






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Atom-efficient arylation of *N*-tosylimines mediated by cooperative $\text{ZnAr}_2/\text{Zn}(\text{C}_6\text{F}_5)_2$ combinations†

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By combining the Lewis acid $\text{Zn}(\text{C}_6\text{F}_5)_2$ with nucleophilic diarylzinc (ZnAr_2) reagents, we report the atom-efficient arylation of *N*-tosylimines under mild conditions. Mechanistic studies through the isolation of key intermediates reveal how the two zinc species act cooperatively to activate the imine substrate and regenerate the ZnAr_2 reagent, enabling a limiting 50 mol% to be employed.

The addition of polar organometallics to unsaturated substrates represents a versatile method to build molecular complexity in a simple step.¹ Exemplified by the Grignard reaction,² which involves the addition of an organomagnesium halide to a carbonyl functionality, these reactions are widely used to construct new C–C bonds and obtain functionalised alcohol products.^{3,4} The analogous addition of organozinc halides to carbonyls was recognised as early as 1887 by Reformatsky⁵ and takes advantage of the lower nucleophilicity of zinc to enable the reaction to occur even in the presence of ester functional groups.⁶ Indeed, the high functional group tolerance and selectivity of organozinc reagents gives them widespread applications in organic synthesis,^{7,8} most notably in Negishi cross-coupling reactions.⁹ Nevertheless, the high selectivity of organozinc reagents comes with the drawback of reduced reactivity, meaning that transition-metal catalysts, additives, or harsh reaction conditions are often needed to facilitate C–C bond formation when using these reagents.^{7,8}

To overcome these limitations, we have previously exploited the use of diarylzinc reagents in combination with the Lewis acidic species $\text{Zn}(\text{C}_6\text{F}_5)_2$ to enable the atom-efficient functionalisation of glycosyl bromides¹⁰ or *N,O*-acetals¹¹ without the need for transition-metal catalysts. Key for the success of these approaches is the lack of co-complexation or ligand scrambling between both types of Zn reagents. We thus considered whether

this same Zn/Zn combination could instead be employed for nucleophilic addition reactions and focused our attention towards the functionalisation of imines to give amine products. Whilst the addition of organolithiums to imines occurs readily,¹² and can even be conducted under aerobic conditions,^{13,14} additives or catalysts are generally needed when employing less nucleophilic Grignard or organozinc reagents. For example, Lewis acid additives such as Me_3SiOTf ($\text{OTf} = \text{OSO}_2\text{CF}_3$) facilitate the addition of Grignard reagents to imines,¹⁵ whilst copper catalysts are needed for the addition of organozinc reagents to *N*-tosylimines.¹⁶ In many cases, a large excess of the organometallic reagent is employed,^{16,17} and these processes have not yet been optimised for arylzinc species.

We first explored the reaction of *N*-(tosyl)-4-fluorobenzylideneamine (**1**) with various phenyl-zinc reagents under different conditions (Table 1).

When using 1 equivalent of ZnPh_2 in THF, only 12% yield of *N*-tosyldiarylmethanamine (**2**) was obtained after quenching the reaction (entry 1). Contrastingly, performing the reaction in toluene gave an 80% yield of **2** (entry 2). Numerous reports have demonstrated that non-donor solvents work best for

Table 1 Reaction optimisation. Yields refer to spectroscopic yields measured using ferrocene as an internal standard. Ar = 4-F- C_6H_4 ; Ts = $\text{SO}_2\text{-C}_6\text{H}_4\text{-CH}_3$

Entry	Phenyl-zinc reagent	Equivalents used	Solvent	Yield (%)
1	ZnPh_2	1	THF	12
2	ZnPh_2	1	Toluene	80
3	ZnPh_2	0.5	Toluene	45
4	$\text{ZnPh}_2 + \text{Zn}(\text{C}_6\text{F}_5)_2$	0.5 each	Toluene	80
5	PhZnBr	1	THF	0
6	PhZnBr	1	Toluene	0
7	Ph_3ZnLi	1	THF	70

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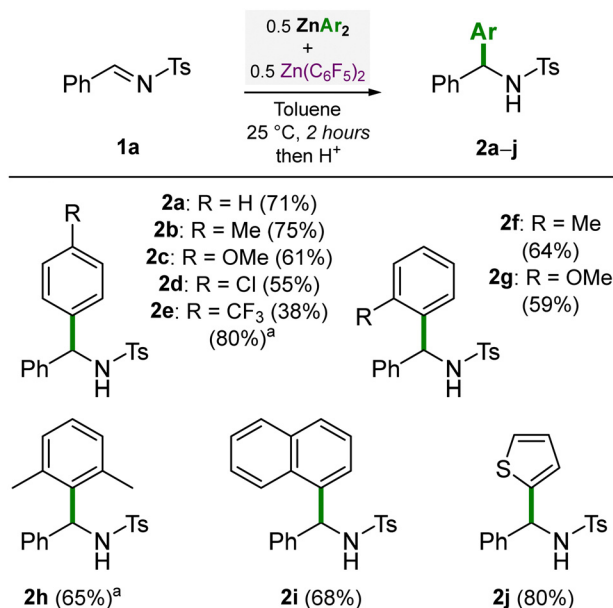
nucleophilic substitution reactions involving diarylzinc reagents.^{10,11,18} This solvent dependence suggests that the pre-coordination of the imine substrate to the Lewis acidic zinc centre plays an essential role in the reaction (*vide infra*). Lowering the equivalents of ZnPh_2 to 0.5, only 45% yield of **2** was obtained, indicating that only one phenyl-substituent from ZnPh_2 is transferred. Using an equimolar amount of $\text{Zn}(\text{C}_6\text{F}_5)_2$ however, restored the high yields (80%, entry 4), with no competitive transfer of the C_6F_5 -substituent observed, allowing for the efficient transfer of both Ph groups to the substrate. Contrastingly, no product was obtained when using PhZnBr , regardless of the solvent employed (entries 5 and 6), reflecting the decreased nucleophilicity of organozinc halides compared to diorganozinc reagents. 70% yield of **2** was observed when using anionically activated lithium zincate,¹⁹ Ph_3ZnLi (entry 7), but here only one phenyl-substituent is transferred and therefore this reagent simply acts as a PhLi surrogate (see ESI† for extended reaction optimisation table).

Having established that 0.5 equivalents each of ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ gave the optimal conditions, we went on to explore the scope of different diarylzinc reagents for the nucleophilic addition reaction to *N*-(tosyl)-benzylideneamine (**1a**) (Scheme 1). Good to high yields of the corresponding addition products **2a–c** were obtained when using 0.5 equivalents of ZnPh_2 , $\text{Zn}(4\text{-Me-C}_6\text{H}_4)_2$ and $\text{Zn}(4\text{-OMe-C}_6\text{H}_4)_2$ respectively. For less nucleophilic ZnAr_2 species, slightly lower yields of 55% (**2d**) and 38% (**2e**) were obtained, but extended heating improved the yield of **2e** up to 80%. *ortho*-Substituted diarylzincs gave good yields of 64% (**2f**) and 59% (**2g**) respectively. Remarkably, concerning the synthesis of **2g**, no product was observed when using 1 equivalent of $\text{Zn}(2\text{-OMe-C}_6\text{H}_4)_2$ in the absence of $\text{Zn}(\text{C}_6\text{F}_5)_2$. This is attributed to the *ortho*-OMe-substituents that can coordinate and quench the Lewis

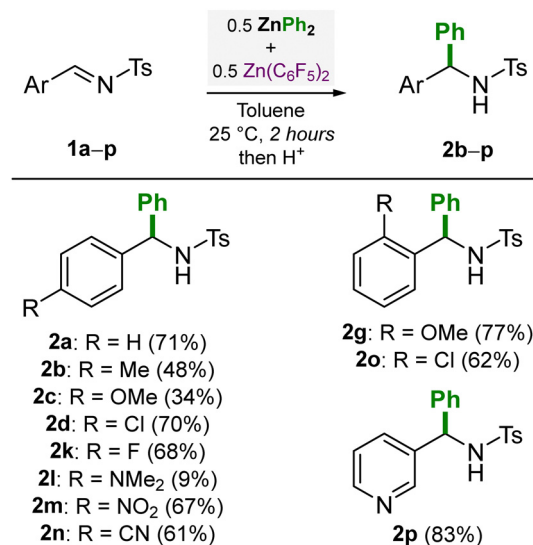
acidity of the Zn centre,^{20,21} which has a similar detrimental role to using ethereal solvents (see Table 1). The sterically encumbered $\text{Zn}(2,6\text{-Me}_2\text{-C}_6\text{H}_3)_2$ gave a good yield of 65% (**2h**) albeit after heating at 80 °C for 20 hours. Electron-deficient $\text{Zn}(1\text{-naphthyl})_2$ gave a good yield of 68% (**2i**) whilst the heteroaryl $\text{Zn}(2\text{-thiophenyl})_2$ gave a high yield of 80% (**2j**). In general, the yields obtained when using 0.5 equivalents each of ZnAr_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ were higher than when simply using 1 equivalent of ZnAr_2 in the absence of $\text{Zn}(\text{C}_6\text{F}_5)_2$, particularly for less nucleophilic ZnAr_2 compounds (see Scheme S1 in the ESI† for full details). This methodology is therefore attractive when employing complex ZnAr_2 species since it allows the atom-efficient transfer of both aryl-substituents, and furthermore, its high functional group tolerance and mild reaction conditions make this approach suitable for late state functionalisation strategies.

We then went on to investigate the scope of different *N*-tosylimines (**1a–p**) using 0.5 equivalents each of ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ (Scheme 2). Modest to high yields (34–83%) of the corresponding addition products **2a–p** were obtained under these reaction conditions. In general, electron-withdrawing substituents (F, Cl, NO_2 , CN) were found to give higher yields due to the increased electrophilicity at the imine carbon, whilst electron-donating substituents (OMe or NMe_2) gave modest or low yields (*e.g.* 9% for **2l**). The synthesis of compounds **2m**, **2n** and **2p** exemplifies the high functional group tolerance of organozinc compounds, as these unsaturated substituents (NO_2 , CN and pyridyl) are typically incompatible with more nucleophilic polar organometallics such as organolithiums.^{14,22,23}

To understand how $\text{Zn}(\text{C}_6\text{F}_5)_2$ facilitates the atom-efficient addition of diarylzinc reagents to *N*-tosylimines, a series of stoichiometric reactions were performed with each component (Fig. 1). The addition of 1 equivalent of ZnPh_2 to *N*-(tosyl)-benzylideneamine (**1a**) in toluene affords the corresponding 1,2-addition product, **3a** (Fig. 1a). Compound **3a** exists a



Scheme 1 Diarylzinc scope for the nucleophilic addition reaction to *N*-(tosyl)-benzylideneamine (**1a**). Yields refer to isolated yields after column chromatography. ^a Heated to 80 °C for 20 hours.



Scheme 2 *N*-tosylimine scope for the nucleophilic addition of ZnPh_2 in the presence of $\text{Zn}(\text{C}_6\text{F}_5)_2$. Yields refer to isolated yields after column chromatography.



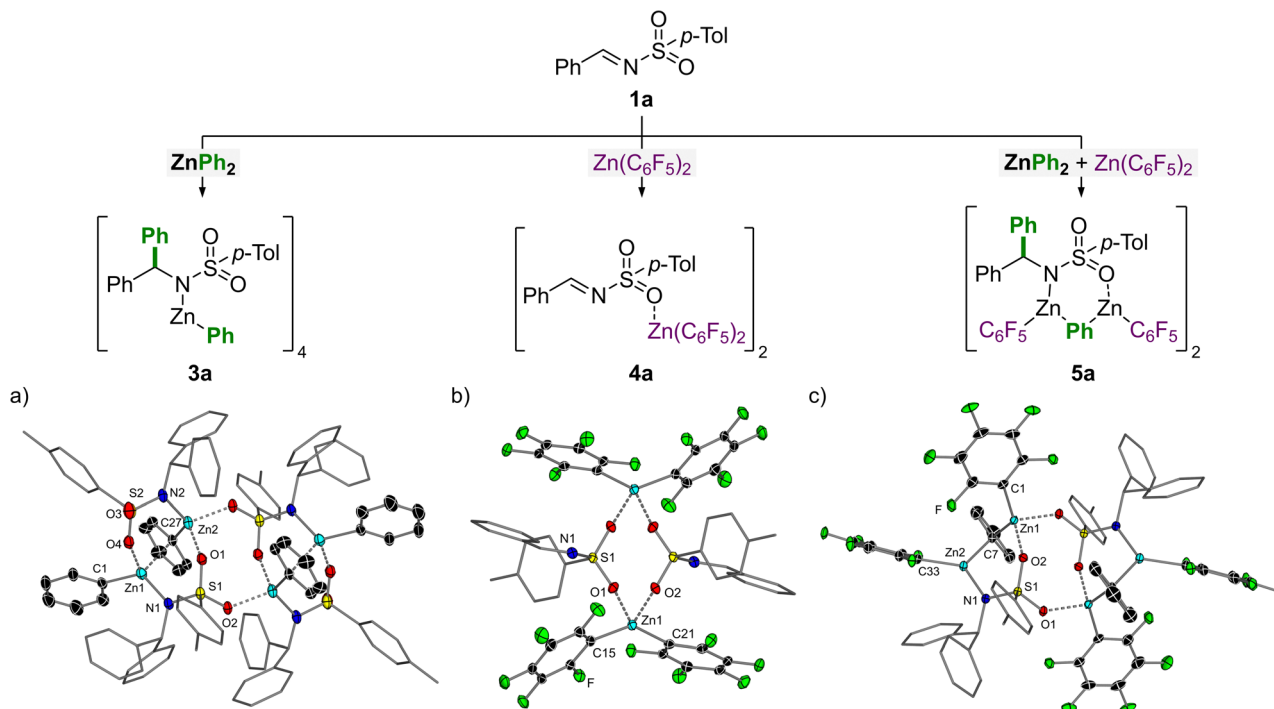


Fig. 1 Stoichiometric reactions of *N*-(tosyl)-benzylideneamine (**1a**) with 1 equivalent of ZnPh_2 and/or $\text{Zn}(\text{C}_6\text{F}_5)_2$ in toluene. (a) Molecular structure of **3a**. Thermal ellipsoids shown at 30% probability. Hydrogen atoms omitted and aryl-substituents not on Zn shown as wireframes for clarity. Selected bond lengths [Å]: Zn1–C1 1.983(3); Zn1···C27 2.364(3); Zn1–N1 2.006(3); O4···Zn1 2.122(2); Zn2–C27 2.003(3); Zn2–N2 1.965(2); O1···Zn2 2.112(2); O2···Zn2 2.033(2). Selected bond angles [°]: C1–Zn1–N1 127.1(1); N2–Zn2–C27 124.4(1). (b) Molecular structure of **4a**. Thermal ellipsoids shown at 30% probability. Hydrogen atoms omitted and aryl-substituents not on Zn shown as wireframes for clarity. Selected bond lengths [Å]: Zn1–C15 1.974(5); Zn1–C21 1.987(5); O1···Zn1 2.200(3); O2···Zn1 2.129(2). Selected bond angles [°]: C15–Zn1–C21 138.8(2). (c) Molecular structure of **5a**. Thermal ellipsoids shown at 30% probability. Hydrogen atoms omitted and aryl-substituents not on Zn shown as wireframes for clarity. Selected bond lengths [Å]: Zn1–C1 1.989(2); Zn1–C7 2.058(2); O1···Zn1 2.055(1); O2···Zn1 2.066(1); Zn2–C7 2.111(2); Zn2–C33 1.983(2); Zn2–N1 1.995(1). Selected bond angles [°]: C1–Zn1–C7 131.41(7); Zn1–C7–Zn2 90.51(6); C7–Zn2–C33 118.22(7); C7–Zn2–N1 115.27(6); N1–Zn2–C33 126.50(6).

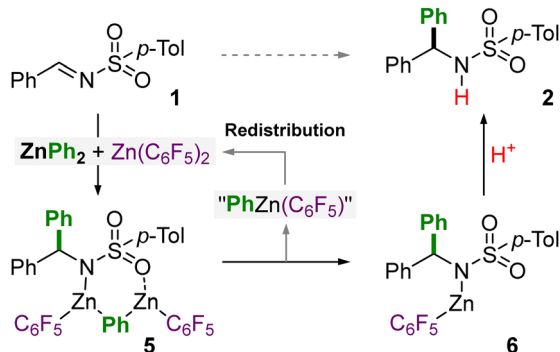
tetramer in the solid-state which oligomerises due to coordination of the sulfonamide oxygens to the Zn centres, forming a central eight-membered $\{\text{ZnOSO}\}_2$ ring. Only one of the phenyl-substituents from ZnPh_2 is transferred to the imine and the remaining phenyl-substituent on Zn occupies either a bridging or terminal position, akin to ZnPh_2 itself which is dimeric in the solid-state in the absence of donors.²⁴ The addition of TMEDA (*N,N,N',N'*-tetramethylethylenediamine) to **3a** leads to deaggregation to give the monomeric and solvated addition product **3a.TMEDA** (see ESI† for the solid-state structure).

The addition of 1 equivalent of $\text{Zn}(\text{C}_6\text{F}_5)_2$ to *N*-(tosyl)-benzylideneamine (**1a**) in toluene affords the corresponding 1:1 Lewis adduct, **4a** (Fig. 1b). Compound **4a** is dimeric in the solid-state and shows coordination of the sulfonamide oxygens to the Lewis acidic Zn centres forming a central eight-membered $\{\text{ZnOSO}\}_2$ ring, akin to **3a**. This coordination serves to increase the electron-withdrawing capacity of the tosyl-substituent which in turn increases the electrophilicity of the imine carbon and thus facilitates nucleophilic addition of the diarylzinc species. Compound **4a** shows comparable structural parameters (O···Zn and $\text{C}_{\text{aryl}}\text{--Zn}$ distances; $\text{C}_{\text{aryl}}\text{--Zn--C}_{\text{aryl}}$ angles) to other reported Lewis adducts such as $(\text{THF})_2\text{Zn}(\text{C}_6\text{F}_5)_2$.²⁵

Finally, the combination of benzylideneamine (**1a**) with 1 equivalent each of ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ affords compound **5a**

in which all three reaction components are incorporated (Fig. 1c). This compound can also be accessed by treating **3a** with $\text{Zn}(\text{C}_6\text{F}_5)_2$, or **4a** with ZnPh_2 . Compound **5a** is dimeric in the solid-state and bears similar structural properties to **3a**. The two unique Zn environments each bear one terminal C_6F_5 -substituent and share a bridging phenyl-substituent. Oligomerisation in the solid-state is again caused by coordination of the sulfonamide oxygens to the Lewis acidic Zn centres to form a central eight-membered $\{\text{ZnOSO}\}_2$ ring, which is a common structural feature in compounds **3a**, **4a** and **5a**.

Based on these stoichiometric studies and our previous work employing ZnAr_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ for nucleophilic substitution reactions with *N,O*-acetals,¹¹ a mechanism for this transformation can be proposed (Scheme 3). The addition of ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ to the *N*-tosylimine substrates affords compound **5** (likely *via* **3a** or **4a**), as shown in Fig. 1. $\text{Zn}(\text{C}_6\text{F}_5)_2$ acts as a strong Lewis acid to activate the imine substrate, as illustrated in compound **4a**, and justifies why non-coordinating solvents (toluene *vs.* THF) are necessary for the transformation. We have previously demonstrated that the addition of $\text{Zn}(\text{C}_6\text{F}_5)_2$ to heteroleptic intermediate RZnPh (where R = OMe for *N,O*-acetals; R = NR_2 for **3a**) results in the formation of $\text{RZn}(\text{C}_6\text{F}_5)$ alongside “ $\text{PhZn}(\text{C}_6\text{F}_5)$ ”.¹¹ The latter species “ $\text{PhZn}(\text{C}_6\text{F}_5)$ ” however dissociates into its favoured homoleptic components



Scheme 3 Proposed mechanism for the atom-efficient nucleophilic addition of ZnPh_2 to N -tosylimines facilitated by $\text{Zn}(\text{C}_6\text{F}_5)_2$.

[e.g. 0.5 equivalents each of ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$] which effectively regenerates the more nucleophilic diarylzinc reagent.^{10,11} In the case of **5a**, the $\text{RZn}(\text{C}_6\text{F}_5)$ and “ $\text{PhZn}(\text{C}_6\text{F}_5)$ ” components are retained together, at least in the solid-state under the conditions employed for crystallisation. In solution however, it is proposed that “ $\text{PhZn}(\text{C}_6\text{F}_5)$ ” dissociates from **5** which gives compound **6** as the ultimate product of the reaction, which affords the corresponding amine **2** upon acidic quench. Multi-nuclear NMR spectroscopy studies show that the dissolution of crystalline **5a** in THF-d_8 affords characteristic signals for both ZnPh_2 and $\text{Zn}(\text{C}_6\text{F}_5)_2$ supporting the dissociation of “ $\text{PhZn}(\text{C}_6\text{F}_5)$ ” and subsequent regeneration of the two homoleptic zinc reagents. The remaining signals observed in the ^1H and ^{19}F NMR spectra are attributed to **5a** and **6**; the latter species can be rationally prepared *in situ* by deprotonative zincation of **2a** with $\text{Zn}(\text{C}_6\text{F}_5)_2$ and further supports the proposed mechanism outlined in Scheme 3 (see ESI† for full spectroscopic details).

$\text{Zn}(\text{C}_6\text{F}_5)_2$ therefore plays two distinct roles in the reaction: (i) it acts as a powerful Lewis acid (see **4a**, Fig. 1) to increase the electrophilicity of the imine and facilitate 1,2-addition of the nucleophilic diarylzinc reagent; and (ii) it enables the effective regeneration of the diarylzinc reagent to allow a limiting 50 mol% to be employed in the reaction. Alternatively, it could be proposed that $\text{Zn}(\text{C}_6\text{F}_5)_2$ simply acts as an innocent Lewis acid to allow RZnPh (e.g. **3a**) to undergo a second nucleophilic addition to N -tosylimine **1**, however this mechanistic proposal was ruled out since this would be expected to be catalytic in $\text{Zn}(\text{C}_6\text{F}_5)_2$ (as well as other Lewis acids) and no evidence to support this pathway could be observed by NMR spectroscopy.

In conclusion, we have demonstrated how Zn/Zn cooperativity can be exploited to facilitate the atom-efficient arylation of N -tosylimines, activating ZnAr_2 reagents towards the transfer of both

of its Ar groups under mild conditions. Mechanistic studies through the isolation and structural characterisation of key intermediates reveals how $\text{Zn}(\text{C}_6\text{F}_5)_2$ acts as a Lewis acid to activate the imine substrate whilst also enabling the regeneration of ZnAr_2 .

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Conflicts of interest

There are no conflicts to declare.

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