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Article

Highly Enantioselective Addition of Dialkylzinc to Trifluoroacetophenones, Catalyzed by 1,2-Diamines. Synthesis of Key Fragments of Inhibitors of the Enzyme 11β-HSD1 and Kinetic Analysis of the Process[†]

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Chiral diamines derived from (*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine and (*S*)- or (*R*)-2,2′-bis-(bromomethyl)-1,1′-binaphthalene perform very well as catalysts in the enantioselective addition of $ZnEt_2$ and $ZnMe_2$ to trifluoroacetophenones, avoiding reduction products, in contrast to the poor results with amino alcohols. Excellent yields (up to 99%) and high enantioselectivity (up to 92%) are achieved with the best ligands. A kinetic study at low temperature (−37 °C) shows that the reduction reaction rate on ligandless $ZnEt_2$ is negligible (2 orders of magnitude slower) compared to the rate of addition reaction on [ZnR_2(N−N)]. Using this new procedure, reported fragments of inhibitors of enzyme 11β-HSD1 that are active against obesity and type 2 diabetes mellitus, as well as new unreported modified fragments of these bioactive molecules, were produced efficiently and enantioselectively.

Introduction

Trifluoromethyl-substituted tertiary alcohols are important substructures in many biologically active natural products and in synthetic pharmaceutical compounds.[1] For instance, the chiral molecule *p*-(HO_2C)-C_6H_4-$C(CF_3)$(Me)OH is the head of a family of products presently being investigated as inhibitors of enzyme 11β-HSD1, against obesity and type 2 diabetes mellitus. This compound is obtained at present by a modest-yielding multistep process.[1b] Other slightly modified molecules that might head new active series, such as *p*-(HO_2C)-C_6H_4-$C(CF_3)$(Et)OH, have not been reported so far.

The asymmetric addition of dialkylzincs to aldehydes and ketones is today a powerful method of access to optically active secondary and tertiary alcohols, respectively.[2−9] The group of Toru and Shibata reported recently a nucleophilic enantioselective trifluoromethylation of aryl ketones using a Cinchona alkaloid/TMAF combination.[10] Noyori's group developed some efficient addition reactions to conventional aldehydes, catalyzed by the presence of amino alcohols.[5,11] Alternatively, the direct alkylation of trifluoromethyl ketones with organometallic reagents is practical for $ZnMe_2$ but fails for higher alkyls (e.g., $ZnEt_2$), due to extensive reduction via β-hydride elimination. The reduction reaction is initiated by nucleophilic attack of the ethyl β-H to the carbonyl carbon atom,[12] which makes the problem particularly acute for ketones with electron-withdrawing substituents, such as trifluoromethyl ketones.[13]

Only recently have more extensive studies facing the reduction problem in trifluoromethyl ketones been reported,[14,15] achieving very efficient additions catalyzed by TMEDA (**1**; Figure 1) and other nonchiral chelating ligands. The screening of a high number of chiral ligands (mostly diamines and bis-oxazolines) attained the best result using TBOX (**2**; Figure 1) as a chiral ligand: 37% enantioselectivity for the catalytic enantioselective addition of $ZnEt_2$ to 1,1,1-trifluoroacetophenone, almost without reduction byproduct. The enantioselectivity increased to 61% at −78 °C. Ligand **3** (Figure 1) also catalyzes the addition of $ZnEt_2$ to trifluoroacetophenone, giving the

[†] This paper is dedicated to Prof. José Barluenga on occasion of his 70th birthday.

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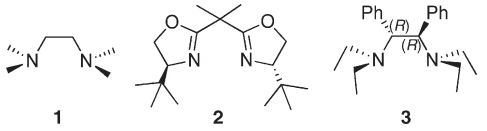


Figure 1

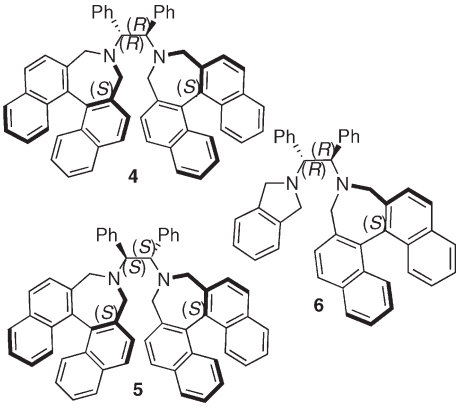


Figure 2

desired 1,1,1-trifluoro-2-phenylbutan-2-ol in 97% yield but only 6% ee.[15]

We considered that higher enantioselectivity might be induced, while still retaining reasonable reactivity, with chiral ligands containing the same N−N skeleton as **3** but having bulkier substituents at the nitrogen atoms that would better match the reagents. A patent on these synthetic results has been filed.[16]

Results and Discussion

(a). Catalytic Syntheses. The reactions of ZnR_2 (R = Me, Et) with trifluoroacetophenone were studied, either in the absence of catalytic ligand or in the presence of nonchiral (**1**) or chiral (**4**−**6**) N−N chelating ligands, using the ratio ZnR_2/trifluoroacetophenone/N−N = 1.2/1/0.1 (10 mol % of N−N relative to the ketone; 8.3 mol % relative to Zn). Ligands **4** (and its enantiomer *ent*-**4**), **5**, and **6** (Figure 2) were synthesized from the commercially available sources (1*R*,2*R*)- or (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine, (*R*)- or (*S*)-2,2′-dimethyl-1,1′-binaphthyl, and 1,2-bis(bromomethyl)benzene, using literature procedures.[17−19] Ligands **4** and **6** have been reported to be efficient in the enantioselective nitro-aldol reaction.[17]

The additions of $ZnEt_2$ and $ZnMe_2$ to trifluoroacetophenone were also checked with Pericàs' type N−O amino alcohol ligands (Figure 3). The commercial chiral amino alcohol **7**, which is remarkably efficient in addition reactions to aldehydes,[20,21] was chosen as standard. The amino alcohol **8**,[22] with the larger N substituents used in the N−N ligands **4**−**6**, was synthesized by us and tested for the reaction.

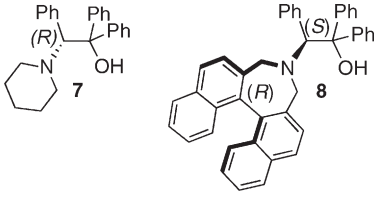
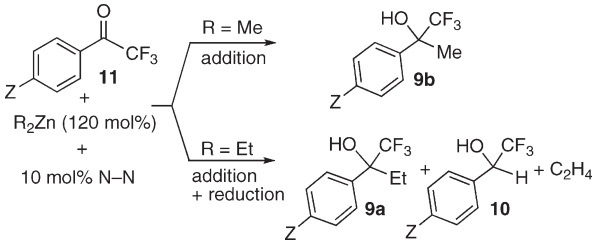


Figure 3

Scheme 1



The reactions produced addition and reduction products, depending on the conditions (Scheme 1). For $ZnMe_2$ the reactions are usually noticeably slower than for $ZnEt_2$ and can give only the addition product **9b**. For the more nucleophilic $ZnEt_2$ the addition to give **9a** competes, depending on the ligand, with the reduction reaction to give **10**. The results of the preparative reactions are shown in Table 1, which includes for comparison the best literature results so far (those of the chiral ligand **2**, entries 5 and 6). Table 1 also includes (in italics) the results of the NMR-monitored reactions, discussed later.

The results collected in Table 1 show clearly that diamine N−N chelating ligands are, with the notable exception of ligand **5**, much more effective than N−O amino alcohols, for the addition of either $ZnMe_2$ or $ZnEt_2$ to trifluoroacetophenone. Among them, ligands **4** and **6** provide the best yields and the best chemo- and enantioselectivities ever reported for the reaction with $ZnEt_2$.

In Table 1, different yields and enantiomeric excesses are found for the addition product **9** in the reactions with N−N*, whereas the reduction product **10**, when observed, was always racemic. For comparison, in the absence of any ligand, "ligandless" $ZnEt_2$[23] reacts easily (although slowly) with trifluoroacetophenone **11**, giving almost exclusively the reduction product **10** in 96% yield, plus a small proportion (3%) of racemic **9** (Table 1, entry 1). This suggests that, on ligandless $ZnEt_2$, β-H elimination is much faster than addition. In the same line, in the case of the slower reagent $ZnMe_2$ (where reduction is excluded) no product was detected after 24 h at room temperature (Table 1, entry 2), showing that the expected addition of ligandless $ZnMe_2$ to ketone does not occur at a perceptible rate.

The addition reaction is activated in the presence of ligands. Thus, using 10% of the nonchiral ligand TMEDA (**1**) afforded high addition reaction rates (for $ZnEt_2$), as well as high addition vs reduction selectivity, although, obviously, with no enantioselectivity (Table 1, entries 3 and 4).

Enantioselective results can be obtained using chiral N−N* ligands, from addition reactions occurring on ZnR_2(N−N*)

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(22) See the Experimental Section and the Supporting Information for details.

(23) By "ligandless" ZnR_2 we mean molecules that are not coordinated by N−N added ligand, although most likely the Zn center is coordinated initially with molecules of the ketone reagent, forming [ZnR_2(trifluoroacetophenone)$_n$] complexes, and later with alcohol- or alkoxy-coordinated products; both oxygen ligands are weaker coordinating molecules than the N−N chelating ligands.

Table 1. Results of the Addition of Diethyl- or Dimethylzinc to Trifluoroacetophenone and its Para-Substituted Derivatives[a]

entry	ZnR_2	Z	L	T (°C)[b]	t (h)	**9** (%)[c]	ee (%)[c] (confign)	**10** (%)[c]
1	$ZnEt_2$	H		−37/rt	10	3		96
1*m*				*−37*	*52*			*82*
2	$ZnMe_2$	H		rt	24	0		
3	$ZnEt_2$	H	**1**	−37/rt	2.5	95		4
3*m*				*-37*	*8*	*99*		*n.o.*[e]
4	$ZnMe_2$	H	**1**	rt	10	97		
5[d]	$ZnEt_2$	H	**2**	−35	0.5	95	51	n.o.[e]
6[d]	$ZnEt_2$	H	**2**	−78	2	85	61	n.o.[e]
7	$ZnEt_2$	H	**4**	−37/rt	10	90	82 (*S*)	8
7*m*				*−37*	*15*	*92*	*84* (*S*)	*5*
8	$ZnEt_2$	H	**4**	−60	48	97	92 (*S*)	n.o.[e]
9	$ZnMe_2$	H	**4**	−37/rt	24	98	83	
10	$ZnEt_2$	H	**5**	−37/rt	10	30	4	58
10*m*				*−37*	*50*	*36*	*5*	*60*
11	$ZnMe_2$	H	**5**	−37/rt	24	85	29	
12	$ZnEt_2$	H	**6**	−37/rt	10	97	75 (*S*)	< 1
12*m*				*−37*	*25*	*95*	*76* (*S*)	*< 1*
13	$ZnMe_2$	H	**6**	−37/rt	24	90	15	
14	$ZnEt_2$	H	**7**	−37/rt	24	12	82 (*R*)	86
15	$ZnMe_2$	H	**7**	−37/rt	24	9	28	
16	$ZnEt_2$	H	**8**	−37/rt	10	6	5	94
17	$ZnMe_2$	H	**8**	−37/rt	24	15	*rac*	
18	$ZnMe_2$	COO-*t*-Bu	**4**	−37/rt	24	85	26	
19	$ZnMe_2$	COO-*i*-Pr	**4**	−37/rt	24	90	26	
20	$ZnMe_2$	COOEt	**4**	−37/rt	24	95	44	
21	$ZnMe_2$	COOMe	**4**	−37/rt	24	95	60	
22	$ZnMe_2$	Br	**4**	−37/rt	24	95	70	
23	$ZnMe_2$	Cl	**4**	−37/rt	24	95	76	
24	$ZnMe_2$	Cl	**4**	−65	48	95	81	
25	$ZnMe_2$	Me	**4**	−37/rt	72	97	54	
26	$ZnMe_2$	Et	**4**	−37/rt	48	97	64	
27	$ZnMe_2$	[f]	**4**	−37/rt	72	99	81	

[a] ZnR_2/trifluoroacetophenone/L = 1.2/1/0.1. Reactions were carried out in 1/2.5 hexane/toluene with $ZnEt_2$ (1 M solution in hexane), and in toluene with $ZnMe_2$ (2 M solution in toluene). Concentration: 1 mmol of ketone in 2 mL of solvent. [b] Except for entries 2, 4, 8 and entries *nm*, the ketone was added to the ZnR_2/L mixture at −35 °C, and then the cooling was removed. rt = room temperature. [c] Determined by GC and HPLC analysis: CHIRASIL-DEX CB (25 m × 0.25 mm × 0.25 mm) and CHIRALPAK AD columns. Determination of the absolute configuration for **9a** was possible by comparison with literature data.[10] Compound **10** is racemic. [d] Literature data.[15] [e] Not observed. [f] The substrate is 3′,5′-dimethyl-1,1,1-trifluoroacetophenone.

enantioselective intermediates (see later) formed in situ (maximum 8.33%) by mixing ZnR_2 and N−N* (10/1). Using 10% of ligand **4**, the reaction of $ZnEt_2$ and trifluoroacetophenone afforded the desired addition product **9a** in 90% yield and 82% ee in 10 h (Table 1, entry 7; the same result with opposite enantioselectivity was obtained with its enantiomer *ent*-**4**). A certain amount of reduction product **10** (8%) was also formed. At −60 °C (48 h) (Table 1, entry 8) the reaction was much more chemoselective, and no reduction product **10** was observed, which increased the yield in addition product to 97%; moreover, the enantiomeric excess increased to 92%. These results outperform by a great deal the best result reported so far in the literature (these were reported for ligand **2**: Table 1, entries 5 and 6). The reaction with $ZnMe_2$ catalyzed with **4** also worked very well, and product **9b** was formed cleanly in 98% yield and 83% ee (24 h, room temperature).

Ligand **4** has the diamine and the binaphthalene moieties with opposite absolute configurations: *S,R,R*. Its diastereoisomer **5**, where the diamine and the binaphthalene substituents are all *S*, performs dramatically worse: the reaction with $ZnEt_2$ is clearly slower and leads, after 10 h, to **9a** in only 30% yield and very low ee (about 4%) and reduction product **10** in 58% yield (Table 1, entry 10). This is in contrast with the good results obtained with **4**, **1**, and **2** and is somewhat closer to the result obtained on ligandless $ZnEt_2$. The reaction showed some improvement at −37 °C (addition/ reduction = 36/60; Table 1, entry 10*m*) but was very slow and still had very poor enantioselectivity (5% ee). The addition of $ZnMe_2$ catalyzed with 10% **5**, however, showed noticeably better results (85% yield, 29% ee, in 24 h), although it was still far from the result with **4** (Table 1, entry 11 vs entry 9).

For ligand **6**, the N substituents at one side of the ligand are smaller than in **4**, thus reducing the crowding in the complex around the Zn center. This difference leads to a notable loss of enantioselectivity in the reaction with $ZnMe_2$ (83% ee for **4** versus 15% for **6**), but not so much in the reactions with the bulkier $ZnEt_2$ (82% ee for **4** versus 75% for **6**, at room temperature) (Table 1, entries 12 and 13). The moderate loss of enantioselectivity in the reaction with $ZnEt_2$ using **6** instead of **4** is somehow compensated by its improved chemoselectivity (almost complete suppression of reduction at room temperature), which rates the performance of **6** as excellent.

For the case of amino alcohol **7** as ligand, the main product of the reaction with $ZnEt_2$ (Table 1, entry 14) was the reduction compound **10** (86%); only a 12% yield of **9a** was obtained, although with good enantioselectivity (82% ee). The reaction with $ZnMe_2$ was worse: only 9% yield in **9b** and 28% ee after 24 h (Table 1, entry 15). With the amino alcohol **8**, with larger N substituents, the results were even more disappointing (Table 1, entry 16): the reaction with $ZnEt_2$ gave, after 10 h, 94% of reduction product and only 6% of the addition product **9b**, with 5% ee. It seems that amino alcohols are not efficient for addition reactions of ZnR_2 on trifluoroacetophenones. Note that the kind of complex intervening in the case of amino alcohols is very different: an alkoxo-bridged dimer $[ZnR(O-N)]_2$ formed by alcoholysis of the starting ZnR_2.[11,24,25]

Entries 18−24 in Table 1 collect reactions using ligand **4**, $ZnMe_2$, and pharmacologically useful para-substituted acetophenones as substrate.[26] The yields are basically unaffected in all cases. However, a clear influence of the para substituent on the ee values is observed, which seems to be related to their bulkiness. Thus, for the series of carboxylates RCO_2 as substituents (Table 1, entries 18−21), the sequence of ee values is *t*-Bu (26%) ≈ *i*-Pr (26%) < Et (44%) < Me (60%). Moving to halide substituents (Table 1, entries 22−24), the ee values are again lower than for trifluoroacetophenone itself but higher than for the carboxylate-substituted molecules and the order depends again, apparently, on the size of the halogen: Br (70%) < Cl (76%). Interestingly, carrying out the reaction at lower temperature (− 65 °C) the reaction of *p*-Cl-C_6H_4-C(O)(CF_3) affords the corresponding chiral alcohol *p*-Cl-C_6H_4-C(CF_3)(Me)OH in 95% yield and 81% ee, which furnishes an appropriate starting head for further functionalization.

Since all the para substituents in entries 18−24 are electron withdrawing, the effect of electron-donating substituents was also checked in entries 25−27, for the sake of completeness. The reactions were clearly slower, as expected,[15] but

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(26) Para substitution on the aryl of trifluoroacetophenone by a synthetically active function is essential for easy modification of this parent product to its biologically investigated derivatives.

longer reaction times afforded good to excellent yields and moderate to very good enantioselectivity.

(b). Kinetic Study. An analysis of all the results in Table 1 leads to the following conclusions. (i) For $ZnMe_2$ the reactions under ligandless conditions are so inefficient that, in the presence of catalytic amounts of ligand, all the addition products must be formed on [ZnR_2(N−N)]. Any loss of enantioselectivity is to be attributed to this complex, not to a competition with reactions occurring on nonchiral ligandless $ZnMe_2$. (ii) For $ZnEt_2$ the activity under ligandless conditions is faster than for $ZnMe_2$, affording less than 3% addition product. This poor rate toward addition will be certainly negligible in front of the faster processes occurring on [$ZnEt_2$(N−N)]. However, since the reduction process is fairly efficient under ligandless conditions, the question still arises whether the percentage of reduction observed in the reactions is occurring on ligandless $ZnEt_2$, on [$ZnEt_2$(N−N)] complexes, or on both pathways, were they competitive. Associated with this is the following question: are the ligands showing lower activity completely coordinated to Zn, or are they partially dissociated? Important dissociation might seriously reduce the proportion of [$ZnEt_2$(N−N)] catalyst in the mixture (in case of complete coordination the expected proportion is 8.33% [$ZnEt_2$(N−N)] vs 91.66% $ZnEt_2$), making the ligandless $ZnEt_2$ catalyst more abundant and more competitive. In order to answer these questions (particularly for the singular case of ligand **5**), the reactions of trifluoroacetophenone with $ZnEt_2$ were monitored by ^{19}F NMR at low temperature (−37 °C), with ligands **1** and **4**−**6**, as well as under ligandless conditions, and their kinetic behavior was inspected.

In the course of these reactions many signals appear in the ^{19}F NMR spectra. They probably correspond to oligomeric intermediates of different complexity (whether free or complexed to Zn),[27] which is supported by the fact that all these signals collapse to only two products (**9a** and **10**) upon hydrolysis (Figure 4).

This complexity before hydrolysis prevents the kinetic monitoring of the reactions through the products, but the reactions could be easily studied, at −37 °C, through the decay of the starting trifluoroacetophenone signal (Figure 5). The final proportion of the two possible products (**9a** and **10**) could be cleanly integrated after hydrolysis, once the reaction was terminated. The latter data are gathered in Table 1 (entries *nm*, data in italics).

The reaction rates of consumption of trifluoroacetophenone follow the trend **1** > **4** ≈ **6** > **5** ≫ no ligand. Assuming bimolecular reactions, the rate of consumption of **11** should obey a rate law composed of addition and reduction processes on complex [$ZnEt_2$(N−N)] plus addition and reduction processes on ligandless $ZnEt_2$. The kinetic behavior might be quite complex if all these components were significant (eq 1).

$$\text{rate} = (k_{ad} + k_{red})[ZnEt_2(N-N)][\mathbf{11}] + (k'_{ad} + k'_{red})[ZnEt_2][\mathbf{11}] \quad (1)$$

However, for all the ligands (even for the apparently peculiar ligand **5**) the reaction rates fit to a pseudo-first-order law: rate = $(k_{ad} + k_{red})$[$ZnEt_2$(N−N)][**11**] = k[**11**], where k = $(k_{ad}+k_{red})$[$ZnEt_2$(N−N)] (see the Supporting Information for details).[28] This proves that (i) practically all the N−N ligand is coordinated to Zn, thus keeping the concentration of $ZnEt_2$-(N−N) constant throughout the reaction,[29] (ii) all the complexes with N−N ligands react very quickly, whether for addition or for reduction, in comparison to the ligandless $ZnEt_2$, so that the contribution of the latter to the products is negligible, and (iii) consequently the addition/reduction rates and the enantiomeric excesses observed, whether high or low, can be attributed almost exclusively to the [$ZnEt_2$(N−N)] complex.

For the reaction in the absence of any L (no ligand, entry 1*m*),[23] the reaction rate should simplify to rate = k'_{red}-[$ZnEt_2$][**11**]. The fitting of our experimental data for this case to a second-order rate equation is reasonably good but shows some irregularity that reveals higher complication. We consider that it is the consequence of a competition of the starting ketone **11** and their oxygen-containing products as ligands for the coordination sphere of Zn, so that the "ligandless" $ZnEt_2$ is changing its nature along the reaction, as oxygen-containing products are being formed, especially at the early stages of the reaction.

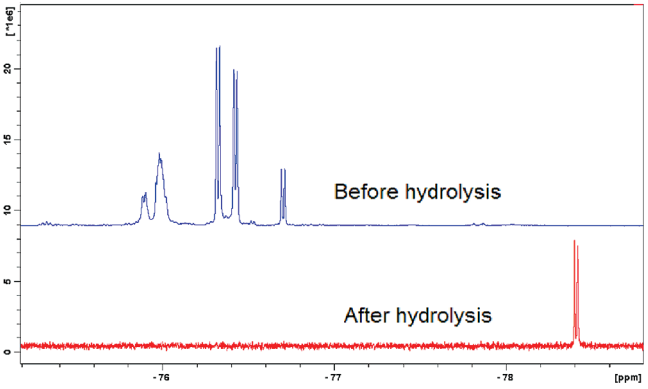

Figure 4. ^{19}F NMR spectra of the reaction mixture for the ligandless reaction (Table 1, entry 1) before (above) and after (below) hydrolysis. Similar spectra are observed for the reactions with ligands.

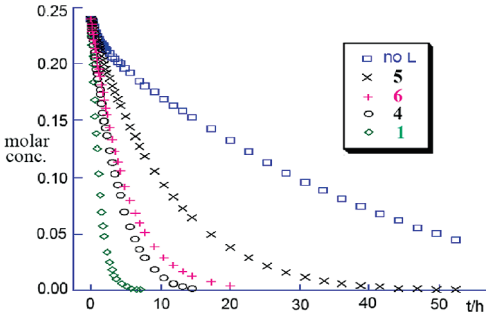

Figure 5. Ligand influence in the rate of consumption of Ph-C(O)-CF_3 (**11**) in reactions with $ZnEt_2$ with or without added ligand (monitored by ^{19}F NMR, in toluene, at −37 °C. ZnR_2/trifluoroacetophenone/L = 1.2/1/0.1. The initial concentration of **11** is 0.24 mmol/mL.

(27) Some probable intermediates in the addition of dialkylzinc to trifluoromethyl ketones have been characterized recently: Hevia, E.; Kennedy, A. R.; Klett, J.; Livingstone, Z.; McCall, M. D. *Dalton Trans.* **2010**, *39*, 520–526.

(28) Note that [$ZnEt_2$L] remains constant to 8.33% of the initial $ZnEt_2$ throughout the reaction until the initial $ZnEt_2$ (91.66%) is close to full consumption.

(29) In other words, the possible ligand-dissociation equilibrium of [$ZnEt_2$(N−N)] is negligible, the concentration of this complex is constant and essentially identical with the concentration of the ligand, and the concentration of free N−N is unobservable. This does not mean that the N−N ligand stays on the same $ZnEt_2$ center all the time. On the contrary, NMR experiments prove that, in a solution of [$ZnEt_2$-(TMEDA)] + TMEDA, there is fairly fast exchange between free and complexed TMEDA.

Table 2. Rate Constants Obtained from the Kinetic Experiments (See Figure 4)

entry	L	K (min^{-1})	$k_{ad} + k_{red}$ (M^{-1} min^{-1})	k'_{red} (M^{-1} min^{-1})
1*m*[a]				0.001 136(8)[b]
3*m*	**1**	0.014 87(10)	0.619(4)	
7*m*	**4**	0.004 052(18)	0.1688(8)	
10*m*	**5**	0.001 528(5)	0.0637(2)	
12*m*	**6**	0.003 355(8)	0.1398(3)	

[a] $ZnEt_2$/trifluoroacetophenone/L = 1/1/0.1. The reaction was carried out in 1/2.5 hexane/toluene with $ZnEt_2$ (1 M solution in hexane). [b] Assuming second order for the reaction.

Table 2 collects the rate constants associated with the experiments in Figure 4, confirming that the reactions on the N−N complexed $ZnEt_2$ are, including the slowest ligand **5**, about 2 orders of magnitude larger than on ligandless $ZnEt_2$. This confirms that only the complex [$ZnEt_2$(N−N)] needs to be considered to analyze the results.

Finally, it is noticeable that the ee values drop from 83% for ligand **4** to 15% for ligand **6** in the reaction with $ZnMe_2$ (entries 9 and 13), whereas the difference is much smaller in the reactions with $ZnEt_2$ (82% vs 75%, entries 7*m* and 12*m*). Also, the addition/reduction ratio with ligand **5** changes dramatically from $ZnMe_2$ (85/0, entry 11) to $ZnEt_2$ (18/81, entry 10). It is also interesting that both the addition/reduction ratio and the enantioselectivity improve at lower temperatures. These observations are compatible with the idea that a tight steric match of the N−N ligand and the ZnR_2 reagent, producing a lower entropy [ZnR_2(N−N)] intermediate, favors higher enantioselectivity in the additions and hinders the reduction process.

Conclusions

While amino alcohols are excellent ligands to catalyze the addition of alkylzincs to aldehydes, they fail with trifluoroacetophenone. In contrast, chelating diamines are very efficient, and we have developed a highly enantioselective addition of $ZnEt_2$ or $ZnMe_2$ to trifluoroacetophenone. The corresponding addition products (trifluoromethyl-substituted tertiary alcohols), are obtained in excellent yield and good enantioselectivity at room temperature, using the appropriate ligand. To the best of our knowledge, this is the first report of addition of the less reactive $ZnMe_2$ to trifluoromethyl ketones. In the case of $ZnEt_2$, working at low temperature (−60 °C) with ligand **4** totally quenches the formation of the reduction product **10** and affords exclusively the addition product in high yield (98%) and higher enantioselectivity (92% ee). Alternatively, ligand **6** also quenches the formation of reduction product at room temperature, although with lower enantioselectivity (75% ee). These are by far the best enantioselective additions to trifluoromethyl ketones reported to date. The chiral alcohol *p*-Cl-C_6H_4-$C(CF_3)$(Me)OH, which is synthetically useful as a head of pharmacologically interesting derivatives, is obtained in 95% yield and 81% ee.

The results of a kinetic monitoring of the reactions with $ZnEt_2$ support that both the addition and the reduction reactions occur exclusively on [$ZnEt_2$(N−N)] complexes for N−N = diamine, because their rates are at least 2 orders of magnitude greater than on ligandless $ZnEt_2$.

Less selective results suggest that this reaction is particularly delicate and a very good match between the sizes of the ligand, the alkyls, and the substituents at the aryl ring is needed to achieve high addition activity and high enantioselectivity.

The N−N diamine ligands, active for additions to ketones, turn out to be complementary to the N−O amino alcohols, active for additions to aldehydes. This different activity must arise from different mechanisms, since the neutral diamines, not having active hydrogens, are not likely to produce the kind of alkoxy-amino Zn intermediates proposed for amino alcohols.

Experimental Section

General Information. All reactions were performed under an argon atmosphere. Toluene was dried over sodium and distilled. Flash chromatography was performed on silica gel (silica gel 60, 230−400 mesh, Merck). Dimethylzinc (2 M in toluene), diethylzinc (1 M in hexanes), and 1,2-bis(bromomethyl)benzene were purchased from Aldrich. (*R*)- and (*S*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene were purchased from TCI Europe. Analytical gas chromatography was performed on a Hewlett-Packard 5890 Series II machine equipped with a CHIRASIL-DEX CB (25 m × 0.25 mm × 0.25 mm) capillary column. All NMR experiments were performed on Bruker AV400, ARX300, and AC300 spectrometers. Optical rotation was measured on a Perkin-Elmer 343 apparatus. Mass spectra were recorded on an Agilent Technologies 5973 Network apparatus.

Synthesis of Amino Alcohol 8. Under an argon atmosphere in dry THF (6 mL) were mixed 0.072 g (0.25 mmol) of (*S*)-2-amino-1,1,2-triphenylethanol,[30] 0.110 g (0.25 mmol) of (*R*)-2,2′-bis(bromomethyl)-1,1′-binaphthalene, and 0.07 mL (0.5 mmol) of triethylamine. The reaction mixture was stirred at 70 °C for 24 h. Then the solvent was removed and the crude product was purified by column chromatography (8/1 hexanes/ethyl acetate) to give 0.104 g (73%) of **8** as white crystals. R_f = 0.38 (8/1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$; δ (ppm)): 3.33 (d, J = 12.31 Hz, 2H, CH_2); 3.62 (d, J = 12.31 Hz, 2H, CH_2); 4.83 (s, 1H, CH); 5.30 (s, 1H, OH); 6.55 (d, J = 8.47 Hz, 2H, Ar); 6.89 (t, J = 6.88 Hz, 1H, Ar); 7.00 (t, J = 7.94 Hz, 2H, Ar); 7.19−7.24 (m, 6H, Ar); 7.35−7.39 (m, 8H, Ar); 7.41 (t, J = 6.88 Hz, 2H, Ar); 7.74 (t, J = 7.94 Hz, 4H, Ar); 7.87 (d, J = 8.47 Hz, 2H, Ar). Anal. Calcd: C, 88.86; H, 5.86; N, 2.47. Found: C, 88.38; H, 5.79; N, 2.43. $[\alpha]_D^{25} = -35°$ (c = 0.7, $CHCl_3$). Mp: 145 °C. MS (EI; m/z (%)) 384 (100), 279 (28), 263 (43), 182 (10), 118 (18), 105 (35), 91 (27), 77 (17), 51(8).

Typical Procedure for the $ZnEt_2$ and $ZnMe_2$ Addition Reactions. In a 50 mL Schlenk flask with a Young's tap and a Teflon stirring bar was introduced 0.025 mmol of the L ligand dissolved in toluene (see Table 1). A 0.3 mmol solution of $ZnEt_2$ or $ZnMe_2$ was added at −35 °C. The mixture was stirred at that temperature for 45 min. Then 0.25 mmol (35 mL) of trifluoroacetophenone were added, also at −35 °C to avoid the overheating associated with this mixing, the cooling bath was removed, and the mixture was allowed to slowly reach room temperature and stirred for the time indicated in Table 1. Then the mixture was carefully hydrolyzed with saturated NH_4Cl solution, extracted with Et_2O, filtered through a short pad of silica and analyzed with GC or HPLC. *GC retention times*: for **9a**, t_1 = 18.7 min, t_2 = 19.9 min; for **10**, t_1 = 27.1 min, t_2 = 28.3 min. GC: 15 min at 100 °C, then 13 min at 120 °C, ramp 10 °C/min; for **9b** (Z = H), t_1 = 23.4 min, t_2 = 24.4 min. GC: isotherm at 100 °C; for **9b** (Z = CN), t_1 = 24 min, t_2 = 25.2 min. GC: isotherm at 140 °C; for **9b** (Z = Cl), t_1 = 15.7 min, t_2 = 16.2 min. GC: isotherm at 125 °C. Compound **10** is racemic. *HPLC retention times*: for **9b** (Z = COOEt), t_1 = 14.7 min, t_2 = 16.5 min (hexane/*i*-PrOH 95/5, 0.5 mL/min); for **9b** (Z = COO-*t*-Bu), t_1 = 15.3 min, t_2 = 17.5 min (hexane/*i*-PrOH 96/4, 0.5 mL/min); for **9b** (Z = COO-*i*-Pr),

(30) Ma, X.; Da, C.-S.; Yi, L.; Jia, Y.-N.; Guo, Q.-P.; Che, L.-P.; Wu, F.-C.; Wang, J.-R.; Li, W.-P. *Tetrahedron: Asymmetry* **2009**, *20*, 1419–1424.

$t_1 = 16.7$ min, $t_2 = 18.1$ min (hexane/*i*-PrOH 96/4, 0.5 mL/min); for **9b** (Z = COOMe), $t_1 = 23.1$ min, $t_2 = 24.6$ min (hexane/*i*-PrOH 96/4, 0.5 mL/min).

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Supporting Information Available: Figures and tables giving ^{1}H NMR spectra of ligands and products and data for the kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.