Exploiting the cooperative action of Lewis acidic Zn(C_6F_5)_2 with diarylzinc reagents, the efficient arylation of N,O-acetals to access diarylmethanamines is reported. Reactions take place under mild reaction conditions without the need for transition-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, diarylzinc compounds are some of the most widely used organometallic reagents in synthesis for C–C bond forming processes. Frequently the use of transition-metal catalysis is required to maximise yields and selectivities. 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). 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. More recently, Knochel has used ArZnX reagents to prepare triarylmethanes via sequential cross-couplings with benzo diacetates. 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. 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 arylation 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 diarylmethanamines, assessing the role played by each organozinc component. Diarylmethanamines are important organic scaffolds present in many pharmaceuticals and biologically active molecules. Previous studies have shown that they are accessible via one-step three component reactions by coupling of arylzinc reagents with secondary amines and aldehydes. 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 diarylmethanamines 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 was obtained (entry 2).

Table 1: Yields were calculated by ^1H NMR spectroscopy using hexamethylocyclotrisiloxane as an internal standard.

| 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          | Bi(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              |
(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 ZnPh₂ is active in the arylation process. Indeed, using 1 equivalent of ZnPh₂, 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(C₆F₅)₂ in combination with 0.5 equivalents of ZnPh₂ increased the yield of 3a up to 63% (entry 4), whilst B(C₆F₅)₃, GaCl₃ or ZnBr₂ surprisingly had much less impact (entries 5–7). This suggests that Zn(C₆F₅)₂ plays a more intimate role beyond simple Lewis acid substrate activation (vide infra). On increasing the quantity of Zn(C₆F₅)₂ up to 50 mol%, complete transfer of both Ph groups in ZnPh₂ was observed to give diacetylmethane 3a in 94% yield (entry 8). Notably, no C₆F₅-substitution was detected, showing that Zn(C₆F₅)₂ is inert towards the direct arylation reaction.

A series of spectroscopic and structural mechanistic studies were carried out to understand how Zn(C₆F₅)₂ enables the substitution of both phenyl groups from ZnPh₂ to the N,O-acetal. When 1-methoxy-[4-fluorophenyl]methyl-piperidine (1f) is treated with 1 equivalent of ZnPh₂ (2a) in toluene-d₈, 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 ¹H NMR spectrum, and appearance of a new benzylic singlet at δ 4.07 for the product (3f) (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 ZnPh₂ being active towards the arylation process.

A rational synthesis of the proposed phenylzinc methoxide was performed by treating ZnPh₂ with an equimolar amount of MeOH in toluene, leading to a mixture of tetrameric [PhZnOMe]₄ (4) and heptanuclear [PhZnOMe₆]₂ZnOMe₂ (5) in approximately a 6:1 ratio (Fig. 1). Heteroleptic (5) is methoxy-rich and is postulated to form via redistribution 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 ZnPh₂, 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 ¹H 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(C₆F₅)₂ in the transformation and explain how it enables the reaction to occur efficiently with a limiting 50 mol% of the diarylzinc reagent.

Combining 1f with one equivalent of Zn(C₆F₅)₂ in toluene-d₈ suggests coordination and adduct formation of I (Scheme 1a) as evidenced by the broadening and shifting of the ¹H and ¹⁹F NMR signals (see Fig. S2–S3 in ESI†). While 1 could not be isolated as a solid and it partially decomposes over time in solution, coordination adduct [PhCH(NC₅H₁₀)₂][Zn(C₆F₅)₃] (7) was obtained and structurally authenticated by treating Zn(C₆F₅)₂ with the related N,N-aminal 1,1-(phenylmethylene)dipiperidine, 6 (Scheme 1a). In 7, the

![Scheme 1](https://example.com/scheme1.png)

**Scheme 1** Mechanistic studies on the arylation of N,O-acetals by ZnAr₂/Zn(C₆F₅)₂ combinations.
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 1 in solution and it does not undergo arylation with ZnPh₂ 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.⁷ 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(C₆F₅)₂ is needed, implying that its role is not catalytic in nature. Instead, we observed that Zn(C₆F₅)₂ reacts directly with the PhZnOMe by-product to regenerate the more nucleophilic diarylzinc reagent together with the formation of (C₆F₅)ZnOMe (Scheme 1a and b). This would justify the necessity for requiring 50 mol% Zn(C₆F₅)₂ to enable complete transfer of both aryl groups from the zinc reagent. Similarly to 4, treating a toluene solution of freshly sublimed Zn(C₆F₅)₂ with equimolar MeOH yields the tetramer species [(C₆F₅)₂ZnOMe]₄ (8) (Fig. 2b). Interestingly, the ¹H and ¹⁹F NMR signals for 8 appear to differ slightly when compared to in situ (C₆F₅)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 (C₆F₅)ZnOMe solutions with THF, almost identical ¹⁹F NMR spectra are obtained when combining isolated [PhZnOMe]₄ (4) with Zn(C₆F₅)₂ (0.25 : 1 ratio), or a mixture of isolated [(C₆F₅)₂ZnOMe]₄ (6), ZnPh₂ and Zn(C₆F₅)₂ (0.25 : 0.5 : 0.5 ratio) (Fig. S8, ESI†).

The participation of Zn(C₆F₅)₂ enables the use of 50 mol% of ZnPh₂, 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.³ We also found that when 1a is reacted with 0.5 equiv. ZnEt₂ no alkylation is observed, whereas introducing Zn(C₆F₅)₂ (0.5 equiv.) furnishes 3q in a 76% yield (Scheme 1c). This can be attributed to the reduced Lewis acidity of ZnEt₂ (in comparison to ZnPh₂), so on its own it cannot activate 1a towards C–O bond cleavage, requiring the initial formation of coordination adduct akin to 1 (Scheme 1a) which can then react with ZnEt₂.

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 ZnAr₂ 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 Et₂O 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 ZnAr₂ 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 ZnPh₂ under the optimised conditions. Compound 3m, derived from morpholine, was obtained in 86% yield, while compound 3n containing N-methylpipерazine, 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
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\textsubscript{0} cooperativity through the use of nucleophilic diarylzinc reagents and Lewis acidic Zn(C\textsubscript{6}F\textsubscript{5})\textsubscript{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\textsubscript{6}F\textsubscript{5})\textsubscript{2}, which not only activates the substrate towards the arylation process but also effectively regenerates ZnAr\textsubscript{2} from the inactive ArZnOMe by-product, allowing a limiting 50 mol\% of ZnAr\textsubscript{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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