected by N–N and OR bridges. Interestingly, the ^{19}F NMR signals of the main product of the reaction ([Zn(Et){OC*(CF_3)(Et)Ph}]$_2$) allowed us to asses *in situ* the enantioselectivity of the processes without the assistance of chiral chromatography.

Introduction

The preparation of chiral molecules bearing a trifluoromethyl group (Figure 1)[1,2] has been the subject of extensive research due to their properties, reactivity, and numerous applications in different areas such as agrochemicals and pharmaceuticals.[3] The presence of a CF_3 group affects the properties of organic molecules, due to its group electronegativity and size, and makes the trifluoromethylated molecules more bioavailable, more lipophilic and more chemically/metabolically stable. These unique properties, together with their binding affinity and selectivity at the molecular level, are responsible of the activity shown by many trifluoromethylated drugs with therapeutic action and many crop protection reagents.

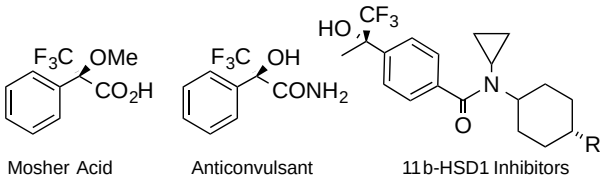
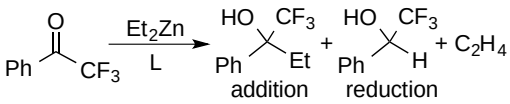


Figure 1. Representative compounds containing CF_3

The asymmetric addition of dialkylzinc compounds ZnR_2 to aldehydes and ketones is a powerful methodology of access to optically active secondary and tertiary alcohols.[4] However, the direct alkylation of trifluoromethylketones[5] with $ZnEt_2$ (and higher alkyls) is very difficult because of extensive formation of the undesired reduction product upon addition of the organometallic reagent (Scheme 1).[6]



Scheme 1. Competing addition *vs*. reduction reaction in the alkylation of trifluoromethylketones

Several examples of catalytic enantioselective addition of $ZnEt_2$ to trifluoromethylketones,[6,7] with high chemoselectivity and up to 61% enantioselectivity at 196 K were achieved with the use

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of the chiral ligand ^{t}BuBOX (^{t}BuBOX = 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline]). In those studies, an efficient but non asymmetric version of the reaction, catalyzed by TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine), was also developed. More recently we have reported [8] the enantioselective addition of ZnR_2 (R = Me, Et) to 2,2,2-trifluoroacetophenone ($PhCOCF_3$) and several related ketones using the bulky chiral diamines **L** and *ent*-**L** (Figure 2) derived from (*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine and (*S*)- or (*R*)-bis(bromomethyl)-2,2'-binaphthalene.[9] These ligands allowed us to prepare both enantiomers of the products with excellent yield (up to 99%) and the highest enantioselectivity reported so far (up to 92%), which was achieved working at 213 K. A drawback of the use of our chiral diamines was the low addition rates observed, compared to ^{t}BuBOX, even for loadings of 10% of ligand.

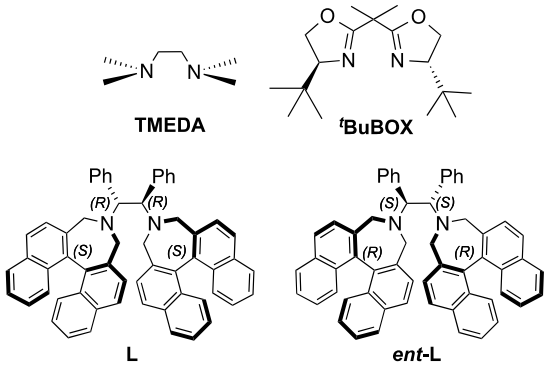
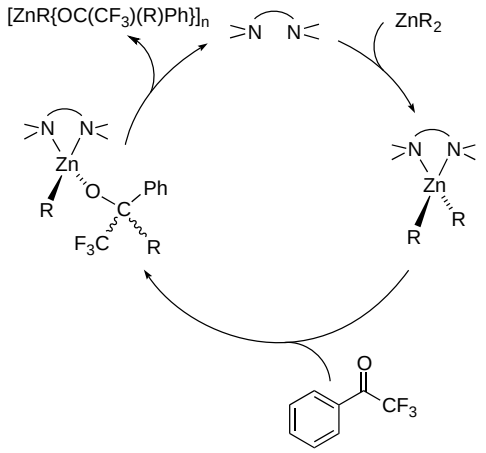


Figure 2. Molecular N–N catalysts

Some clues for the mechanism of these addition reactions, has been provided by Hevia and coworkers in a non chiral model (TMEDA), showing that stoichiometric reactions of $PhCOCF_3$ with [ZnR_2(TMEDA)] produce alkylation (R = Me, Et) or reduction (R = ^{t}Bu) products [(TMEDA)Zn(R){$OC(CF_3)$(R/H)Ph}], and their corresponding Zn(alkyl)(alkoxide) polymers.[10] These observations support the proposal in Scheme 2.

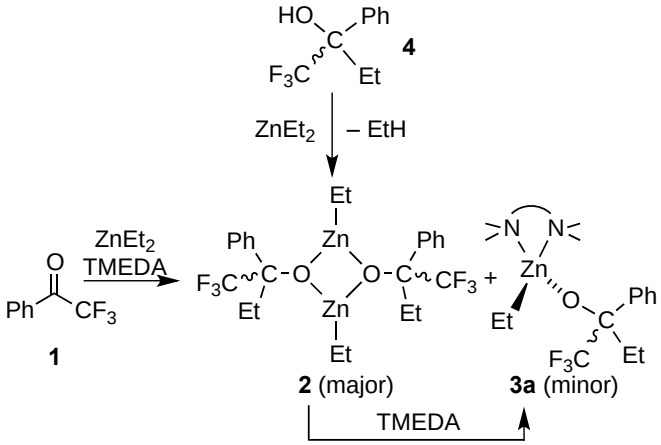


Scheme 2. Proposed cycle for alkylation of $PhCOCF_3$ using TMEDA as catalyst.

As discussed below, preliminary experiments with the chiral ligand **L** revealed the necessity of additional models in order to explain the special features of the enantioselective catalysis with **L**, and prompted us to explore in more detail the reactions with TMEDA, ^{t}BuBOX and **L** using ^{1}H and ^{19}F NMR spectroscopy in order to clarify the interaction between these diamines and the reactants and products. This study has lead us to propose a more complex catalytic cycle for the bulkier ligand **L** and, in a practical aspect, to improve the chiral-ligand economy in the enantioselective addition of $ZnEt_2$ to $PhCOCF_3$.

Results and Discussion

Identification of intermediates in the reactions. The monitoring by ^{19}F NMR of the reaction of $ZnEt_2$ (in toluene-d_8 solution) with $PhCOCF_3$ (**1**), in the presence of the non-chiral ligand TMEDA (10% relative to **1**), at 244 K (for the detailed procedure see SI) reveals the formation of two main fluorinated products, as shown in Scheme 3: [Zn(Et){$OC(CF_3)$(Et)Ph}]$_2$ (**2**), and [(TMEDA)Zn(Et){$OC(CF_3)$(Et)Ph}] (**3a**). The major product (**2**), is a dimer with trifluoromethyl carbinol bridges, and can be transformed quantitatively into the monomer (**3a**) by addition of TMEDA.



Scheme 3. Synthesis of alkyl(alkoxide) compounds **2** and **3a**

Consistent with the dimeric structure proposed for **2**, the ^{19}F NMR spectrum (Figure 3) displays two singlets of very similar intensity, corresponding to the three expected stereoisomers of similar stability: two enantiomers (**2*RR***, **2*SS***, *ca*. 25% each, with the same chemical shift), and the meso diastereomer (**2*RS***, *ca.* 50%). Higher aggregates would show very complicated spectra, as observed for [Zn_4(^{t}Bu)$_2${$OC(CF_3)$(H)Ph}$_6$],[10] and are not observed. Compound **2** was also prepared in independent experiments by the reaction of $PhC(OH)(CF_3)(Et)$ (**4**) (either racemic or enantiopure) with $ZnEt_2$ in toluene-d_8. If the reaction is carried out with either *R*- or *S*-$PhC(OH)(CF_3)(Et)$ (**4*R***, **4*S***) only one singlet is observed in both ^{19}F NMR spectra which corresponds to **2*RR*** or, respectively, **2*SS*** and allows for unambiguous assignment of the two singlets as shown in Figure 3. The chemical shift of this singlet coincided with the chemical shift of the most shielded one observed when racemic **4** was used in the synthesis.

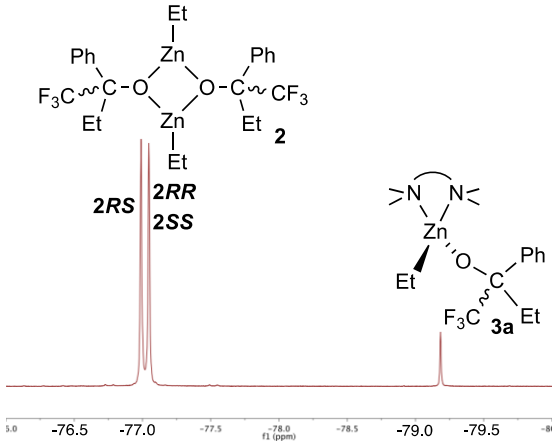


Figure 3. ^{19}F NMR spectrum for the reaction of **1** and $ZnEt_2$, using TMEDA (10%) as catalysts, in toluene-d_8 at 244 K

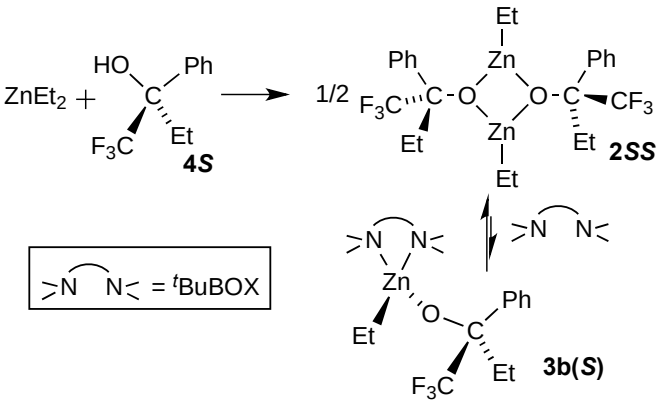
Monitoring the reaction of PhC(OH)(CF_3)(Et) (**4**) with $ZnEt_2$ by ^{19}F NMR spectroscopy shows, along the process, broadening of the signals due to exchange of the alkoxide fragment {OC(CF_3)(Et)Ph} between the dimer [Zn(Et){OC(CF_3)(Et)Ph}]$_2$ (**2**) and **4**, as confirmed by a ^{19}F EXSY experiment at 293 K. Only when a full conversion of **4** is achieved does the ^{19}F NMR spectrum of the solution show sharply the two singlets of similar intensity assigned to compounds **2**. ^{1}H NMR spectra are less informative since the signals of the ethyl groups of the two aforementioned stereoisomers partially overlap. Yet, these spectra clearly show two distinct sets of resonances for the ethyl groups directly linked to zinc atoms and those bonded to carbon. In addition, an exchange process of these ethyl groups between **2** and free $ZnEt_2$ could be proven by variable temperature ^{1}H NMR experiments.

The enantioselective addition reaction of **1** with $ZnEt_2$ in the presence of a chiral ligand (N-N: ^{t}BuBOX or **L**), in the same conditions indicated for TMEDA, also shows in the ^{19}F NMR spectra the formation of the dinuclear complexes [Zn(Et){OC(CF_3)(Et)Ph}]$_2$ (**2**). In the two cases the different abundances of the *R*- or *S*-[OC(CF_3)(Et)Ph] fragments, generated in the enantioselective addition, result in different intensity of the signals of the groups of diastereomers observed (see SI). Considering that the statistical distribution of *R* and *S* fragments in the mixture is given by **2*RR***:**2*SS***:**2*RS*** = (%*R*)^2:(%*S*)^2:2(%*R*)(%*S*), the ratio of the integrals of the singlets observed for the isomers of **2** can be correlated to the enantioselectivity of the reaction, determined by GC analysis of the tertiary alcohol obtained after hydrolysis (Table 1). The good correlation of the values in Table 1 supports that the enantioselectivity of the processes can be estimated fairly accurately by ^{19}F NMR spectroscopy, without the assistance of chiral GC.

Table 1. Observed and calculated ratio of stereoisomers in 2

Ligand	ee (%)	2*RR* + 2*SS* / 2*RS* ratio	
	(confign)	from NMR	from GC
^{t}BuBOX	55 (*S*)	1.8/1	1.9/1
L	83 (*S*)	5.7/1	5.4/1

In the case of reactions catalysed by ^{t}BuBOX, the monomeric [(^{t}BuBOX)Zn(Et){OC*(CF_3)(Et)Ph}] (**3b**) can be detected by ^{19}F NMR, along with the signals of **2**. The defined chirality of the ligand ^{t}BuBOX gives rise to diastereomers: [(^{t}BuBOX)Zn(Et){*S*-[OC(CF_3)(Et)Ph]}] **3b**(***S***), and the corresponding **3b**(***R***). In order to unequivocally assign their signals, **2*SS*** (prepared by reaction of the enantiomerically pure PhC(OH)(CF_3)(Et) (**4*S***) with $ZnEt_2$ in toluene-d_8) was treated with ^{t}BuBOX (1:2 ratio) (Scheme 4). The analysis of the corresponding ^{19}F NMR spectrum shows only the more intense singlet of the two observed in the catalytic reaction with ^{t}BuBOX (it corresponds to the less shielded one), which allowed us to assign it to **3b(*S*)**. In contrast, in the case of reactions catalyzed by **L**, signals of the expected [(**L**)Zn(Et){OC(CF_3)(Et)Ph}] (**3c**) could not be detected suggesting that **L** is a much worse coordinating ligand than ^{t}BuBOX or TMEDA. Models suggest that the hindrance between the two halves of **L** will hardly allow it to coordinate as chelate to the same Zn atom. This is further supported by the discussion on equilibria that follows.

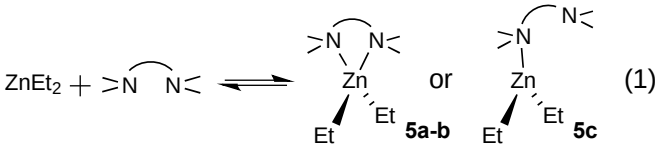


Scheme 4. Enantioselective synthesis of **2*SS*** and **3b(*S*)**

Stoichiometric reactions. The catalytic cycle in Scheme 2, applied to N–N ligands, takes the shape of the transformations depicted in Equations (1)-(3). However, we have found substantially different behavior of the three ligands, which requires some considerations.

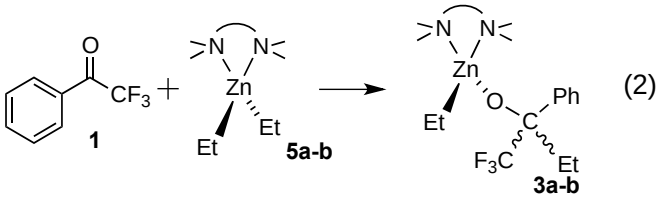
Equation (1): The initial coordination of N–N to $ZnEt_2$ gives rise to [(N–N)$ZnEt_2$] (**5a-c**), a stronger Et nucleophile than $ZnEt_2$. The addition of an equimolar amount of TMEDA or ^{t}BuBOX to a solution of $ZnEt_2$ in toluene-d_8 results in the quantitative formation of [(N-N)$ZnEt_2$] (N-N = TMEDA (**5a)**, ^{t}BuBOX (**5b**)), which were observed in the NMR spectra. In contrast, for N-N = **L** the corresponding complex was not observed as such. However, addition of $ZnEt_2$ to the solution produced the shift of the signals (particularly those of **L**) suggesting that in this case Eq. 1 corresponds to a fast dissociation equilibrium. This different behavior of **L** is easily understood considering that, as a consequence of excessive steric congestion, **L** coordinates as monodentate and not as chelate, which makes **L** dissociation a much lower activation energy process than for the chelating ligands. The coordination equilibrium constant for **L** was calculated from the shift of the more shielded protons of the CH_2 groups of **L**, which afforded K = 1.9 mol^{-1} L^{-1} at 244 K (compare

with quantitative formation for TMEDA and ^{t}BuBOX). Obviously this equilibrium determines a much lower effective concentration of the active nucleophilic species [(**L**)ZnEt$_2$] (**5c**).



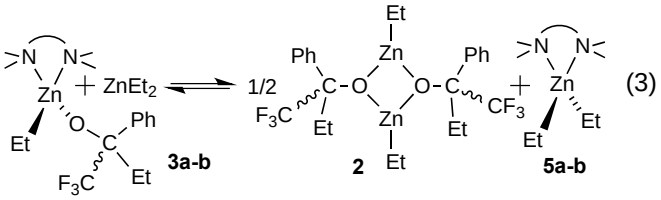
(1)

Equation (2): The stoichiometric addition reaction of [(N–N)ZnEt$_2$] to **1**, is quantitative and fast for TMEDA and ^{t}BuBOX, affording [(N–N)Zn(Et){OC(CF$_3$)(Et)Ph}] (**3a-b**). However, this reaction does not occur with **L**, and the expected complex **3c** is not detected. This is an intriguing observation considering that the same reaction works in catalytic conditions using smaller **L**:Zn ratios and will be discussed later.



(2)

Equation (3): Finally, the rearrangement of intermediates **3a-b** with ZnEt$_2$ to produce alkoxy product **2** and generate new alkylating reagent **5a-b** in equilibrium occurs easily. This equation was studied for **3a** using isolated complex; the equilibrium constant in toluene-d_8 at 244 K is K = 0.87 mol$^{-1/2}$ L$^{1/2}$.[11] For **3b** the tendency to produce **2** was much higher, so that it is produced spontaneously even in the conditions of Eq. 2

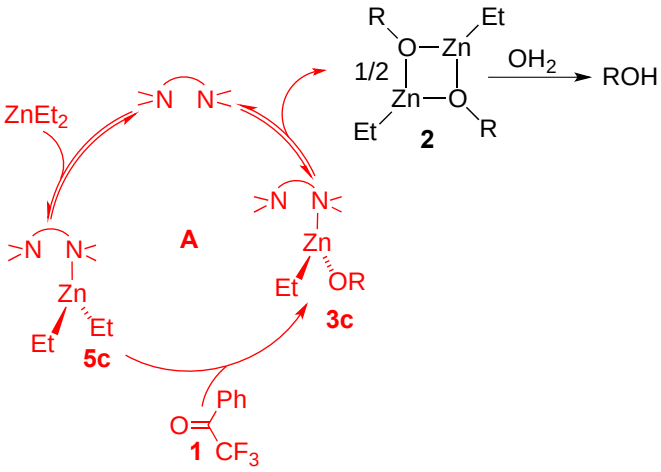


(3)

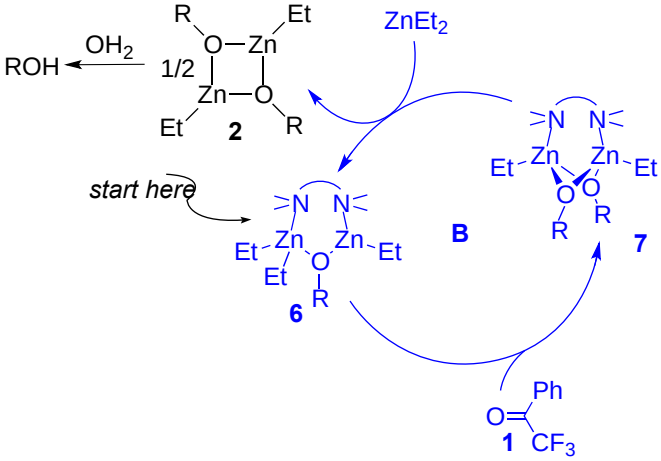
(absence of free ZnEt$_2$). In other words, complex **3b** releases ^{t}BuBOX spontaneously. Since Eq. (2) does not work for **L** this process could not be studied. Looking at Eq. 3 in the reverse mode, adding 2 mols of TMEDA to **2**, **3a** is produced stoichiometrically; with ^{t}BuBOX, an equilibrium between **3b** and **2** is produced; but in the same conditions **L** does not produce detectable amounts of the expected **3c** complex.

Catalytic reactions. Singular behavior of L. From the experiments discussed so far, the catalytic cycle in Scheme 2 explains perfectly the behavior observed for TMEDA and ^{t}BuBOX: these chelating ligands activate efficiently the nucleophilicity of the Et groups in their complexes and give rise to efficient fast reactions. Chelate complexes are observed as starting materials or as intermediates.

In contrast, for ligand **L** the putative complexes [**L**ZnEt$_2$] or [**L**Zn(Et){OC(CF$_3$)(Et)Ph}] cannot be observed (although the formation of [**L**ZnEt$_2$] in equilibrium with free **L** can be deduced from chemical shifts in the NMR spectra). Assuming that **L** can act only as monodentate towards a single Zn atom, and that the concentration of complexed ZnEt$_2$ must be very small (much lower than for the chelating ligands), it is easy to understand that a cycle similar to Scheme 2 (cycle **A** in Scheme 5) should be quite inefficient. In fact the addition reaction catalyzed with **L** is initially very slow, but further catalytic studies showed that it was accelerated to achieve good rate after an activation period. Our proposal is that cycle **A** is the initial pathway that follows the reaction during the activation period until faster cycle **B** in Scheme 6 takes the lead. Further features of the catalysis with **L** are the observation of *enantioselective autoinduction*,[12] and an *inverse* dependence of the reaction rate on **L** loading, that have to be explained.



Scheme 5. Initial catalytic cycle for the addition reaction of **1** with ZnEt$_2$ and **L**. R = C(CF$_3$)(Et)Ph



Scheme 6. Faster catalytic cycle operating after induction for the addition reaction of **1** with ZnEt$_2$ and **L**. R = C(CF$_3$)(Et)Ph

a) Induction time and kinetics. According to the conventional mechanism in Scheme 2, an increase in the catalyst (ligand) loading is expected to induce an increased reaction rate, since it increases the concentration of the reactive complex. This behavior has been confirmed for the cases of TMEDA and ^{t}BuBOX, but kinetic studies on reactions with **L** reveal a striking *inverse* dependence of the reaction rate on catalyst loading (Chart 1).

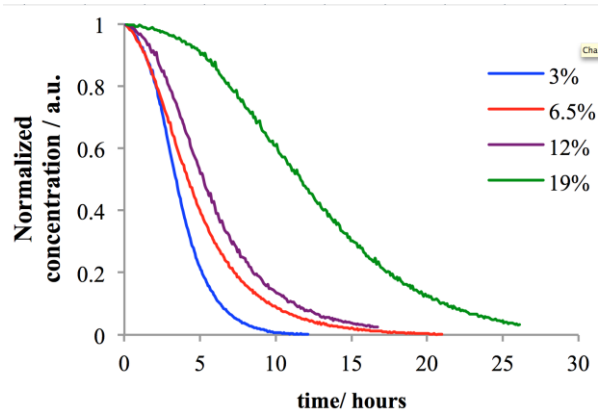
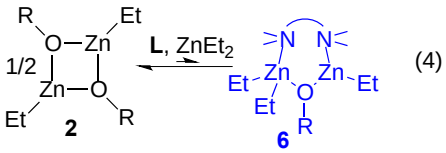


Chart 1. Catalytic cycles for the addition reaction of **1** with $ZnEt_2$ (1:1.2) and different amount of **L**. Starting concentrations: [**1**] = 0.20 M, [$ZnEt_2$] = 0.24 M (3, 6.5 and 12% **L**); [**1**] = 0.10 M, [$ZnEt_2$] = 0.12 M (19% **L**).

It is obvious that cycle **A** (Scheme 5) cannot account for the kinetic behavior of **L**. This observation prompted us to consider, alternative pathways involving active species with Zn:**L** ratios higher than 1. Thus we propose that the reaction of **L**, **2**, and $ZnEt_2$ generates a small concentration of the dinuclear intermediate **6** (Eq. 4). This opens the alternative pathway **B** (Scheme 6), which turns out to be faster. This faster addition is to be expected as the Et groups are more nucleophilic in the tetracoordinate $ZnEt_2$ fragment of **6** than in the tricoordinate **5c**. Note that initially the amount of **6** available to the catalysis is very small, as it depends on the amount of **2**, produced in the inefficient cycle. Although always low, the concentration of **6** will somewhat increase with time as cycle **B** proceeds, producing an autocatalytic effect.

For a given concentration of **2** (at a given moment of the catalysis) one might expect from Equation 4 that increasing the loading of **L** should increase the concentration of **6** and make the reaction faster. However, the opposite effect is observed, as shown in Chart 1: Higher loading of **L** retards the reaction. In fact, when loading of **L** reaches the proportion Zn:**L** = 1:1, the addition reaction does not proceed at all, as commented in the study of stoichiometric reactions above. This apparent paradox can be explained if we consider that the predictions derived from consideration of the thermodynamic equilibria in a static situation cannot be applied to a dynamic system where the concentration of **6** is not that predicted by thermodynamics but that corresponding to a steady state. Intermediate **6** contains bridging bonds that can be split by extra **L**. If the formation of **6** is slow and its destruction by additional **L** is faster, in some instances the increase in concentration of **L** will diminish the steady state concentration of the catalyst **6**, hence the reaction rate. The real system is far too complicated to describe it mathematically in the lack of quantitative experimental data, but a simpler model with arbitrary data has been calculated as a proof of concept and is given in SI.



(4)

The shapes of the curves in Chart 1 reveal an autocatalytic process. For a better understanding, three successive catalytic cycles were performed (Chart 2). The first catalytic run was monitored by ^{19}F NMR using $PhCOCF_3$ (**1**), $ZnEt_2$, and **L** (1:1.2:0.02) in toluene-d_8 at 244 K and showed the typical S shape of autocatalysis. After completion, an additional equivalent of $PhCOCF_3$ and 1.2 equivalents of $ZnEt_2$ were added (second run) and, when the reaction was complete, another equivalent of $PhCOCF_3$ and 1.2 equivalents of $ZnEt_2$ were added to the reaction mixture (third run). The second and third runs showed a higher reaction rate and a normal shape confirming that the more active catalyst (**6** in Scheme 6) has been formed during the first run and remains active in the others. In other words, once catalyst **6** has been formed the catalytic cycle **B** becomes kinetically dominant.

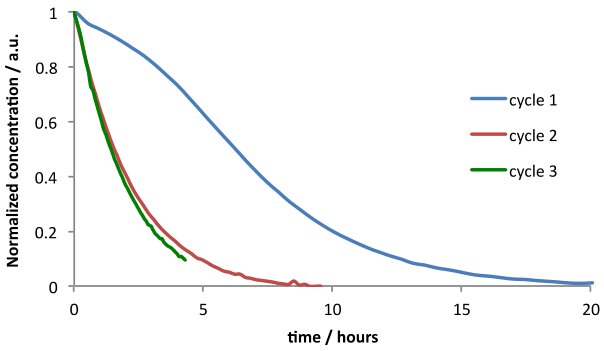


Chart 2. Variation of the concentration of $PhCOCF_3$ (1) for the addition reaction of 1, $ZnEt_2$ and L (1:1.2:0.02) in three successive catalytic cycles after the addition of 1 equivalent of 1 and 1.2 eq. of $ZnEt_2$

b) Enantioselective autoinduction. Catalytic reactions were performed using $PhCOCF_3$ (**1**), $ZnEt_2$ (1:1.2) and a **L** catalyst loading as low as 2%, in toluene-d_8 at 253 K. Aliquots were periodically quenched and ee and chemical yields were determined, respectively, by GC and ^{19}F NMR. A significant enantioselectivity enhancement was observed as the reaction proceeded, from a moderate initial ee of 55 % to a highly enantioselective value of 88% when the full conversion of the ketone was reached (Chart 3). According to these results, the more active catalyst **6**, formed during the reaction, is also more enantioselective than the initial slow catalyst (**5c** in Scheme 5). This looks reasonable considering that **6** has a more rigid structure that defines better the space around Zn that the flexible and easy to dissociate **5c**.

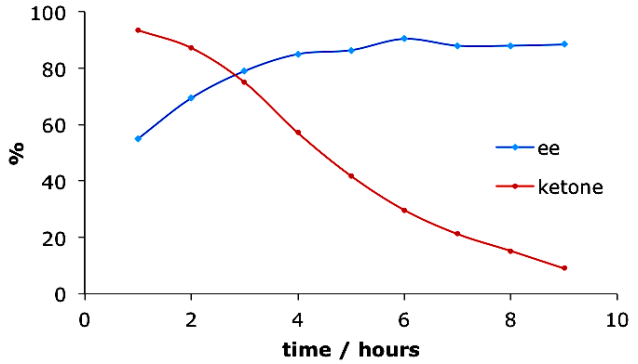


Chart 3. Autocatalytic asymmetric enhancement in the reaction **1**:$ZnEt_2$:**L** (1:1.2:0.02) in toluene-d_8 at 253 K. Initial volume of the reaction: 5 mL; initial concentration of $PhCOCF_3$: 0.144 M; volume (constant) of the aliquot periodically extracted = 0.2 mL.

As a matter of fact catalyst **6** can show two diastereomers and its chiral conformation is defined by the chirality of **L**, which is fixed, and by the chiral conformation of the alkoxy group (*S* or *R*), which is being created competitively during the catalysis. In order to determine the effect of the chiral conformation of the alkoxy group in the enantioselectivity of the products, three different experiments were made to produce **6** directly from their components (avoiding cycle **A**) and were monitored by ^{19}F NMR in toluene-d_8 at 244 K: three NMR tubes were charged each with one equivalent of *S*-, *R*- or *rac*-PhC(OH)(CF_3)(Et) (**4**), and a mixture of $ZnEt_2$ and **L** was added (2.4:0.02); after formation of the dimer **2** and complete disappearance of the free alcohol **4** (about 20 min) one equivalent of $PhCOCF_3$ (**1**) was added. The kinetic profiles of the three experiments overlapped almost perfectly (see plot in section S6, SI), indicating that the two diastereomers of **6** are almost equally active. In sharp contrast with the reaction in the absence of added alcohol **4**, in these three experiments the induction time was significantly reduced (although not totally suppressed, showing that formation of **6** is slow and still being formed), and the reaction was complete after 3 h instead of 20 h. The reaction produced as the mayor product after hydrolisis *S*-PhC(OH)(CF_3)(Et) (**4*S***), showing that the conformation of the bridging alcohol in **6** has only little influence on the conformation of the product. The ee in the newly formed alcohol (ee_{prod}) depends mostly on the configuration of **L**. The enantioselectivity found for the initial addition of one equivalent of **4*R***, **4*rac***, or **4*S***, calculated discounting the originally added chiral carbinol was ee_{prod} = 80.9, 86.1, and 91.1 respectively, in all cases of the S alcohol. Considering that these figures come from just one run, in a normal catalysis with small loads of catalyst and many turnovers the effect on enantioselectivity of feeding initially with chiral carbinol would be negligible. Moreover, the accelerating effect of initial feeding with alcohol requires a significant amount of this additional reagent, which eventually would contaminate the product unless it is the same alcohol being produced. Thus, at the moment this accelerating procedure has not synthetic importance and it is more convenient to use successive runs as in Chart 2.

Conclusions

The NMR study of the catalytic addition reaction of $ZnEt_2$ with $PhCOCF_3$ in the presence of three very efficient catalysts (TMEDA, ^{t}BuBOX, and **L**) reveals strong differences in their behavior. The ^{19}F NMR signals of the main product, $[Zn(Et)\{OC(CF_3)(Et)Ph\}]_2$, allow us to estimate fairly accurately the enantioselectivity of the process for the chiral ligands. By far the more enthralling behavior corresponds to the bulky ligand **L**. The observation of an autocatalytic asymmetric enhancement during the reaction and an unusual concentration dependence on the reaction rate support the participation, for this ligand, of a catalytic cycle additional to the one operating for the other two ligands. This second cycle, favored by the coordination preferences of **L**, explains the unique behavior of ligand **L** and the increased efficiency of the process via a dinuclear intermediate with bridging alkoxy and **L** groups. The improved procedure reported here provides a new synthetic record as it affords basically the same ee (93% *vs*. the previous 92%) but at a higher temperature (244 K *vs*. 213 K), thanks to reduction of the percentage of catalyst used, which produces a stronger influence of the autocatalytic asymmetric enhancement effect of ligand **L**.

Experimental Section

Improved Procedure for the Enantioselective addition of $ZnEt_2$ to 2,2,2-trifluoroacetophenone. Diethylzinc (1.0 M in toluene, 0.58 mL, 0.58 mmol) was added to a solution of **L** (7.4 mg, 0.0096 mmol, 2 mol %) in anhydrous toluene (1 mL) under argon at room temperature. The solution was stirred for 5 minutes and 2,2,2-trifluoroacetophenone (0.48 mmol) was added at 244 K and this temperature was retained. After the reaction was complete, it was quenched with saturated ammonium chloride solution, and extracted with ether. The solvents were removed under reduced pressure and the crude product was purified by chromatography in silica gel using pentane:dichlorometane 3:1 as eluent. 1,1,1-trifluoro-2-phenylbutan-2-ol was isolated as a colourless oil. Chemical yield: 95%, ee: 93%.

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Keywords: asymmetric addition • diethylzinc • diamine • autocatalytic asymmetric enhancement • trifluoromethylketone

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[11] In the equilibrium constant for Eq. 3, $ZnEt_2$ is taken as monomeric according to the recent X-ray determination that shows a linear monomer in the crystal: Bacsa, F. Hanke, S. Hindley, R. Odedra, G.R. Darling, A. C. Jones, A. Steiner, *Angew. Chem.* **2011**, *123*, 11889–11891; *Angew. Chem. Int. Ed.* **2011**, *50*, 11685–11687. Note that the K we are defining is just for practical purposes. Obviously it is likely that in solution $ZnEt_2$ will contain coordinated ketone (in fact the chemical shift of the ketone changes in the presence of Zn species), which we do not specify for simplicity, but this will not change the nuclearity of the Zn species.

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