Direct asymmetric catalytic 1,2-addition of RZnX to aldehydes promoted by AlMe₃ and reversal of expected stereochemistry[†]

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Addition of AlMe₃ to commercial THF solutions of RZnX (R = aryl, functionalised aryl, vinyl; X = Br, I) simultaneously promotes Schlenk equilibria (leading to competent nucleophiles) and the formation of an Al–Zn-ligand catalyst delivering 80–90% ee for $Ar^1CH(OH)Ar^2$ formation from aldehydes.

Since their rise to popularity in the 1990s¹ the potential of diorganozinc species (ZnR2) in asymmetric catalysis has been intrinsically restricted by the fact that only eight of these have wide commercial availability (R = Me, Et, Pr, Prⁱ, Bu, Buⁱ, Ph and C_6F_5). For example, of 1200 publications dealing with 1,2carbonyl additions using ZnR2 in the Scifinder database over half use just ZnEt₂!² While hydroboration,³ alkyne-zincation⁴ and metal-halide⁵ exchange-based methods have been developed as more general routes to diorganozinc species, all these preparations tend to involve significant additional synthetic work. In some cases handling of highly air-sensitive (pyrophoric) intermediates is also required. We were attracted to the possibility of using organozinc halides (RZnX) which, in contrast to ZnR2, are widely available as commercial, readily handled, 0.5 M THF solutions.⁶ The well known superb functional group tolerance of organozinc halides is an additional potential advantage of such an approach. Unfortunately, RZnX species show very low reactivity and their use has been mainly in Pd-catalysed Negishi couplings.⁷ Only isolated examples of the use of RZnX in asymmetric catalysis have appeared.8-10

We recently converted RZnX species into mixed organozinc reagents by addition of ZnMe₂ (Equation 1).¹¹ Fortunately the MeZnX byproduct is unreactive and does not take part in any subsequent catalysis. Conceptually our approach is related to that of Bolm who developed an *in situ* formation of PhZnEt (Equation 2) to mitigate the high background reactivity of ZnPh₂¹² and the unknown aluminium–zinc Schlenk process (Equation 3). As PhZnEt is of utility in asymmetric 1,2-additions to aldehydes¹² we speculated that the use of ArZnX species might allow asymmetric preparation of diarylcarbinols carrying functional groups on both aryl rings. For initial studies commercially available (1*R*,2*S*)-(+)-dibutylnorephedrine (**L1**) was used in arylation studies using 4-CIPhCHO (**1b**) and PhZnBr (**2a**) (Scheme 1) to allow direct comparison with Bolm's results.

$$RZnX + ZnMe_2 \rightleftharpoons RZnMe + MeZnX$$
(1)

$$ZnPh_2 + ZnEt_2 \rightleftharpoons 2 PhZnEt$$
 (2)

$$ArZnX + AlMe_3 \rightleftharpoons ArZnMe + Me_2AlX$$
 (3)

$$\begin{array}{cccc} & 2 \operatorname{Ar}^{2} \operatorname{ZnX} & (2) \\ & 2 \operatorname{AlMe}_{3} & & OH \\ & & 2 \operatorname{AlMe}_{3} & & OH \\ & & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & & \\ (1) & & & & & \\ & & & & \\ (1) & & & & & \\ (1) & & & & & \\ & & & & \\ (1) & & & & & \\ (1) & & & & & \\ (1) & & & & \\ (1) & & & & \\ (1) & & & & \\ (1) & & & & \\ (1) & & & & \\ (2) & & & & \\ (1) & & & \\ (1) & & & \\ ($$

Ar¹: Ph (**a**), 4-ClPh (**b**), 4-FPh (**c**), 4-BrPh (**d**), 4-MePh (**e**) 4-MeOPh (**f**), 3-ClPh (**g**), 3-MePh (**h**), 2-MePh (**i**) Ar²: Ph (**a**), 4-FPh (**c**), 4-MeOPh (**f**), 4-CNPh (**j**), 4-EtO₂CPh (**k**)

Scheme 1

As a base line result PhZnEt with L1 was found to give an 80% yield of **3ba** in 83% ee in toluene and a low ee in toluene–THF mixtures. Unfortunately, attempted promotion of PhZnBr **2a** with ZnR₂ (R = Me, Et) afforded **3ba** in only poor yields (<40%) and as near racemates. Unexpectedly, however, use of the putative AlMe₃ promoted Schlenk procedure (Equation 3) gave acceptable results (Table 1).

Table 1 Additions of ArZnX to aldehydes promoted by AlMe₃^a

Run	Ar ¹	Ar ²	Х	Product	Yield/%	Ee/% ^b
1	4-ClPh	Ph	Br	3ba	67	83 (<i>S</i>)
2	4-ClPh	Ph	Ι	3ba	50	89 (S)
3	4-FPh	Ph	Br	3ca	76	90 (<i>S</i>)
4	4-BrPh	Ph	Br	3da	55	88 (S)
5	4-MePh	Ph	Br	3ea	61	89 (S)
6	4-MeOPh	Ph	Br	3fa	70	86 (S)
7	3-ClPh	Ph	Br	3ga	58	91 (S)
8	3-MePh	Ph	Br	3ha	58	91 (S)
9	2-MePh	Ph	Br	3ia	51	86 (S)
10	Ph	4-MeOPh	Ι	3af	73	$84(R)^c$
11	Ph	4-CNPh	Br	3aj	50	79 (R)
12	Ph	4-EtO ₂ CPh	Ι	3ak	73	81 (R)
13	4-MeOPh	4-FPh	Br	3fc	72	$87 (R)^d$
14	4-ClPh	4-MeOPh	Ι	3bf	56	87 $(S)^{d}$

^{*a*} ArZnX (0.5 mmol), AlMe₃ (0.5 mmol), L1 (0.025 mmol) and aldehyde 1 (0.25 mmol) in THF-toluene. Yields by isolation, ee determination by HPLC: OB, OD and AD columns. Neither residual starting materials nor reduction products are isolated in above trace levels. ^{*b*} Using the stereochemical correlations of Bolm (ref. 12), Soai (ref. 13) and Mosher (ref. 14). All other stereochemical outcomes implied based on Scheme 1 and transition state C (Scheme 2). ^{*c*} Enantiomer of **3fa**. ^{*d*} Assigned on the basis of the model C in Scheme 2; apparent reversal of stereochemistry due to CIP rules.

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While the enantioselectivities realised are modest the reaction of Scheme 1 is remarkable for three reasons. Firstly, the ability of the reaction to tolerate functionality in both coupling partners is apparent (runs 11–12) and competing methyl transfer is minimal (typically 2–7%). While recent PrⁱMgX exchange procedures allow the preparation of Grignard reagents containing some functional groups,¹⁵ thus far, the conditions under which these are prepared can be incompatible with asymmetric catalysis. Secondly, our reaction is technically very simple to carry out: the ArZnX and AlMe₃ solutions are simply mixed under an inert atmosphere in the presence of L1 and the dry aldehyde added slowly at ambient temperature.[‡] Finally, the stereochemistry of this process is unexpectedly reversed and this deserves separate comment.

Soai showed that ligand L1 promotes the addition of both ethyl and aryl nucleophiles to the *Re* face of RCHO when ZnR_2 (R = Et, Ph) reagents are used.¹³ Such selectivity is thought to arise from the so called *'anti'* transition state **A** or its near relatives (Scheme 2).¹⁶ Clearly, the opposite stereochemistry results in Scheme 1 where *Si* face addition to the aldehyde is observed for PhZnX (runs 1–9). Pointers to this reversal of stereoinduction can be found in the work of Shiina.¹⁷ Thioether L2 performs poorly in ZnEt₂ addition *via* an *'anti'* transition state related to **A** but upon use of ZnEt₂–B(OPrⁱ)₃ is proposed to attain transition state **B** leading to *Si* face addition in 92% ee. Our working model is that L1, in the presence of ArZnX and AlMe₃, engenders the related transition state **C** when X is a large group (X = Br, I).§



Scheme 2

A number of experiments were carried out to probe the authenticity of transition state C. Firstly, ¹³C NMR studies of mixtures of PhZnBr and AlMe₃ in THF were conducted.¶ These indicated that extensive and rapid ligand exchange between the zinc and aluminium takes place. A requirement for the presence of a halide and both metals in the selective step is strongly supported by the inefficiency of the following 1 : 1 mixtures (**3ba** yield, ee% using L1 in parentheses): ZnPh₂–AlMe₃ (97, 0); AlPh₃–ZnMe₂ (72, 0); AlPh₃–AlMe₃ (84, 0). As expected, changing the nature of the added Lewis acid perturbed the structure of C unfavourably. For example, lower ee values (for **3ba**) were realised using AlEt₃ (43% ee) and Et/Buⁱ transfer strongly competed. Use of the stabilised AlMe₃ source DABAL-Me₃¹⁸ also resulted in

lower selectivities (56% ee). Consistent with the proposed proximity of the migrating Ph group and the dialkylamino group in **C**, changing the latter had a significant effect on the ee in the model reaction leading to **3ba** (**L3–L5**, Scheme 3). Similarly, while changing the 'top-face' 2-methyl to a phenyl (**L6**) had only a minor effect, introduction of a 1-Ph substituent on the crowded bottom face had a catastrophic outcome (**L7**).



Scheme 3 Value of 3ba ee in catalysis using L3–L7.

Interestingly, it appears that this new AlMe₃ promoted reaction can also be applied to non-aryl organozinc halide reagents. For example, in preliminary studies, CH₂=CHZnBr reacted with **1b** under the conditions of Scheme 1 to afford 4-ClPhCH(OH)CH= CH₂ in 95% yield and 50% ee. Additionally, PhCH₂ZnBr added to benzaldehyde under AlMe₃ promotion to afford the desired *sec*alcohol in high yield (80%) but as a racemate. Conversely, preliminary studies of the reaction of PhZnBr with aliphatic *cyclo*-C₆H₁₁CHO afforded the phenylated product with good ee value (96%) but modest isolated yield (41%).

In conclusion, we have described a simple system for the activation of organozinc halides towards 1,2-aldehyde additions using only readily available reagents and a simple ligand (commercially available as both enantiomers). The process features the coupling of new AlMe₃ promoted zinc Schlenk processes and proceeds by an atypical transition state. The potential for the use of this new process in a wide range of sp² and sp³ based RZnX species carrying a range of functional groups is clear. However, further ligand/process optimisation is required in these non-aryl systems and that is our present goal.

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Notes and references

‡ In a flame-dried Schlenk tube under argon, ArZnBr (1.0 ml of 0.5 M THF solution, 0.5 mmol) and AlMe₃ (0.25 ml of 2.0 M toluene solution, 0.5 mmol) were mixed for 5 min at ambient temperature. Ligand L2 (10 mol%, 0.025 mmol) in toluene (2.0 ml) was added and stirred (20 min), followed by a solution of aldehyde (2.0 ml of 0.125 M toluene solution, 0.25 mmol) over 1 h. The yellow solution was stirred (16 h) at room temperature during which time it often developed a pale yellow precipitate.

A modified transition state where the carbonyl oxygen is coordinated to the aluminium (*i.e.* an additional O···Al contact in C) is also consistent with the present experimental data and predicts the same stereochemical outcome.

¶ Equimolar solutions of PhZnBr and AlMe₃ were mixed. Ambient temperature ¹³C NMR spectra indicated the presence of two, time averaged broad methyl signals ($\delta_{\rm C}$ -7.8, -10.4) assigned to mixtures of species containing both AlMe and ZnMe. Analysis of the phenyl region is complicated by the low intensity of the *ipso*-Ph signals and the presence of secondary exchanges.

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