# Direct asymmetric catalytic 1,2-addition of RZnX to aldehydes promoted by $AlMe_3$ and reversal of expected stereochemistry†

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**Addition of $AlMe_3$ 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 1990s[1] the potential of diorganozinc species ($ZnR_2$) in asymmetric catalysis has been intrinsically restricted by the fact that only eight of these have wide commercial availability (R = Me, Et, Pr, $Pr^i$, Bu, $Bu^i$, Ph and $C_6F_5$). For example, of 1200 publications dealing with 1,2-carbonyl additions using $ZnR_2$ in the Scifinder database over half use just $ZnEt_2$![2] While hydroboration,[3] alkyne-zincation[4] and metal-halide[5] 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 $ZnR_2$, 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 $ZnMe_2$ (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 $ZnPh_2$[12] and the unknown aluminium–zinc Schlenk process (Equation 3). As PhZnEt is of utility in asymmetric 1,2-additions to aldehydes[12] 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-ClPhCHO (**1b**) and PhZnBr (**2a**) (Scheme 1) to allow direct comparison with Bolm's results.

$$RZnX + ZnMe_2 \rightleftarrows RZnMe + MeZnX \quad (1)$$

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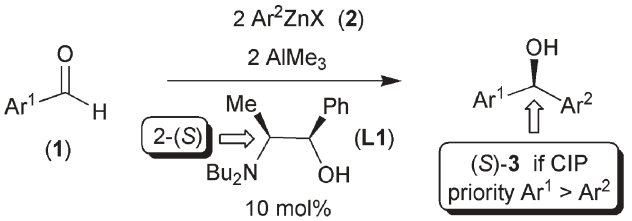
$$ZnPh_2 + ZnEt_2 \rightleftarrows 2\ PhZnEt \quad (2)$$

$$ArZnX + AlMe_3 \rightleftarrows ArZnMe + Me_2AlX \quad (3)$$




$Ar^1$: 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**)
$Ar^2$: Ph (**a**), 4-FPh (**c**), 4-MeOPh (**f**), 4-CNPh (**j**), 4-$EtO_2$CPh (**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 $ZnR_2$ (R = Me, Et) afforded **3ba** in only poor yields (<40%) and as near racemates. Unexpectedly, however, use of the putative $AlMe_3$ promoted Schlenk procedure (Equation 3) gave acceptable results (Table 1).

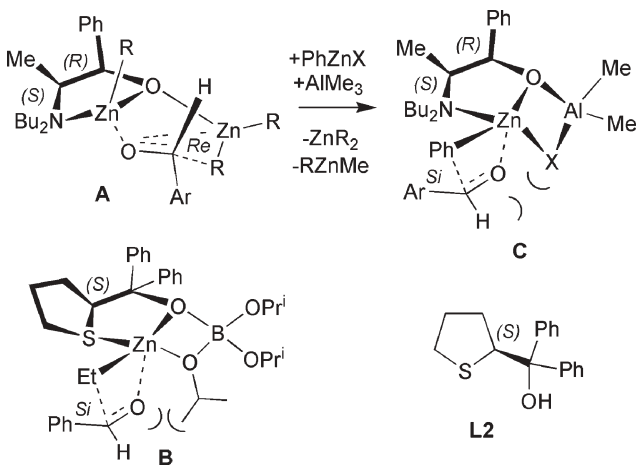
**Table 1** Additions of ArZnX to aldehydes promoted by $AlMe_3$[a]

| Run | $Ar^1$ | $Ar^2$ | X | Product | Yield/% | Ee/%[b] |
|---|---|---|---|---|---|---|
| 1 | 4-ClPh | Ph | Br | **3ba** | 67 | 83 (*S*) |
| 2 | 4-ClPh | Ph | I | **3ba** | 50 | 89 (*S*) |
| 3 | 4-FPh | Ph | Br | **3ca** | 76 | 90 (*S*) |
| 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 | I | **3af** | 73 | 84 (*R*)[c] |
| 11 | Ph | 4-CNPh | Br | **3aj** | 50 | 79 (*R*) |
| 12 | Ph | 4-$EtO_2$CPh | I | **3ak** | 73 | 81 (*R*) |
| 13 | 4-MeOPh | 4-FPh | Br | **3fc** | 72 | 87 (*R*)[d] |
| 14 | 4-ClPh | 4-MeOPh | I | **3bf** | 56 | 87 (*S*)[d] |

[a] ArZnX (0.5 mmol), $AlMe_3$ (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.

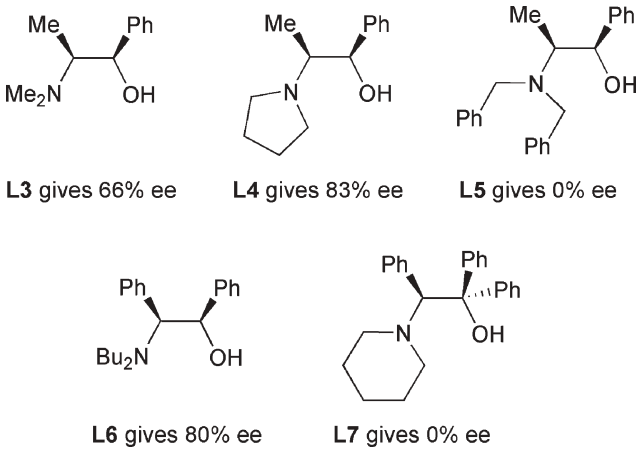
While the enantioselectivities realised are modest the reaction of Scheme 1 is remarkable for three reasons. Firstly, the ability of the reaction to tolerate functionality in both coupling partners is apparent (runs 11–12) and competing methyl transfer is minimal (typically 2–7%). While recent $Pr^iMgX$ 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 $AlMe_3$ 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 $ZnEt_2$ addition *via* an '*anti*' transition state related to **A** but upon use of $ZnEt_2$–$B(OPr^i)_3$ 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 $AlMe_3$, 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, $^{13}C$ NMR studies of mixtures of PhZnBr and $AlMe_3$ 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): $ZnPh_2$–$AlMe_3$ (97, 0); $AlPh_3$–$ZnMe_2$ (72, 0); $AlPh_3$–$AlMe_3$ (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 $AlEt_3$ (43% ee) and $AlBu^i_3$ (48% ee) and Et/$Bu^i$ transfer strongly competed. Use of the stabilised $AlMe_3$ source DABAL-$Me_3$[18] 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 $AlMe_3$ promoted reaction can also be applied to non-aryl organozinc halide reagents. For example, in preliminary studies, $CH_2$=CHZnBr reacted with **1b** under the conditions of Scheme 1 to afford 4-ClPhCH(OH)CH=$CH_2$ in 95% yield and 50% ee. Additionally, $PhCH_2ZnBr$ added to benzaldehyde under $AlMe_3$ 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*-$C_6H_{11}CHO$ 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 $AlMe_3$ 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 $sp^2$ and $sp^3$ 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 $AlMe_3$ (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.

 

The reaction was quenched ($NH_4Cl$ solution) and worked up in the normal way to afford pure **3** after silica chromatography (see electronic supporting information for details).

§ 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 $AlMe_3$ were mixed. Ambient temperature $^{13}C$ NMR spectra indicated the presence of two, time averaged broad methyl signals ($\delta_C$ −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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