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The Dual-Catalyzed (Amino Alcohol/Lewis Acid) Enantioselective Addition of Diethylzinc to *N*-Diphenylphosphinoyl Imines

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Abstract. Optimal structural characteristics within a family of (2*R*,3*R*)-1-alkoxy-3-dialkylamino-3-phenyl-2-propanols have been determined for maximum enantioselectivity in the addition of diethylzinc to *N*-diphenylphosphinoyl imines (1-alkoxy = trityloxy; 3-dialkylamino = piperidino). The simultaneous use of silylating agents acting as Lewis acids to induce rate acceleration has been investigated, allowing the identification of triisopropylsilyl chloride and *tert*-butyldiphenylsilyl chloride as the most efficient mediators in terms of rate enhancement and enantiomeric excess of the resulting phosphinamides.

Keywords: imines, addition reactions, zinc and compounds, asymmetric induction

The amino alcohol mediated enantioselective addition of dialkylzinc reagents to aldehydes has received considerable attention, and very efficient ligands have been developed for this process both in terms of turnover and enantiomeric excess of the resulting alcohols.[1] However, the closely related addition to imines is still far from having a satisfactory solution.[2] Imines are considerably less reactive than aldehydes, and activation of the imino group is required in order to allow the reaction to proceed at practical rates. Such activation has been achieved in the form of *N*-acyl imines (1) [arising from *N*-(amidobenzyl)benzotriazoles][3] and, more usually, in the form of *N*-diphenylphosphinoyl imines (2)[4] (Figure 1). Even in these cases, the substituted imines still behave poorly as electrophilic species, so that excess dialkylzinc reagent (up to 300%), stoichiometric amounts of amino alcohol ligand, and very prolonged reaction times are required to ensure high conversion and enantioselectivity.[4]

In an alternative strategy, the non-enantioselective addition of dialkylzinc reagents to ketones[5] and imines[6] has been successfully promoted by soft Lewis acids, such as trialkylsilyl halides. Most probably, activation takes place in these cases through interaction of silicon with the electronegative terminus of the polar double bond, which results in greatly enhanced electrophilicity of the sp^2 carbon (Figure 1).

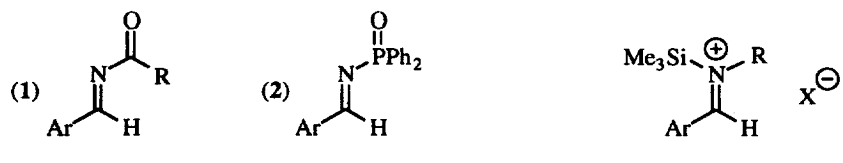

Figure 1. Strategies for Diethylzinc Addition to Imines

Up to now, the apparently incompatible use of amino alcohol ligands and silylating agents has never been combined. However, considering the accepted mechanism of the amino alcohol mediated addition of

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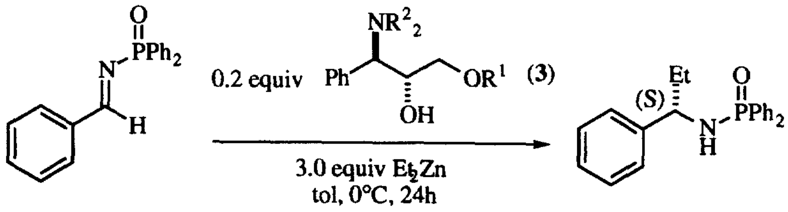
diethylzinc to aldehydes,[1b,7] which involves as a first step the formation of a very stable ethylzinc alkoxide chelate from diethylzinc and the amino alcohol we reasoned that, when introduced in the right order in the reaction medium, the free amino alcohol ligand would never coexist with the trialkylsilyl halide. In this way, both activation modes could be, in principle, compatible. We wish to report here on the successful development of this idea.

As an initial goal in this project, we wanted to determine the optimal amino alcohol ligand for the addition to imines among a family of (2*R*,3*R*)-1-alkoxy-3-dialkylamino-3-phenyl-2-propanols (**3**) which have been previously used with success in the enantioselective addition of diethylzinc to aldehydes.[8] To this end, the *N*-diphenylphosphinoyl imine of benzaldehyde (**2a**) was treated with 3 equiv of diethylzinc and a 20% molar amount of ligand (**3**) in toluene at 0°C, and the mixture stirred for 24 h at that temperature (Scheme 1).



Scheme 1

Under these conditions, conversions were low and no emphasis was put on yield determination. Rather, the crude reaction mixtures were directly studied by HPLC on a Chiralcel OD column (hexane/isopropanol: 97/3) in order to determinate the enantiomeric excess of the resulting phosphinamide.[9] The trial-and-error process leading to the optimal 3-dialkylamino and 1-alkoxy substituents is summarized in Table 1.

Table 1. Structural Optimization of Ligand **3** in the Enantioselective Addition of Diethylzinc to Benzaldehyde Diphenylphosphinoyl Imine.

OR^1	NR^2_2	e.e. **4a** [%]
$OSiBu^tMe_2$	(*S*)-2-methoxymethyl-1-pyrrolidinyl	14
$OSiBu^tMe_2$	1-perhydroazepinyl	50
$OSiBu^tMe_2$	1-pyrrolidinyl	51
$OSiBu^tMe_2$	(*R*)-2-methoxymethyl-1-pyrrolidinyl	67[a]
$OSiBu^tMe_2$	**piperidino**	**69**
$OCPh_3$	(2-dimethylaminoethyl)methylamino	2[a]
$OCPh_3$	diisopropylamino	13
$OCPh_3$	di-n-butylamino	56
$OCPh_3$	4-methyl-1-piperazinyl	58
$OCPh_3$	cis-2,6-dimethylpiperidino	64
$OCPh_3$	**piperidino**	**71**
OCH_3	piperidino	14
OCH_2Ph	piperidino	44
$OCHPh_2$	piperidino	63

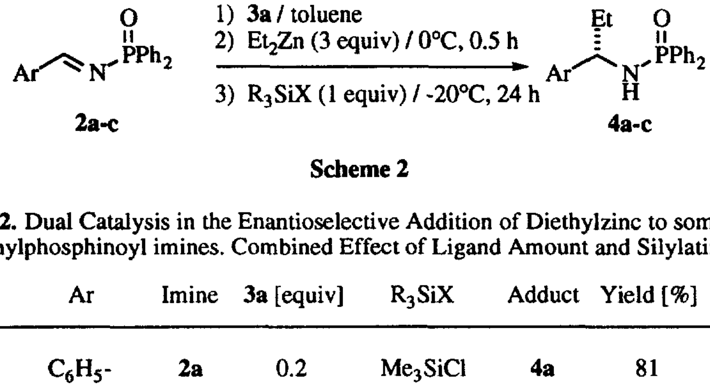
[a]The *R* enantiomer predominates

As can be seen, highest enantioselectivities are recorded with ligands incorporating a very bulky primary alcohol protecting group and a cyclic, six-membered ring amine as the dialkylamino substituent.

Interestingly, these characteristics are identical to those of optimal ligands in the same family when employed in the enantioselective addition of diethylzinc to aldehydes.[8] This represents solid evidence in favor of a close similarity of transition states in these two processes.

For preparative purposes, 0.5 equiv of ligand **3a** ($R^2{}_2N$ = piperidino; R^1O = trityloxy) were employed; even under these conditions, the standard addition to **2a** required 4 days at 0°C for completion, and the enantiomeric excess of the resulting phosphinamide (isolated in 82% yield) increased to 78%.

In an attempt to enhance reaction rate, while leaving asymmetric induction untouched, the use of silylating agents acting as Lewis acids was considered. As already mentioned, success in this dual (amino alcohol/Lewis acid) activation would critically depend on: a) the lack of temporary coexistence of free amino alcohol and silylating agent, which would lead to deactivation of the chiral ligand, and b) the stability towards Lewis acids of the initially formed ethylzinc alkoxide chelate. To ensure maximum fulfillment of these conditions, the following experimental protocol (Scheme 2) was followed; the starting imine and the ligand (**3a**) were dissolved in toluene, the solution was cooled to 0°C, and diethylzinc (1M in hexanes, 3 equiv) was added at that temperature. After 0.5 h, the solution was cooled to -20°C, and the silylating agent (1 equiv) was introduced. After 24 h stirring at that temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with dichloromethane (3x20 mL), and the resulting phosphinamide was isolated with the yields and enantiomeric compositions shown in Table 2.



Scheme 2

Table 2. Dual Catalysis in the Enantioselective Addition of Diethylzinc to some Aromatic Diphenylphosphinoyl imines. Combined Effect of Ligand Amount and Silylating Agent.

Entry	Ar	Imine	**3a** [equiv]	R_3SiX	Adduct	Yield [%]	e.e. [%]
1	C_6H_5-	**2a**	0.2	Me_3SiCl	**4a**	81	16
2	C_6H_5-	**2a**	0.2	Me_3SiOTf	**4a**	88	17
3	C_6H_5-	**2a**	0.2	Ph_3SiCl	**4a**	67	23
4	C_6H_5-	**2a**	0.2	Bu^tMe_2SiCl	**4a**	68	41
5	C_6H_5-	**2a**	0.2	Bu^tPh_2SiCl	**4a**	79	46
6	C_6H_5-	**2a**	0.5	Bu^tPh_2SiCl	**4a**	75	79
7	C_6H_5-	**2a**	1.0	Bu^tPh_2SiCl	**4a**	80	84
8	C_6H_5-	**2a**	0.2	$^iPr_3SiCl$	**4a**	71	72
9	C_6H_5-	**2a**	0.5	$^iPr_3SiCl$	**4a**	70	82
10	C_6H_5-	**2a**	1.0	$^iPr_3SiCl$	**4a**	70	87
11	p-$CH_3C_6H_4$-	**2b**	1.0	$^iPr_3SiCl$	**4b**	63	91
12	2-naphthyl	**2c**	1.0	$^iPr_3SiCl$	**4c**	75	85

As clearly seen in Table 2, the most reactive silylating agents (like trimethylsilyl triflate) induce a very fast addition reaction, but at the expense of a greatly decreased enantioselectivity. Very interestingly, silylating agents containing the bulkiest silyl groups still provoke a substantial rate increase, while the observed enantioselectivity remains high. For those silylating agents providing the most promising results (Bu^tPh_2SiCl and $^iPr_3SiCl$), experiments were performed using increasing amounts of amino alcohol ligand (entries 5-7 and 8-10). In these experiments, the isolated yields of resulting phosphinamide were essentially constant, while the enantiomeric excess significantly increased. This seems to confirm that in the dual catalytic system under investigation, turnover is primarily controlled by the silylating agent while, as expected, enantioselectivity depends on the nature and amount of the amino alcohol ligand. In this context, although the role of the silylating agent in the dual catalytic system has not been investigated in detail, AM1 calculations[9] indicate that, for **2a**, silylation (Me_3Si) at the phosphinoyl oxygen is favored by 60 $kcal.mol^{-1}$ over silylation at nitrogen. This observation, together with the fact that *N*-silyl phosphinamides are never observed in the reaction mixtures, suggests a different activation mechanism than for simple imines.

The optimized experimental conditions for the benzaldehyde derived imine **2a** (entry 10) were employed in the addition to the corresponding imines of *p*-tolualdehyde (**2b**) and 2-naphthaldehyde (**2c**) (entries 11 and 12, respectively), satisfactory yields and high enantioselectivities being also observed in these cases.[10] As in the case of **2a**, the resulting phosphinamides are crystalline solids which can be very easily enantioenriched. Thus, the enantiomeric purity of **4c** can be upgraded to 94% by a simple crystallization from hexane/ether.

Although further work in this area is still needed, the results presented here, which are among the best so far reported for the considered reaction in terms of reaction rate, yield and enantioselectivity, clearly show that the dual catalysis concept introduced here can provide a satisfactory solution to the problem of the catalytic enantioselective addition of dialkylzincs to imines. Efforts along this line, now in progress in our laboratories, will be reported in due course.

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