DOI: 10.1002/chem.200901803

On the Scope of Trimethylaluminium-Promoted 1,2-Additions of ArZnX Reagents to Aldehydes

Daniel Glynn, Jonathan Shannon, and Simon Woodward*[a]

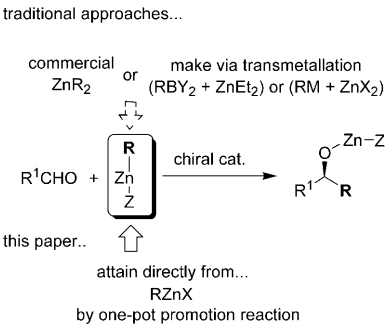
Abstract: A practical asymmetric 1,2-addition of functionalised arylzinc halides to aromatic and aliphatic aldehydes is described by the use of aminoalcohol catalysis in the presence of $AlMe_3$. The process is simple to carry out, uses only commercially available reagents/ligands and provides moderate to good (80–96% *ee*) enantioselectivities for a wide range of substrates. Either commercial ArZnX reagents or those prepared in situ from low cost aryl bromides can be used. In the latter case electrophilic functional groups are tolerated (CO_2Et, CN). The reaction relies on rapid exchange between ArZnX and $AlMe_3$ to generate mixed organometallic species that lead to the formation of a key intermediate that is distinctly different from the classic "*anti*" transition states of Noyori. NMR monitoring and related experiments have been used to probe the validity of the proposed selective transition state.

Keywords: alcohols · asymmetric catalysis · organometallic compounds · synthesis · zinc

Introduction

Since the seminal papers of Oguni (1984, first use of an aminoalcohol ligand),[1] Noyori (1986, first highly enantioselective catalyst),[2] Chaloner (1987, first use of an ephedrine-based ligand)[3] and Soai (1991, first asymmetric use of Ph–zinc reagents)[4] the addition of ZnR_2 species to aldehydes has become one of the "workhorse" reactions of asymmetric catalysis (Scheme 1). The legions of papers generated by this field are well documented in comprehensive reviews.[5] However, fewer endeavours (summarised in Table 1) have concentrated on methods for adding nucleophiles other than the ubiquitous $ZnEt_2$ or $ZnMe_2$.

Notwithstanding the successes of Table 1, a significant irritation in this field is a lack of low cost, widely commercially available, diorganozinc reagents (other than ZnR_2, R = Me, Et, Ph). This situation necessitates the preparation of the zinc organometallic prior to its use. Generally, these reactions can be both technically demanding and necessitate the handling of very air-sensitive/pyrophoric reagents. Recently, we described the first general method for direct activation of poorly nucleophilic, but commercially available, ArZnX (X = Br, I) for enantioselective addition to aromatic aldehydes.[12] This paper provides details of the full scope, extensions and limitations of such procedures and casts some light on the origins of the reaction's selectivity.



Scheme 1. Routes to diorganozinc species and their use in asymmetric 1,2-additions; **R** = transferred organo group, Z = ideally a non transferable group to avoid loss of valuable nucleophile.

Results and Discussion

There are more than 160 commercially available organozinc halides with over 70 being functional arylzinc halides.[13] However, at the outset of our investigations no asymmetric 1,2-addition of organozinc halides to aldehydes was known. We aimed to use a promoter to convert the organozinc

[a] D. Glynn, Dr. J. Shannon, Prof. S. Woodward
School of Chemistry, The University of Nottingham
Nottingham NG7 2RD (UK)
Fax: (+44) 115-9513464
E-mail: simon.woodward@nottingham.ac.uk

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901803.

Table 1. Highlight publications in non-Et/Me organozinc 1,2-additions to aldehydes.

R^1CHO	**R**-Zn-Z[a]	*ee* [%]	Comments	Ref.
aryl, alkenyl	$Zn\{(CH_2)_nFG\}_2$	80–96	*n* must be >3, transmetallated from BEt_2 derivative with $ZnEt_2$.	[6]
aryl, alkenyl, alkyl	***Ph***ZnEt	50–94	by exchange with $ZnEt_2$ preventing uncatalysed additions by $ZnPh_2$	[7]
2-BrPh	***Ph***ZnEt	68–88	via transmetallation from BPh_3 and positive solvent additive effects	[8]
aryl	***Ar***ZnBu	78–99	ArLi + $ZnCl_2$ plus sequestration of LiCl by $Et_2NCH_2CH_2NEt_2$	[9]
aryl	ZnR_2 (**R** = Alkyl, aryl)	93–98	RMgX + $Zn(OMe)_2$ giving precipitation of $Mg(OMe)_2$	[10]
aryl	***RCH*=*CH***ZnEt	63–99	via transmetallation from RCH=CHM (M = $ZrClCp_2$, BR_2)	[11]

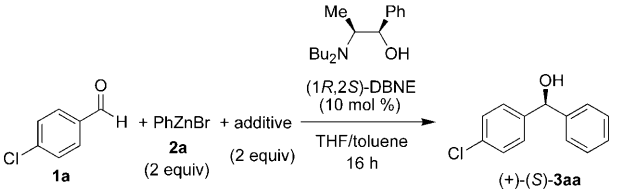
halide into a reactive mixed organozinc species which would selectively add to an aldehyde in the presence of a chiral ligand (Scheme 1). Initial investigations were carried out with aryl species, especially PhZnBr, due to the innately more transferable nature of the phenyl group and to allow stereochemical correlation with known literature examples.

Scope of the promoter: Our experience with the promoted zinc Schlenk equilibrium[14] led us to investigate the utility of Lewis acids with known high halide affinities as PhZnBr activators (Table 2). A readily attained system of 0.5 M PhZnBr in THF, 4-chlorobenzaldehyde and (1*R*,2*S*)-*N*,*N*-dibutylnorephedrine (hereafter (1*R*,2*S*)-DBNE) was selected for this initial screening for a number of reasons: i) the aminoalcohol ligand used is commercially available in both enantiomeric forms; ii) PhZnBr is also commercially available as a 0.5 M THF solution via the Rieke Corporation; iii) the product (*S*)-**3aa** is already known and an already established literature HPLC assay[8] provides both the *ee* value and absolute sense of the asymmetric induction for this substrate. We have carried out reactions using both enantiomers of DBNE but for convenience within this paper all Tables report the outcomes from use of the (1*R*,2*S*) ligand. Initially, we sort to promote the formation of mixed organozinc species through exchange of PhZnX with ZnR_2 (R = Me, Et) by analogy with the preparation of PhZnEt from $ZnPh_2$ and $ZnEt_2$ by Pu[7] and Bolm.[8] Unfortunately, none of the diorganozinc promoters tried (entries 1–3) led to the desired outcome. Boron-based promotion (entries 9–11) was, at best, only partially effective. Unexpectedly however, a number of organoaluminium species (entries 4–8) gave encouraging results of which $AlMe_3$ was the best.

Scope of the aldehyde and organozinc components: Slowing the rate of addition of the substrate **1a** led to significant improvements in both the yield and enantioselectivity providing synthetically useful levels (Table 3, entry 1). To identify potential limitations in this basic procedure a range of cases in both coupling partners has been investigated. Initially, we screened a range of aldehydes using a standard PhZnBr/$AlMe_3$ conditions.

In general, the procedure of Table 3, using commercially available PhZnBr **2a**, gave moderate to acceptable behaviour across a wide range of both aromatic and aliphatic aldehydes (Table 3) with respect to both yield and *ee* value. From an isolated yield perspective aromatic aldehydes (Table 3, entries 1–9) were preferred, whereas from an enantioselectivity basis the use of aliphatic aldehydes was normally optimal (Table 3, entries 10–13). Such behaviour is commonly attributed to the presence of a greater non-catalysed background reaction for aromatic aldehydes in asymmetric zinc-based 1,2-addition chemistry. Conveniently, in all cases only trace amounts of competing methyl transfer addition was observed. In eight cases the sense of enantiofacial selectivity could be explicitly checked against literature results.[15] In the remaining cases the stereochemistry has been tentatively assigned based on our preliminary disclosed model.[12] This is further discussed later (see Section on Stereochemical correlations). The most challenging substrates proved to be 2-substituted benzaldehyde derivatives. If the substituent at this position became too large the enantioselectivity started to fall (Table 3, entries 3 vs 8). It is interesting to note that preparation of hindered **3ja** was particularly effective and that other synthetic methodology, including asymmetric ketone hydrogenation,[16] can find this motif challenging. Finally, we noted that under these conditions acidic functional groups in the aldehyde component were not tolerated including: NH_2 and NHBoc. These reactions

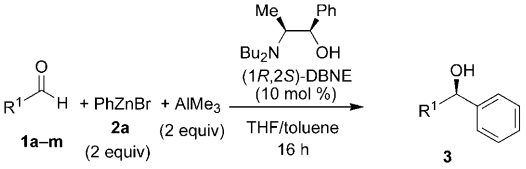
Table 2. Promoter effects in reactions of 4-chlorobenzaldehyde **1a** with PhZnBr **2a**.[a]



Entry	Additive	*T* [°C]	Yield **3aa** [%][b]	*ee* (*S*)-**3aa** [%][b]
1	$ZnMe_2$	0	40	0
2	$ZnEt_2$	0	n.d.[c]	0
3	$ZnBu_2$	0	n.d.	0
4	$AlMe_3$	0	43	86
5	$AlEt_3$	0	13	43
6	MAO	0	27	58
7	DABAL-Me_3	RT	24	57
8	$Al(iBu)_3$	15	n.d.	48
9	BEt_3	15	n.d	35
10	$B(OMe)_3$	15	n.d.	0
11	$BF_3{\cdot}Et_2O$	15	n.d.	0

[a] PhZnBr **2a** (1 mL of 0.5 M solution in THF, 0.5 mmol), additive (0.5 mmol), (1*R*,2*S*)-DBNE (6.9 μL, 0.025 mmol) and toluene (2 mL) stirred at RT for 20 min. Subsequently 4-chlorobenzaldehyde **1a** (0.25 mmol in 2 mL toluene) was added over 5 min at correct temperature. [b] Isolated yield; *ee* determined by HPLC analysis (Chiracel AD column; sense of induction by polarimetry, see ref. [15] and Supporting Information). [c] Not determined.

Table 3. Aldehyde scope in reactions with PhZnBr **2a**.[a]



Entry	R^1	Product	Yield **3** [%]	*ee* **3** [%][b]	Stereo-correlation[c]
1	4-ClPh	**3aa**	67	89 (*S*) (+)	✓
2	3-ClPh	**3ba**	62	90 (*S*) (−)	–[d,e]
3	2-ClPh	**3ca**	51	78 (*S*) (−)	✓
4	4-FPh	**3da**	76	90 (*S*) (+)	–
5	4-BrPh	**3ea**	55	88 (*S*) (+)	✓
6	4-MePh	**3fa**	61	89 (*S*) (−)	✓
7	3-MePh	**3ga**	58	91 (*S*) (−)	–
8	2-MePh	**3ha**	51	86 (*S*) (+)	✓
9	4-(MeO)Ph	**3ia**	70	86 (*S*) (−)	✓
10	*t*Bu	**3ja**	92	96 (*R*) (+)	✓
11	*i*Pr	**3ka**	55	92 (*R*) (+)	✓
12	*c*-C_6H_{11}	**3la**	41	96 (*R*) (+)	✓
13	*n*Bu	**3ma**	51	80 (*R*) (+)	✓

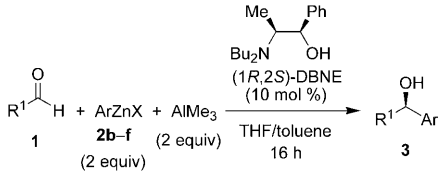
[a] PhZnBr **2a** (1 mL of 0.5 M solution in THF, 0.5 mmol), $AlMe_3$ (0.25 mL of 2 M toluene solution, 0.5 mmol), (1*R*,2*S*)-DBNE (6.9 μL, 0.025 mmol) and toluene (2 mL) stirred at RT for 20 min. Subsequently aldehyde **1** (0.25 mmol in 2 mL toluene) was added over 1 h at RT. Isolated yield and *ee* determined by HPLC analysis. [b] If no stereo-correlation available assignments made on the basis Scheme 2. [c] In accord with Scheme 2 (via polarimetry, see ref. [15] and Supporting Information). [d] Only $[\alpha]_D$ value known (no stereo assignment available in literature), assigned here that (*S*) corresponds to the (−) antipode. [e] Literature comparison data not available.

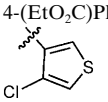
resulted in very poor conversions even when excesses of ArZnX **2** were used. Next the possibility of using arylzinc halide nucleophiles **2** bearing functional groups of various reactivity was investigated. For completeness additions to both aromatic and aliphatic aldehydes were investigated (Table 4). The versatility of the methodology is clear as electrophilic components are tolerated in the nucleophilic coupling partner **2**.

Using commercial Rieke corporation derived ArZnX **2** reagents, a general processes affording synthetically useful isolated yields and stereoselectivities (>10:1 e.r.) for a range of ArZnX species **2b–f** was attained. In the majority of cases the efficacy of the reaction was independent of the halide in the ArZnX **2** reagent. However, in the case of 4-(MeO)PhZnBr **2c** inadequate enantioselectivities were attained (49% *ee* in addition to **1a**) necessitating the use of the iodide reagent for additions to the more reactive aryl aldehydes (entries 4–5 vs 6–8). The most significant chemoselectivity issues arose in the use of the 4-CN derivative **2d**. In this case both the enantioselectivity and chemical yield were suppressed (Table 5, entry 9). In the case of the latter, the low yields were associated with co-formation of 4,4′-dicyannobiphenyl. The aldehyde is suspected of being a sacrificial oxidant in this reaction leading this Wurtz coupling product but we were unable to detect the expected alcohol or pinacol reduction products of benzaldehyde.

Use of in situ prepared ArZnX 2 reagents: One significant disadvantage of the use of commercially produced ArZnX **2** reagents is their high costs (which can amount to greater than 150 Euro per 100 mmol). In our hands, attempted in-house reaction of $LiC_{10}H_8$ with $ZnCl_2$ followed by addition of ArX (X = Br, I) under literature procedures[17] led to ArZnX **2** with vastly inferior properties. Such solutions afforded products **3** in diminished yields and with low *ee* values regardless of the procedures employed to remove by-product lithium salts from them (ICPMS analyses revealed that, in the case of PhZnBr **2a**, we typically prepared reagents containing less than 20 ppm lithium ions). Because of these limitations we sought for an alternative method to unlock the synthetic potential of commercial aryl bromides. In 2003 a robust method for the formation of ArZnBr **2**

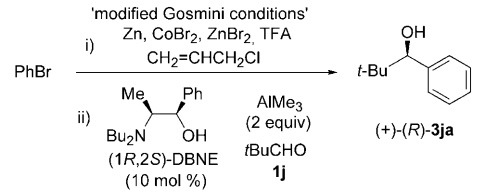
Table 4. Scope of ArZnX **2** 1,2-additions to aromatic and aliphatic aldehydes.[a]



Entry	R^1	Ar	X	Product	Yield **3** [%]	*ee* **3** [%][b]	Stereo-correlation[c]
2	4-(MeO)Ph	4-FPh	Br	**3ib**	72	87 (*R*) (+)[d]	–[e]
3	*c*-C_6H_{11}	2-FPh	Br	**3li**	74	89 (*R*) (+)	–
5	4-ClPh	4-(MeO)Ph	I	**3ac**	94	87 (*S*) (+)	–
6	*t*Bu	4-(MeO)Ph	Br	**3jc**	96	93 (*R*) (+)	✓
7	*c*-C_6H_{11}	4-(MeO)Ph	Br	**3lc**	93	88 (*R*) (+)	–
8	*n*Bu	4-(MeO)Ph	Br	**3mc**	87	82 (*R*) (+)	✓
9	Ph	4-(CN)Ph	Br	**3nd**	50	79 (*R*) (−)	–
10	Ph	4-(EtO_2C)Ph	I	**3ne**	73	81 (*R*) (−)	–
11	*t*Bu	4-(EtO_2C)Ph	Br	**3je**	76	96 (*R*) (+)	–
12	*i*Pr	4-(EtO_2C)Ph	Br	**3ke**	48	93 (*R*) (+)	–
13	*c*-C_6H_{11}	4-(EtO_2C)Ph	Br	**3le**	53	97 (*R*) (+)	–
14	*n*Bu	4-(EtO_2C)Ph	Br	**3me**	63	85 (*R*) (+)	–
15	*t*Bu		Br	**3jf**	88	84 (*R*) (−)	-
16	*c*-C_6H_{11}		Br	**3lf**	85	75 (*R*) (−)	–
17	4-FPh	4-(MeO)Ph	Br	*ent*-**3ib**	68	87 (*S*) (−)	–

[a] ArZnBr **2b–f** (1 mL of 0.5 M THF solution, 0.5 mmol), $AlMe_3$ (0.25 mL of 2 M solution in toluene, 0.5 mmol), (1*R*,2*S*)-DBNE (6.9 μL, 0.025 mmol) and toluene (2 mL) stirred at RT for 20 min. Subsequently aldehyde **1** (0.25 mmol in 2 mL toluene) was added over 1 h at RT. Yield by isolation and *ee* determined by HPLC analysis. [b] Stereochemical assignments made on the basis Scheme 2. [c] In accord with Scheme 2 (via polarimetry, see ref. [15] and Supporting Information). [d] Very low specific rotation value. [e] Literature comparison data not available.

Table 5. Optimisation of in situ PhZnBr **2a** preparation procedure.[a]



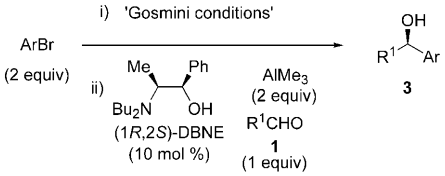
Entry	$CoBr_2$ (mol %)	$ZnBr_2$ (mol %)	Yield **3ja** [%]	*ee* **3ja** [%][b]
1	10	10	58	91 (*R*) (+)
2	5	5	62	91 (*R*) (+)
3	2.5	2.5	86	91 (*R*) (+)
4	1.3	1.3	30	91 (*R*) (+)
5	2.5	–	88	91

[a] MeCN (5 mL) stirred with zinc (0.94 g, 14.4 mmol), $CoBr_2$ (87 mg, 10 mol %, or as otherwise indicated), $ZnBr_2$ (90 mg, 10 mol %, or as otherwise indicated), CF_3CO_2H (20 μL, 0.27 mmol), allylchloride (60 μL, 0.74 mmol) and PhBr (4.0 mmol) stirred 1.5 h. An aliquot of derived PhZnBr **2a** (2 mL of 0.8 M MeCN solution, 1.6 mmol) was added to $AlMe_3$ (0.5 mL of a 2 M toluene solution, 1.0 mmol), (1*S*,R*S*)-DBNE (20 μL, 0.025 mmol, 10 mol %) tridecane (50 μL) (internal standard) and toluene (4 mL) and the mixture stirred at RT for 20 min. Subsequently aldehyde **1** (63 mg, 0.75 mmol in toluene (2 mL) was added over 1 h at RT yield and *ee* determined by GC analysis (see Supporting Information). [b] Facial selectivity authenticated against known literature values (via polarimetry, see ref. [15] and Supporting Information).

from ArBr and Zn was published by Gosmini et al.[18] This chemistry gives excellent yields of FG-ArZnBr (**2**, FG = 3- or 4-substituted CO_2R, CN, OAc, OMe, all provide 80–99 % **2**) and the procedure was subsequently expanded to allow use of ArCl, $ArOSO_2R$ (R = CF_3, Me) as starting materials.[19,20] These zinc powder derived ArZnBr reagents **2** have been employed in a range of "Negishi-type" couplings,[20] but to the best of our knowledge no asymmetric process has been disclosed. Of significant concern to us was the possibility that the additives used to promote this chemistry would downgrade the performance of ArZnBr/$AlMe_3$/(1*R*,2*S*)-DBNE in subsequent chiral catalysis. After some preliminary trials we found that mixtures of $CoBr_2$ with or without added $ZnBr_2$ were optimal for test substrates **2a** and **1j** (Table 5, entry 1). When 10 mol % of $CoBr_2$ and $ZnBr_2$ were used this modified Gosmini protocol gave acceptable yields and enantiomeric excesses. However, to minimise the possibilities for Zn/Co induced side reactions in the second step the cobalt/zinc loading was systematically lowered. Best results were attained at a 2.5 mol % level of $CoBr_2$/$ZnBr_2$ (Table 5, entry 3) below this level poorer yields of **3ja** (Table 5, entry 4) suggesting inefficient formation of PhZnBr **2a**. It is well known that both the particle size and surface covering of elemental zinc samples profoundly affect its reactivity. To insure maximum reproducibility of the procedure for in situ ArZnBr **2** generation procedure various commercially available zinc samples were subjected to the trial. A very high correlation between the yield of the coupled product **3ja** and the median size of the zinc particles was found (see Supporting Information). Free flowing zinc powders with diameters in the range 1–10 μm (microns) were highly active in the preparation of ArZnX **2** reagents under these "modified Gosmini conditions" provided these particles were not aggregated into larger species (as evidenced by electron microscopy). Oxide coating of the particles, normally considered to be the most detrimental factor for the formation of organozinc reagents, was not a major problem in the zinc samples we examined by EDX-backscatter techniques. Of far greater importance was the median particle size—those zinc sources with individual or aggregated median diameters >10 μm (microns) performed poorly regardless of the zinc purity level. Two routinely robust sources have been suggested (see Supporting Information). If poor results are encountered it is recommended that the quality of the zinc dust should be checked by electron microscopy.

The optimised in situ procedure was used to prepare a range of ArZnX **2** reagents (X = Br, I) which were then used directly (in two-fold excess) to arylate a range of aldehydes (Table 6).

Table 6. Direct use of aryl bromides in preparation of secondary alcohols.[a]

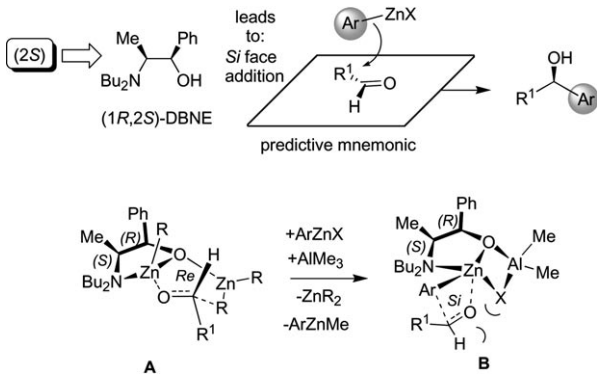


Entry	R^1	Ar	X	Product	Yield **3** [%]	*ee* **3** [%][b]	Stereo-correlation[c]
1	*t*Bu	Ph	Br	**3ja**	91	93 (*R*) (+)	✓
2	*c*-C_6H_{11}	Ph	Br	**3la**	82	89 (*R*) (+)	✓
3	*n*Bu	Ph	Br	**3ma**	72	84 (*R*) (+)	✓
4	*t*Bu	4-(EtO_2C)Ph	Br	**3je**	76	92 (*R*) (−)	–[d]
5	*i*Pr	4-(EtO_2C)Ph	Br	**3ke**	68	84 (*R*) (−)	–
6	*c*-C_6H_{11}	4-(EtO_2C)Ph	Br	**3le**	67	94 (*R*) (−)	–
7	*t*Bu	4-(MeO)Ph	I	**3jc**	81	69 (*R*) (+)	✓
8	*n*Bu	4-(MeO)Ph	I	**3mc**	63	30 (*R*) (+)	✓
9	*t*Bu	4-(MeO)Ph	I	**3jc**	81	89[e] (*R*) (+)	✓
10	*c*-C_6H_{11}	4-(MeO)Ph	Br	**3lc**	92	30 (*R*) (+)	–
11	*c*-C_6H_{11}	4-(MeO)Ph	I	**3lc**	78	57 (*R*) (+)	–
12	4-FPh	3-(AcO)Ph	Br	**3dh**	75	81 (*S*) (+)	–

[a] MeCN (5.0 mL) stirred with zinc (0.94 g, 14.4 mmol), $CoBr_2$ (22 mg, 2.5 mol %), $ZnBr_2$ (23 mg, 2.5 mol %), CF_3CO_2H (20 μL, 0.27 mmol), allylchloride (60 μL, 0.74 mmol) and ArBr (4.0 mmol) stirred 2 h. An aliquot of derived ArZnBr (2 mL of 0.8 M MeCN solution, 1.6 mmol) was added to $AlMe_3$ (0.5 mL of 2.0 M toluene solution, 1.0 mmol), (1*R*,2*S*)-DBNE (20 μL, 0.075 mmol) and toluene (4 mL) and the mixture stirred at RT for 20 min. Subsequently aldehyde **1** (0.75 mmol in toluene 2 mL) was added over 1 h at RT. Isolated yield and *ee* determined by HPLC analysis. [b] Facial selectivity assigned on the basis of Scheme 2. In accord with Scheme 2 (via polarimetry, see ref. [15] and Supporting Information). [d] Literature comparison data not available. [e] In the presence of 0.02 M LiBr.

Application of the two-step processes of Table 6 allowed use of electronically neutral (Table 6, entries 1–3), electronic-deficient (Table 6, entries 4–6) and electronic-rich (Table 6, entries 7–12) zinc reagents derived from ArX. Although the *ee* values of realised **3** are modest, many are still at a synthetically usable level. Some limitations were noted: use of 1,4-$C_6H_4Br(CN)$ led to acceptable levels of stereoselectivity (e.g., 85% *ee* for additions to **1l**). However, unacceptable synthetic yields were isolated due to competing dimerisation to 4,4′-dicyanobiphenyl (typically a 2:1 dimer/1,2-addition product ratio) as had been the case for Rieke-derived 4-CNPhZnBr **2d**. The reagent 4-$NO_2C_6H_4ZnBr$ could not also not be used as only a very low yield of the organometallic was realised in the zinc insertion step. In general, the enantioselectivities realised through application of the ArBr/Zn dust procedure were only slightly below those realised through the commercial Rieke samples of **2** with the exception of the 4-MeOPhZnBr **2c**. While the Rieke derived **2c** gave acceptable levels of selectivity (82–93% *ee* for **3c**; Table 4, entries 6–8). Those using **2c** attained directly from 4-MeOPhBr/Zn yielded **3c** with poor selectivity (30–69% *ee* for **3**, Table 6, entries 7–8, 10–11). Due to this very dramatic difference in the level of selectivity generated by these nominally identical samples of 4-MeOPhZnBr **2c** (commercial Rieke zinc produced vs in situ "Gosmini-derived" reagents) further investigations were carried out. Samples of **2c** from both "commercial Rieke" and "modified Gosmini conditions" derived 4-MeOPhZnBr **2c** were quenched with water leading to immediate quantitative precipitation of ZnO, ArH and HBr. The supernatant aqueous solutions were subjected to titration with standard base and metal ICPMS analysis. While both contained 0.5 M "$MeOPh^-$", within experimental error (based on NaOH titration), the lithium content of the two samples was very different. Commercial Rieke-derived **2c** contained 0.02 M Li^+ while **2c** prepared either by "in-house" $ZnCl_2/2\,LiC_{10}H_8$ and extensive washing of the precipitated Zn* or by the Gosmini direct insertion procedure contained <0.0001 M Li^+. The possibility that Li^+ might enhance the stereoselectivity was investigated through deliberately by preparing a 0.5 M solution of Zn dust (Gosmini) derived **2c** from 4-MeOPhBr containing 0.02 M LiBr to generate an equivalent level of lithium ions. This reagent was added to **1j** to under standard $AlMe_3$/(1*R*,2*S*)-DBNE catalysis to afford **3jc** in 89% *ee* (Table 6, entry 9). The implication of this result is that, in at least the case of reagent **2c**, LiBr provides a powerful structural modification of the active catalyst structure leading to a ×3 improvement in the reaction's selectivity (5.45:1 vs 17.18:1 with LiBr). Further investigations of the generality this "Li-promoter effect" are under active investigation in our laboratory.

Stereochemical correlations: In our preliminary work[12] all of the reactions we tried were in accord with the mnemonic of Scheme 2 whereby the aryl nucleophile attacks from the *Si* face of the aldehyde when the (1*R*,2*S*)-DBNE aminoalcohol ligand is used. This facial selectivity is opposite to that which is expected for the classic *anti* transition state **A** delineated by Noyori in seminal early studies on aminoalcohol catalysis of ZnR_2 additions to RCHO.[2,5] We have proposed that this reversal of stereoselectivity might be accounted for by equilibration of the "Noyori-*anti*" transition state **A** with an alternative Lewis acid promoted structure **B**.[12] In early work Soai showed that, using stoichiometric (1*R*,2*S*)-DBNE, phenylzinc reagents derived from $ZnCl_2$ and PhMgBr also add to the *Si* face of aldehydes.[4] Such behaviour is likely to be closely related to our own system due to the presence of Lewis acidic MgX_2 in the reaction mixture, but no comment was made by Soai.



Scheme 2. Predictive mnemonic for the stereochemistry of the products **3** and associated transition states.

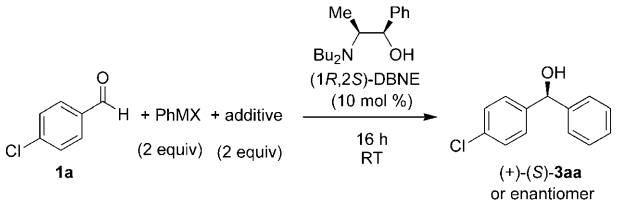
Within the wider range of combinations of Tables 2–6 eleven explicit stereochemical correlations with previous literature results can be called upon (Tables 3, 4, 6).[15] As determined (via polarimetry) all of the isolated samples of **3** produced here from use of (1*R*,2*S*)-DBNE are in accord with the mnemonic of Scheme 2. In our original communication[12] several structural changes to the aminoalcohol ligand that were consistent with transition state **B** being the active form of the catalyst. As screening of further aminoalcohol and related ligands did not provide more selective catalysts than the commercially available DBNE ligand this was not pursued further.

Spectroscopic and mechanistic studies: The key prediction of Scheme 2 is that, after addition of $AlMe_3$ to PhZnBr **2a**, that PhZnMe and **B** will be generated at some level in the reaction mixture. We have undertaken ^{13}C NMR studies in an attempt probe the speciation of the reaction mixture. As the ^{13}C NMR spectrum of PhZnBr **2a** had not been adequately described in the literature its ^1H coupled carbon spectrum was recorded. In THF at ambient temperature 0.4–0.5 M PhZnBr **2a** provides the expected five signals against a C_6D_6 reference. The $^{2,3}J_{CH}$ coupling patterns allow the triplet fine structure on the signal at 124.4 ppm to be equated with the *para* carbon, while the related couplings allow the signals at 125.5 and 138.5 ppm can be equated with the *ortho* and *meta* positions, respectively. A final, rather broad ($w_{1/2}$ ~25 Hz), signal at 159.6 ppm is assigned to

the *ipso* carbon. As ambient temperature is optimal for the catalytic addition reaction (Tables 2–6) NMR studies of PhZnBr **2a** and $AlMe_3$ were also carried out at room temperature. Up to 17 potential exchange partners can be generated from $PhZnBr/AlMe_3$, namely, $ZnPh_xBr_yMe_z$ ($x+y+z = 2$) and $AlPh_xBr_yMe_z$ ($x+y+z = 3$) if complete exchange of all substituents is possible. The addition of $AlMe_3$ (1.0 equiv) to PhZnBr **2a** (0.4–0.5 M in 4:1 THF/toluene) thus produces a relatively complicated ^{13}C NMR spectrum at ambient temperature. Only overlapped broad *ipso* carbon signals are observed ≈160 ppm so that number of aryl species in the mixture cannot be directly determined on this basis. The total number of signals in the much better dispersed *meta* region (136–141 ppm) indicates there are five aryl species present in the mixture (2 major, 3 very minor; see Supporting Information). At room temperature the main component in the $PhZnBr/AlMe_3$ mixture is PhZnBr **2a** based on signal position comparison with a genuine sample (*meta* 138.5 ppm). The concentration of the second highest component (*meta* 136.4 ppm, *ortho* 125.1 ppm, *para* 123.9 ppm) increases as the temperature decreases and this also causes a decrease in the concentration of PhZnBr **2a**, suggesting that these two components are in equilibrium. By using genuine PhZnMe, in an equivalent solvent system, we could equate the second most populated aryl species (*meta* 136.4 ppm) to PhZnMe in line with the proposal for the formation of **B** (Scheme 2). The observed slowing of the PhZnBr/PhZnMe ^{13}C NMR exchange below 0 °C exactly mirrors the real temperature behaviour of the catalytic system for the addition of PhZnBr **2a** to **1a**. The *ee* of the isolated **3** falls smoothly from 90 % at ambient temperature to 83 % at −20 °C for catalytic trials carried out at intervening temperatures. We propose that the 3 minor species present in the reaction mixture (*meta* signals at 136.9, 136.2 and 140.1 ppm) are associated with secondary exchanges of the primary $PhZnMe/AlMe_2Br$ products but due to their low abundance they were not assigned. The methyl region of the ^{13}C NMR spectrum of $PhZnBr/AlMe_3$ mixtures at room temperature is uninformative. Just two signals, a broad signal at 8.5 ppm (assigned to average Al/Me environments) and a sharper signal 10.4 ppm (assigned to average Zn/Me signals) are seen.

Because of the potential for extensive substituent exchange in ^{13}C NMR spectra of $PhZnBr/AlMe_3$ mixtures an alternative insight into the active catalytic structure was sought. We deliberately investigate the reactivity of potential secondary exchange products from the $PhZnBr/AlMe_3$ mixtures with aldehydes **1a** (Table 7).

Table 7. Asymmetric addition of organometallic mixtures to 4-chlorobenzaldehyde **1a** in presence of (1*R*,2*S*)-DBNE.[a]



Entry	'PhMX'	Additive	Solvent	Yield [%]	*ee* [%]	Configuration[b]
1	PhZnBr		toluene/THF 4.25:1	trace	34	*S*
2	PhZnBr	$ZnMe_2$	toluene/THF 4.25:1	40	0	
3	PhZnBr	$AlMe_3$	toluene/THF 4.25:1	67	89	*S*
4	PhZnBr	$AlMe_2Cl$	toluene/THF 4.25:1	40	86	*S*
5	PhZnBr	$AlMeCl_2$	toluene/THF 4.25:1	0[c]	0	
6	PhZnEt		toluene	80	83	*R*
7	PhZnEt		toluene/THF 4.25:1	75	25	*S*
8	$AlPh_3$		toluene/THF 4.25:1	87	0	
9	$AlPh_3$	$ZnMe_2$	toluene/THF 4.25:1	72	0	
10	$AlPh_3$	$AlMe_3$	toluene/THF 4.25:1	84	0	

[a] "PhMBr" (1 mL, 0.5 mmol, 0.5 M solution in THF), Additive (0.25 mL, 0.5 mmol), (1*R*,2*S*)-DBNE (6.9 μL, 0.025 mmol) and toluene (2 mL) stirred at RT for 20 min. Then **1a** (0.25 mmol in 2 mL) was added over 1 h at RT. Isolated yield; *ee* determined by HPLC analysis. [b] Determined by comparing $[\alpha]_D$ with literature (ref. [15]). [c] Mainly just recovered starting material.

Firstly, aside from any effects due to organometallic speciation, a clear solvent effect is apparent. The use of THF/toluene mixtures favours the "*anti*-Noyori" (*S*)-**3aa** product over the use of pure toluene (Table 7, entries 1 and 7 vs 6). It is THF favours the formation of Shiina-type[21] intermediates related to **B** but with the $AlMe_2X$ unit replaced by less effective zinc-based Lewis acids (Table 7, entry 7). The viability of $AlMe_2Cl$ (Table 7, entry 4) is also consistent with proposal **B**. The exchange of one "Me" for a "Cl" in the $AlMe_2X$ motif of **B** still affords a closely related selective catalyst. Use of $AlMeCl_2$ leads to an inactive catalyst (Table 7, entry 5). An exchange with ArZnBr is expected to form $AlCl_2Br$. Aluminium trihalides promote the formation of halide bridged oligomers and it is likely that such behaviour prevents access to the equivalent B catalyst. It is clear that $AlPh_3$ is *not* an active intermediate in the $PhZnBr/AlMe_3$ exchange process as its use results in no conversion (Table 7, entries 7–9). While it is not possible to draw a complete overview of the behaviour of this system, due to the complexity of potential secondary exchanges, the data are all most in accord with the proposed transition state **B**.

Conclusions

The combination $ArZnX/AlMe_3$ offers good potential for the synthesis of chiral secondary alcohols through (1*R*,2*S*)-DBNE promoted additions to prochiral aldehydes. The procedure reliably delivers moderate to good enantioselectivi-

ties (80-96% *ee*) with highly reliable enantioface selectivity and functional group tolerance in both coupling partners. Uniquely, the required FG–ArZnBr species can be generated in situ directly from FG–ArBr (FG = OMe, CO_2Et, CN) and zinc dust. The enantioselectivity of the reaction may also be upgraded by an unprecedented lithium effect through simple addition of LiBr to the ArZnBr species. Overall, the simplicity of the process together with its functional group tolerance and wide commercial availability of all the starting materials make this an attractive process for synthetic chemistry.

Experimental Section

General experimental procedure: Proton and ^{13}C NMR spectra were recorded on a Bruker AV400 in $CDCl_3$. Chemical shifts are reported as δ values in ppm relative to $CHCl_3$ (7.27 ppm for ^1H; 77.0 ppm for ^{13}C) in $CDCl_3$. IR spectra were measured on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra (MS) were recorded at high resolution (HRMS) on a micromass LCT or VG micromass 70E mass spectrometers using electrospray ionisation (ESI). Column chromatography was performed with Fluorochem Davisil silica gel (35–70 μm) using mixtures of ethyl acetate and petrol ether (40–60 °C) as eluents. Toluene was freshly distilled from sodium/benzophenone under argon. Aldehydes were distilled under reduced pressure in a Kugelrohr. All other commercially available compounds were used without further purification.

General procedure for the asymmetric 1,2-addition of ArZnBr 2 to aldehydes 1: A flame-dried Schlenk tube with stirr bar and under argon was charged with arylzinc bromide (2.0 mL of 0.5 M THF solution, 1.0 mmol). To this toluene (4 mL), trimethyl aluminium (0.5 mL of 2 M toluene solution, 1.0 mmol) (**CAUTION**! pyrophoric) and (*1R*,*2S*)-(+)-dibutylnorephedrine (20 μL, 10 mol%) was added and the solution left to stir for ca.10 min. Pivaldehyde (0.75 mmol) dissolved in toluene (2 mL) was added using a syringe pump dropwise over 2 h. The solution was left to stir for 16 h overnight. For details of individual preparations see Supporting Information.

In situ preparation and use of FG–ArZnBr and use: A modified procedure, based on that of Gosmini was employed.[22] Under a argon atmosphere, a flame-dried Schlenk tube was charged with zinc dust (1.74 g, 26.6 mmol), $CoBr_2$ (42 mg, 0.19 mmol), $ZnBr_2$ (44 mg, 0.19 mmol), freshly distilled acetonitrile (7 mL), trifluoroacetic acid (35 μL, 53 mg, 0.46 mmol) and allyl chloride (60 μL, 56 mg, 0.74 mmol). The suspension was then stirred at room temperature for 15 min. To the resultant light brown mixture the functionalised arylbromide (8.0 mmol) was added in acetonitrile (3 mL) in two portions and the light brown mixture left to stir (1.5 h). The solution, nominally 0.8 M in ArZnBr **2**, was then left to stand for 30 min and a suitable amount of the supernatant solution transferred via syringe to the reaction vessel. The organozinc reagent was used as above; full compound data for the derived alcohols is available in the Supporting Information.

Acknowledgements

We thank GlaxoSmithKline (GSK) for support of a studentship in association with the Engineering and Physical Sciences Research Council (EPSRC). We are also appreciative to GSK for help with HPLC and ICPMS assays and for valuable suggestions (Mr. Andrew Kennedy). Helpful input from the COST D40 Programme on "Innovative Catalysis" is acknowledged by S.W. and from the UK government (EPSRC grant EP/F033478/1).

[1] N. Oguni, T. Omi, *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
[2] M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072.
[3] P. A. Chaloner, S. A. R. Perera, *Tetrahedron Lett.* **1987**, *28*, 3013–3014.
[4] K. Soai, Y. Kawase, A. Oshio, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1613–1615.
[5] Reviews; a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; b) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833–856; c) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470.
[6] a) P. Knochel, P. Jones, F. Langer in *Organozinc Reagents: A Practical Approach* (Eds.: P. Knochel, P. Jones), Oxford University Press, Oxford, **1999**, Chapter 5, pp. 77–99; b) "Functionalised Organozinc Compounds": P. Knochel, H. Leuser, L.-Z. Gong, S. Perrone, F. F. Kneisel in *Chemistry of Organozinc Compounds, Part 1* (Eds.: Z. Rappoport, I. Marek), Wiley, New York, **2006**, pp. 287–393.
[7] W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 4222–4223.
[8] a) C. Bolm, N. Hermanns, J. P. Hildebrand, K. Muniz, *Angew. Chem.* **2000**, *112*, 3607–3609; *Angew. Chem. Int. Ed.* **2000**, *39*, 3465–3467; b) J. Rudolph, M. Lormann, C. Bolm, S. Dahmen, *Adv. Synth. Catal.* **2005**, *347*, 1361–1368.
[9] J. G. Kim, P. J. Walsh, *Angew. Chem.* **2006**, *118*, 4281–4284; *Angew. Chem. Int. Ed.* **2006**, *45*, 4175–4178.
[10] A. Côté, A. B. Charette, *J. Am. Chem. Soc.* **2008**, *130*, 2771–2773.
[11] a) P. Wipf, W. Xu, *Org. Synth.* **1996**, *74*, 205–211; b) P. Wipf, W. Xu, *Tetrahedron Lett.* **1994**, *35*, 5197–5200; c) W. Oppolzer, R. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170–173.
[12] J. Shannon, D. Bernier, D. Rawson, S. Woodward, *Chem. Commun.* **2007**, 3945–3947.
[13] The structures of >160 commercially available RZnX species are available through the Sigma–Aldrich web site: http://www.sigmaaldrich.com.
[14] a) P. Goldsmith, S. Woodward, *Angew. Chem.* **2005**, *117*, 2275–2277; *Angew. Chem. Int. Ed.* **2005**, *44*, 2235–2237; b) A. J. Blake, J. Shannon, J. C. Stephens, S. Woodward, *Chem. Eur. J.* **2007**, *13*, 2462–2472.
[15] Polarimetry data used for known examples of **3** [R^1,Ar] as portrayed in Scheme 3: a) (+)-(*S*)-**3aa**[4-ClPh,Ph] {[α]$_D$ = +13.7 (*c* = 20, $CHCl_3$, 20 °C, for >99% *ee*)} B. Wu, H. S. Mosher, *J. Org. Chem.* **1986**, *51*, 1904–1906; b) (−)-(*S*)-**3ca**[2-ClPh,Ph] {[α]$_D$ = −21.5 (*c* = 1.14, $CHCl_3$, for 97% *ee*)} T. Ohkuma, M. Koizumi, H. Ikehara, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *5*, 659–663; c) (+)-(*S*)-**3ea**[4-BrPh,Ph] {[α]$_D$ = +21.0 (*c* = 0.8, C_6H_6, 20 °C for >99% *ee*)} B. Wu, H. S. Mosher, *J. Org. Chem.* **1986**, *51*, 1904–1906; d) (−)-(*S*)-**3fa**[4-MePh,Ph] {[α]$_D$ = −9.7 (*c* = 4.4, C_6H_6 for 96% *ee*)} B. Weber, D. Seebach, *Tetrahedron.* **1994**, *50*, 7473–7484; e) (+)-(*S*)-**3ha**[2-MePh,Ph] {[α]$_D$ = +6.4 (*c* = 0.91, $CHCl_3$, 22 °C for 93% *ee*)} T. Ohkuma, M. Koizumi, H. Ikehara, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *5*, 659–663; f) (−)-(*S*)-**3ia**[4-MeOPh,Ph] {[α]$_D$ = −13.9 (*c* = 1.00, benzene, 25 °C for 97% *ee*)} I. Sato, Y. Toyota, N. Asakura, *Eur. J. Org. Chem.* **2007**, 2608–2610; g) (+)-(*R*)-**3ja** [*t*Bu,Ph] {[α]$_D$ = +25.9 (*c* = 2.24, C_6H_6, 22 °C for >99% *ee*) R. MacLeod, F. J. Welch, H. S. Mosher, *J. Am. Chem. Soc.* **1960**, *82*, 876–880; h) (+)-(*R*)-**3ka** [*i*Pr,Ph] {[α]$_D$ = +47.7 (*c* = 7.0, Et_2O, 20 °C for >99% *ee*)} R. MacLeod, F. J. Welch, H. S. Mosher, *J. Am. Chem. Soc.* **1960**, *82*, 876–880; i) (+)-(*R*)-**3la** [*c*-C_6H_{11},Ph] {[α]$_D$ = +28.3 (*c* = 3.0, C_6H_6, 22 °C) for >99% *ee*)} J. P. Vigneron, J. Jacquet, *Tetrahedron* **1976**, *32*, 939–944; j) (+)-(*R*)-**3ma** [*n*Bu,Ph] {[α]$_D$ = +37.6 (*c* = 3, C_6H_6, ≈20 °C) for >99% *ee*)} J.-P. Mazaleyrat, D. J. Cram, *J. Am. Chem. Soc.* **1981**, *103*, 4585–4586; k) (+)-(*R*)-**3jc** [*t*Bu,4-MeOPh] {[α]$_D$ = +15.2 (*c* = 5.87, C_6H_6, 25 °C for >99% *ee*)} T. Kinoshita, K. Komatsu, K. Ikai, T. Kashimura, S. Tanikawa, A. Hatanaka, K. Okamoto, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1875–1884; l) (−)-(*S*)-**3mc** [*n*Bu,4-MeOPh]) {[α]$_D$ = −22.5 (*c* = 1.1, MeOH, ≈20 °C for 97% *ee*)} B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473–7484.
[16] M. B. Diaz-Valenzuela, S. D. Phillips, M. B. France, M. E. Gunn, M. L. Clarke, *Chem. Eur. J.* **2009**, *15*, 1227–1232.

[17] a) Review: R. D. Rieke, *Aldrichimica Acta* **2000**, *33*, 52–60; b) A. Guijarro, D. M. Rossenburg, R. D. Rieke, *J. Am. Chem. Soc.* **1999**, *121*, 4155–4167; c) R. D. Rieke, P. T.-J. Li, T. P. Burns, S. T. Uhn, *J. Org. Chem.* **1981**, *46*, 4323–4324.
[18] H. Fillon, C. Gosmini, J. Périchon, *J. Am. Chem. Soc.* **2003**, *125*, 3867–3870.
[19] a) I. Kazmierski, C. Gosmini, J.-M. Paris, J. Périchon, *Synlett* **2006**, 881–884; b) C. Gosmini, M. Amatore, S. Claudel, J. Périchon, *Synlett* **2005**, 2171–2174.
[20] Overviews: a) C. Gosmini, J.-M. Bégouin, A. Moncomble, *Chem. Commun.* **2008**, 3221–3233; b) M. Amatore, C. Gosmini, *Chem. Commun.* **2008**, 5019–5021; c) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221–3224.
[21] I. Shiina, K. Konishi, Y. Kuramoto, *Chem. Lett.* **2002**, 164–165.
[22] I. Kazmierski, J. Paris, J. Périchon, C. Gosmini, *Tetrahedron Lett.* **2003**, *45*, 6417–6420.

Received: June 30, 2009
Revised: September 4, 2009
Published online: November 24, 2009

