ChemComm

COMMUNICATION

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Cite this: *Chem. Commun.*, 2021, 57, 8905

Received 30th July 2021,
Accepted 10th August 2021

DOI: 10.1039/d1cc04137a

rsc.li/chemcomm

Atom-efficient transition-metal-free arylation of *N,O*-acetals using diarylzinc reagents through Zn/Zn cooperativity†

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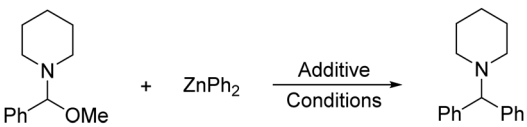
Exploiting the cooperative action of Lewis acid $Zn(C_6F_5)_2$ with diarylzinc reagents, the efficient arylation of *N,O*-acetals to access diarylmethylamines is reported. Reactions take place under mild reaction conditions without the need for transtion-metal catalysis. Mechanistic investigations have revealed that $Zn(C_6F_5)_2$ not only acts as a Lewis acid activator, but also enables the regeneration of nucleophilic $ZnAr_2$ species, allowing a limiting 50 mol% to be employed.

Capable of exceptional functional group tolerance, arylzinc compounds are some of the most widely used organometallic reagents in synthesis for C–C bond forming processes.[1] Frequently the use of transition-metal catalysis is required to maximise yields and selectivities.[2] However, recent advances have shown that in certain cases organozinc reagents can react effectively with organic electrophiles in the absence of catalysts. Thus, direct cross-coupling with aryl halides has been reported by Uchiyama and Wang although harsh reaction conditions are required (90–130 °C, 24 h).[3] Ingleson has also shown that coupling of benzyl and alkyl halides with $ZnAr_2$ can take place efficiently at room temperature using non-ethereal solvents.[4] More recently, Knochel has used ArZnX reagents to prepare triarylmethanes *via* sequential cross-couplings with benzal diacetates.[5] These reactions are proposed to operate *via* a two-step S_N1-type mechanism with the initial formation of a reactive ketone oxonium intermediate. Related to Knochel's work, we have reported the stereoselective cross-coupling between glycosyl bromides and $ZnAr_2$ reagents facilitated by Lewis acidic bis(pentafluorophenyl)zinc, $Zn(C_6F_5)_2$.[6] These processes are underpinned by the special cooperation between the two different types of arylzinc reagents, with $Zn(C_6F_5)_2$ facilitating bromine abstraction of the substrate, forming a highly electrophilic oxocarbenium species that, in turn, reacts with $ZnAr_2$ to give the desired arylated product. Extending the scope of this Zn/Zn′ cooperative partnership beyond glycosylation reactions, here we report a new transition-metal free method to access synthetically relevant functionalised diarylmethylamines, assessing the role played by each organozinc component. Diarylmethylamines are important organic scaffolds present in many pharmaceuticals and biologically active molecules.[7] Previous studies have shown that they are accessible *via* one-step three component reactions by coupling of arylzinc reagents with secondary amines and aldehydes.[8] On the downside, these processes typically require cobalt or copper catalysis, as well as the use of excess arylzinc reagent and/or high reaction temperatures. Therefore, this study asked, could we develop a method to circumvent these additional requirements?

We first attempted the direct synthesis of diarylmethylamines from *N,O*-acetals using diarylzinc reagents. However, no reaction is seen on treating *N,O*-acetal (**1a**) with 0.5 equivalents of $ZnPh_2$ (**2a**) in THF at room temperature (Table 1, entry 1).

Contrastingly, switching to toluene as the reaction solvent, a 47% yield of the corresponding diarylmethanamine product

Table 1 Yields were calculated by ^{1}H NMR spectroscopy using hexamethylcyclotrisiloxane as an internal standard



1a **2a** **3a**

Entry	Conditions	$ZnPh_2$ (mol%)	Additive (mol%)	Yield of **3a** (%)
1	1 h, THF, rt	50	—	0
2	1 h, toluene, rt	50	—	47
3	1 h, toluene, rt	100	—	93
4	1 h, toluene, rt	50	$Zn(C_6F_5)_2$ (10)	63
5	1 h, toluene, rt	50	$B(C_6F_5)_3$ (10)	43
6	1 h, toluene, rt	50	$GaCl_3$ (10)	52
7	1 h, toluene, rt	50	$ZnBr_2$ (10)	47
8	**1 h, toluene, rt**	**50**	**$Zn(C_6F_5)_2$ (50)**	**94**

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† Electronic supplementary information (ESI) available. CCDC 2099646–2099649. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc04137a

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(**3a**) was obtained after 1 hour (entry 2), although approximately half of the *N*,*O*-acetal did not react suggesting that only one phenyl from $ZnPh_2$ is active in the arylation process. Indeed, using 1 equivalent of $ZnPh_2$, a 93% yield of **3a** was now obtained (entry 3). Striving for a more atom-economical process, the reaction was attempted with PhZnBr, but this only gave a 21% yield of **3a**, likely due to the poor solubility of the zinc reagent in non-donor solvents (see ESI† for further screening and optimisation). Considering the marked solvent effect observed, we pondered if the use of Lewis acids as additives could facilitate the atom-efficient arylation process. Pleasingly, adding 10 mol% $Zn(C_6F_5)_2$ in combination with 0.5 equivalents of $ZnPh_2$ increased the yield of **3a** up to 63% (entry 4), whilst $B(C_6F_5)_3$, $GaCl_3$ or $ZnBr_2$ surprisingly had much less impact (entries 5–7). This suggests that $Zn(C_6F_5)_2$ plays a more intimate role beyond simple Lewis acid substrate activation (*vide infra*). On increasing the quantity of $Zn(C_6F_5)_2$ up to 50 mol%, complete transfer of both Ph groups in $ZnPh_2$ was observed to give diarylmethanamine **3a** in 94% yield (entry 8). Notably, no C_6F_5-substitution was detected, showing that $Zn(C_6F_5)_2$ is inert towards the direct arylation reaction.

A series of spectroscopic and structural mechanistic studies were carried out to understand how $Zn(C_6F_5)_2$ enables the substitution of both phenyl groups from $ZnPh_2$ to the *N*,*O*-acetal. When 1-methoxy-(4-fluorophenyl)methyl-piperidine (**1f**) is treated with 1 equivalent of $ZnPh_2$ (**2a**) in toluene-d_8, complete consumption is observed within 20 minutes; this is marked by the almost complete disappearance of the benzylic singlet at δ 4.51 in the ^{1}H NMR spectrum, and appearance of a new benzylic singlet at δ 4.07 for the product (**3i**) (see Fig. S1 in ESI†). An additional singlet is observed at δ 3.63, which is attributed to PhZnOMe, the expected by-product of the reaction. This species does not appear to react further with an excess of **1f**, which is consistent with only one phenyl group from $ZnPh_2$ being active towards the arylation process.

A rational synthesis of the proposed phenylzinc methoxide was performed by treating $ZnPh_2$ with an equimolar amount of MeOH in toluene, leading to a mixture of tetrameric $[PhZnOMe]_4$ (**4**) and heptanuclear $[\{PhZnOMe\}_6ZnOMe_2]$ (**5**) in approximately a 6 : 1 ratio (Fig. 1). Heteroleptic (**5**) is methoxy-rich and is postulated to form *via* redistribution[9] of **4** since it was present in similar ratios with respect to **4** for repeated syntheses and recrystallisations. Isolated in low yields by adjusting the stoichiometry and crystallisation conditions (see ESI†), **5** is not observed in the reaction between **1f** and $ZnPh_2$, and there is no evidence from variable temperature NMR studies to suggest that **4** and **5** can interconvert. The OMe signal of **4** in the ^{1}H NMR spectrum matches the PhZnOMe species that is formed in the reaction mixture (Fig. S1, ESI†). Consistent with the reactivity studies described above, no further formation of arylation product **3a** was observed when treating *N*,*O*-acetal **1a** with isolated crystals of phenylzinc methoxide **4**.

The next step was to investigate the role of $Zn(C_6F_5)_2$ in the transformation and explain how it enables the reaction to occur efficiently with a limiting 50 mol% of the diarylzinc reagent.

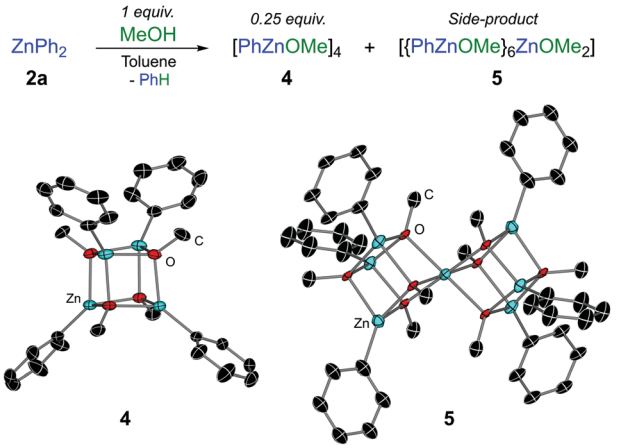
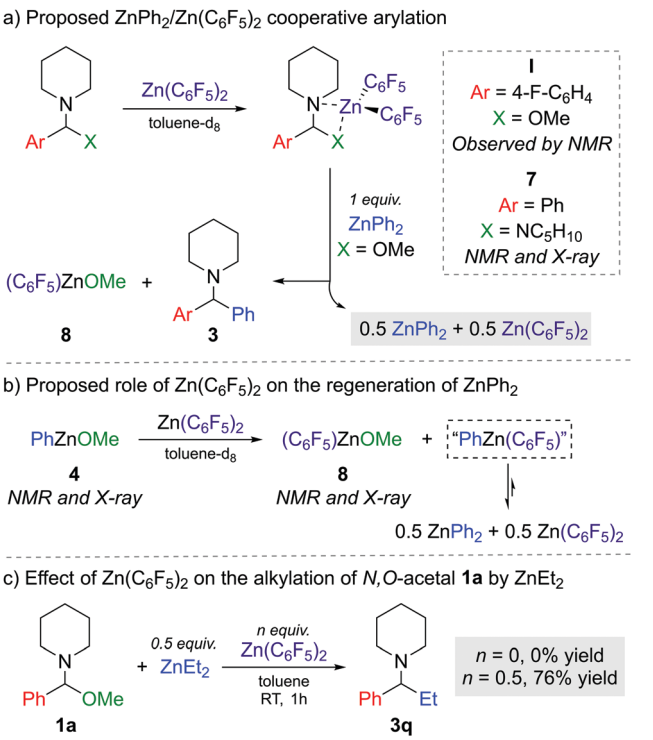


Fig. 1 Synthesis of stoichiometric and OMe-rich phenyl zinc-methoxides, **4** and **5**. Molecular structures of **4** and **5**. Thermal ellipsoids shown at 30% probability. Hydrogen atoms and solvents of crystallisation have been omitted for clarity.

Combining **1f** with one equivalent of $Zn(C_6F_5)_2$ in toluene-d_8 suggests coordination and adduct formation of **I** (Scheme 1a) as evidenced by the broadening and shifting of the ^{1}H and ^{19}F NMR signals (see Fig. S2–S3 in ESI†).

While **I** could not be isolated as a solid and it partially decomposes over time in solution, coordination adduct $[\{PhCH(NC_5H_{10})_2\}Zn(C_6F_5)_2]$ (**7**) was obtained and structurally authenticated by treating $Zn(C_6F_5)_2$ with the related *N*,*N*′-aminal 1,1 (phenylmethylene)dipiperidine, **6** (Scheme 1a). In **7**, the



Scheme 1 Mechanistic studies on the arylation of *N*,*O*-acetals by $ZnAr_2$/$Zn(C_6F_5)_2$ combinations.

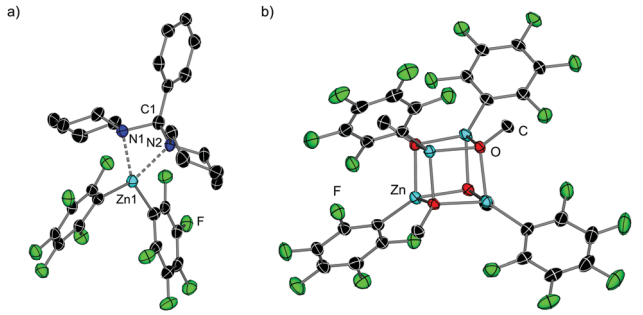


Fig. 2 Molecular structures of (a) [{PhCH(NC$_5$H$_{10}$)$_2$}Zn(C$_6$F$_5$)$_2$] (**7**) and (b) [(C$_6$F$_5$)ZnOMe]$_4$, (**8**). Thermal ellipsoids shown at 30% probability. Hydrogen atoms and solvent molecules of crystallisation omitted for clarity.

N,*N*′-aminal coordinates to the Zn centre in a chelating fashion *via* its two N atoms (Fig. 2a). Interestingly, **7** is significantly more robust that **I** in solution and it does not undergo arylation with $ZnPh_2$ even under forcing refluxing conditions. This can be attributed to the greater strength of the C–N bonds in the *N*,*N*′-aminal *versus* the C–O bond in **1f**.[10] Related to these findings it can be hypothesised that the coordination of *N*,*O*-acetal to the Lewis acid would increase the electrophilicity of the substrate and enable the less nucleophilic PhZnOMe intermediate to transfer its remaining Ph group. However, no other Lewis acids appeared to promote the reaction and 50 mol% of $Zn(C_6F_5)_2$ is needed, implying that its role is not catalytic in nature. Instead, we observed that $Zn(C_6F_5)_2$ reacts directly with the PhZnOMe by-product to regenerate the more nucleophilic diarylzinc reagent together with the formation of (C_6F_5)ZnOMe (Scheme 1a and b). This would justify the necessity for requiring 50 mol% $Zn(C_6F_5)_2$ to enable complete transfer of both aryl groups from the zinc reagent. Similarly to **4**, treating a toluene solution of freshly sublimed $Zn(C_6F_5)_2$ with equimolar MeOH yields the tetrameric species [(C_6F_5)ZnOMe]$_4$ (**8**) (Fig. 2b). Interestingly, the ^{1}H and ^{19}F NMR signals for **8** appear to differ slightly when compared to *in situ* '(C_6F_5)ZnOMe', prepared from isolated [PhZnOMe]$_4$ (**4**) with regeneration of the nucleophilic diarylzinc reagent (Fig. S4–S5, ESI†). We attribute these differences to the formation of different aggregates and/or solvates in solution, but the possibility of heteroleptic/mixed aryl zinc alkoxides cannot be fully discarded. However, on spiking each of the three (C_6F_5)ZnOMe solutions with THF, almost identical ^{19}F NMR spectra were obtained, consistent with the hypothesis that different aggregates/solvates coexist (Fig. S6, ESI†). Furthermore, $ZnPh_2$ (now as the THF adduct) can be identified by ^{1}H NMR spectroscopy (Fig. S7, ESI†), illustrating the ability of $Zn(C_6F_5)_2$ to regenerate the more nucleophilic diarylzinc reagent. Overall, we propose that $Zn(C_6F_5)_2$ first coordinates to the *N*,*O*-acetal **1**, forming adduct **I**, activating the substrate towards arylation by nucleophilic $ZnPh_2$ to give the corresponding diarylmethanamine **3** and PhZnOMe (Scheme 1a and b). This step may occur *via* the *in situ* formation of an iminium intermediate or in a concerted manner.[5,11] The marked solvent effect observed in these transformations, with Lewis donor THF completely inhibiting formation of **3**, supports the key role of the coordination of $Zn(C_6F_5)_2$ to the substrate to facilitate the arylation process.[6] By-product PhZnOMe reacts in turn with $Zn(C_6F_5)_2$ to form (C_6F_5)ZnOMe (the ultimate by-product of the reaction, Scheme 1a and b), along with the regeneration of 0.5 equivalents of $ZnPh_2$ and $Zn(C_6F_5)_2$, resulting from the redistribution of PhZn(C_6F_5) (Scheme 1b).[6,12] The regenerated $ZnPh_2$ can react further with *N*,*O*-acetal, whilst the unreacted 0.5 equivalents of $Zn(C_6F_5)_2$ enable the continued recycling of PhZnOMe that is formed in the reaction. In this regard almost identical ^{19}F NMR spectra are obtained when combining isolated [PhZnOMe]$_4$ (**4**) with $Zn(C_6F_5)_2$ (0.25 : 1 ratio), or a mixture of isolated [(C_6F_5)ZnOMe]$_4$ (**6**), $ZnPh_2$ and $Zn(C_6F_5)_2$ (0.25 : 0.5 : 0.5 ratio) (Fig. S8, ESI†).

The participation of $Zn(C_6F_5)_2$ enables the use of 50 mol% of $ZnPh_2$, which can be particularly useful when employing more complex aryl scaffolds on zinc, as only limiting amounts are required to achieve high yields, in contrast to other methods where an excess of the organozinc reagent is typically needed.[8]

We also found that when **1a** is reacted with 0.5 equiv. $ZnEt_2$ no alkylation is observed, whereas introducing $Zn(C_6F_5)_2$ (0.5 equiv.) furnishes **3q** in a 76% yield (Scheme 1c). This can be attributed to the reduced Lewis acidity of $ZnEt_2$ (in comparison to $ZnPh_2$), so on its own it cannot activate **1a** towards C–O bond cleavage, requiring the initial formation of coordination adduct akin to **I** (Scheme 1a) which can then react with $ZnEt_2$.

Having gained some mechanistic insights, we then went on to explore the scope of the reaction (Fig. 3). Diarylmethanamine products (**3b–3g**) were realised in high isolated yields (84–92%) using a range of diarylzinc reagents (**2b–g**) furnished with electron-donating or electron-withdrawing groups, *ortho*-substituents and even heteroaryls. For the synthesis of **3d** and **3g**, the reaction was performed at 90 °C due to the poor solubility of the $ZnAr_2$ species in toluene. In all cases, although the reactions were complete within 1 hour, it was critical that the diarylzinc reagents were free of residual Et_2O to enable the transformation. Next, the scope of the *N*,*O*-acetals was probed (Fig. 3). The reaction was successfully carried out with a variety of substrates bearing different functional groups in the aromatic ring. Product yields and reaction times remained consistent in the case of both electron-donating and electron-withdrawing groups. Compounds **3b**, **3c** and **3e** could be prepared in similar yields when compared to varying the $ZnAr_2$ reagent, offering a second route to mixed-diarylmethanamine species. Additionally, products **3k** and **3l**, containing sensitive cyano and nitro-functional groups, could be obtained in good yields (81% and 58% respectively) with no significant signs of substrate decomposition or side-products. *N*,*O*-acetals prepared from amines other than piperidine also reacted smoothly with $ZnPh_2$ under the optimised conditions. Compound **3m**, derived from morpholine, was obtained in 86% yield, while compound **3n** containing *N*-methylpiperazine, was isolated in 72% yield. Compound **3n** is commonly known as Cyclizine, and is a widely employed anticholinergic drug, which highlights the potential of the reaction to access relevant bioactive molecules. The reaction could also be performed with the acyclic *N*,*O*-acetal, resulting in product **3o** in 76% yield. Finally, the reaction was

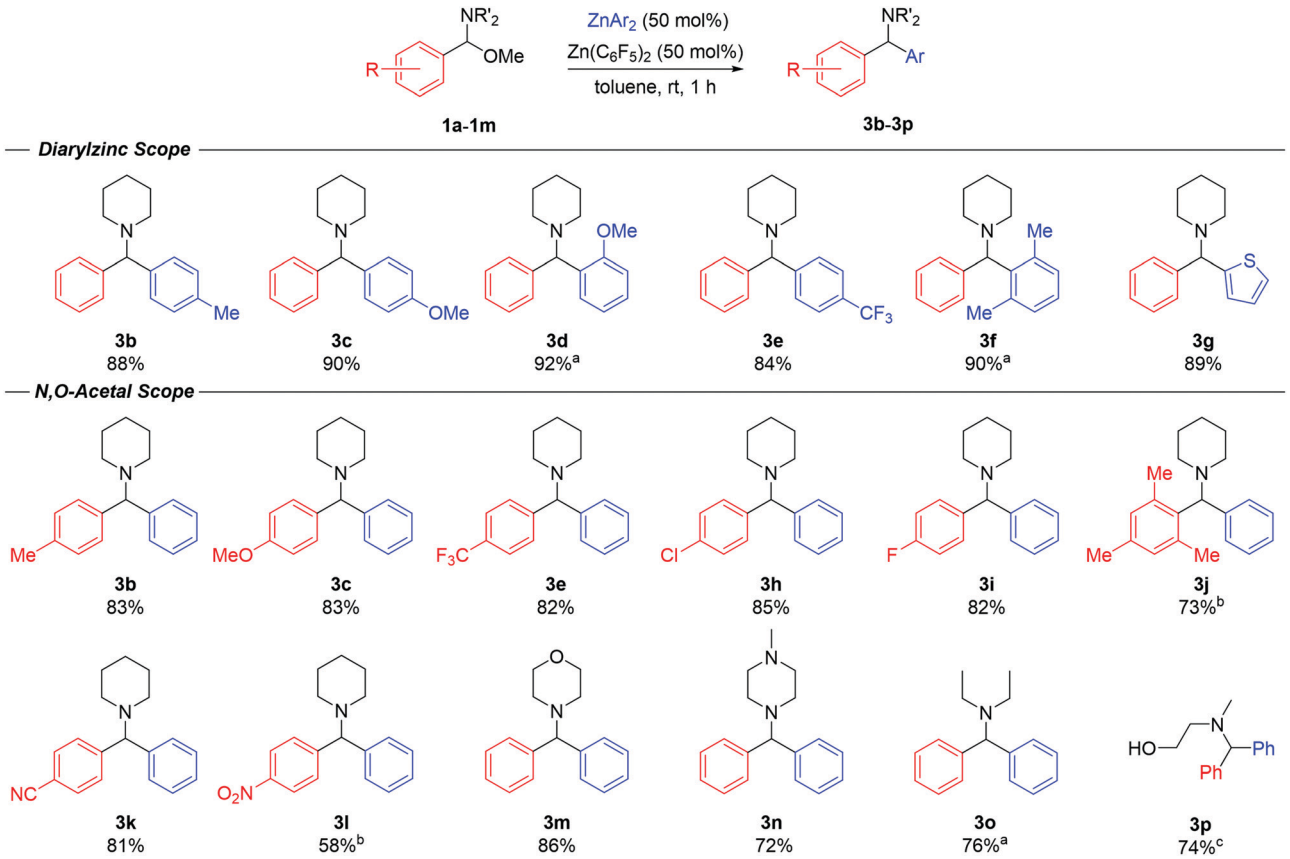


Fig. 3 Substrate scope for the arylation of *N,O*-acetals with diarylzinc reagents. Yields refer to isolated compounds after column chromatography. [a] Reaction performed at 90 °C. [b] The *N,O*-acetal was employed without prior purification. [c] Yield determined by ^{1}H NMR spectroscopy using hexamethylcyclotrisiloxane as an internal standard.

also possible with an *N*-substituted oxazolidine, which resulted in smooth ring opening to afford amino-alcohol **3p** in a 74% yield.

To conclude, we have demonstrated how Zn/Zn′ cooperativity through the use of nucleophilic diarylzinc reagents and Lewis acidic $Zn(C_6F_5)_2$, enables the atom-efficient and transition-metal free arylation of *N,O*-acetals to afford a range of diarylmethanamines. Mechanistic studies show the double role of $Zn(C_6F_5)_2$ which not only activates the substrate towards the arylation process but also effectively regenerates $ZnAr_2$ from the inactive ArZnOMe by-product, allowing a limiting 50 mol% of $ZnAr_2$ to be employed.

We thank the SNSF (188573) and the University of Bern for their generous sponsorship of this research.

Conflicts of interest

There are no conflicts to declare.

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