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Lithium zincate-enabled divergent one-pot dual C–C bond formation in thiophenes†

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We present a lithium zincate-enabled, divergent one-pot synthesis for regioselective dual C–C bond formation in thiophenes. By modifying the zinc coordination environment, a single set of reagents ($ZnCl_2$, R^1Li, and diethyl (5-halo)thenylphosphate) was found to generate two distinct products. This approach extends the versatility of lithium organozincates to regioselective $C_{Ar}(sp^2)$–$C_{thienyl}(sp^2)$ and $C_{thenyl}(sp^3)$–$C_{Ar}(sp^2)$ couplings without requiring transition metals and/or arenes pre-activated with a boronic acid.

Recent outbreaks of epidemic and pandemic diseases, such as those caused by Ebola, SARS-CoV-2, and the Mpox virus, emphasise the urgency of rapid drug discovery. Each crisis spurs a swift search for treatments, driving efforts to develop new therapies or improve existing ones. In this context, synthetic chemists, alongside biologists, are equally mindful of the importance of efficient methods for accessing diverse molecular libraries.[1] High-throughput screening of structurally related compounds often serves as a starting point for identifying potential treatments,[2] requiring synthetic methods that are both rapid and scalable. Synthetic strategies that quickly produce diverse, yet structurally related molecules are critical in this process. "One-pot synthesis" is particularly advantageous for such demands as it enables multiple bond-forming reactions within a single reaction vessel.[3] This strategy encompasses domino, consecutive, and independent reaction sequences, streamlining processes by eliminating the need to isolate intermediates.[4] Similarly, ligand-enabled metal-promoted divergent synthesis offers flexibility[5] by allowing different products to form from the same starting material by adjusting the ligand environment around the metal. However, these strategies are generally applied independently and have limited integration. A reagent capable of adapting to a wide range of reaction pathways could combine the principles of one-pot and divergent synthesis, offering increased versatility.

We hypothesised that lithium zincate (LiZn) of the PAIRiodic table,[6]—a synergistic complex combining group 1 and group 12 elements—could fulfil this role (Scheme 1a). When $ZnCl_2$ reacts with three equivalents of an organolithium compound (R^1Li), a 16-electron mono-anionic complex, $(R^1)_3ZnLi$, is formed. This complex features a dynamic Li–Zn bond (Scheme 1b), whose strength and adaptivity were recently demonstrated computationally for $Et_3ZnLi{\cdot}2THF$ (Scheme 1c).[7] Lithium triorganozincates demonstrate significant structural flexibility in THF, existing as a network of dynamic equilibria between three distinct forms (Scheme 1d).[7] This flexibility underpins their broad reactivity profile,[8] which includes metallation *via* I/Zn exchange,[9] deprotonation,[10] and homologation through 1,2-ligand migration.[11] Additionally, they participate in 1,2- and 1,4-ligand additions to electrophiles,[12] enabling both ligand-enabled divergent synthesis[13] and sequential carbon–carbon bond formation in one-pot synthesis.[14] In addition to these capabilities, reacting $ZnCl_2$ with four equivalents of R^1Li produces an 18-electron di-anionic complex, $(R^1)_4ZnLi_2$ (Scheme 1b)[15] which is thermodynamically more stable, kinetically more active and provides additional synthetic opportunities such as Br/Zn exchange metallations,[15] cross-coupling reactions,[16] conversions of carboxylic acid to ketones[17] and transition metal catalyst-free conjugate addition to nitroolefins.[18] With these characteristics established, we conceptualised two lithium zincate-mediated pathways as a framework for achieving regioselective functionalisation of thiophene derivatives. Using diethyl (5-halo)thenylphosphate **1** as a model substrate, we sought to explore their feasibility.

In the first pathway (Scheme 1e), treating **1a** (X = I) with two equivalents of lithium triorganozincate $(R^1)_3ZnLi$ (**2**) initiates an I/Zn exchange to produce intermediate **I**. The coexistence of a formally negatively charged Zn centre and a potentially cationic centre at the thenyl position could drive a homologation reaction *via* a 1,2-migration of an R^1 ligand, yielding intermediate **II** with temporary dearomatisation. A formally [1,5] metallotropic rearrangement

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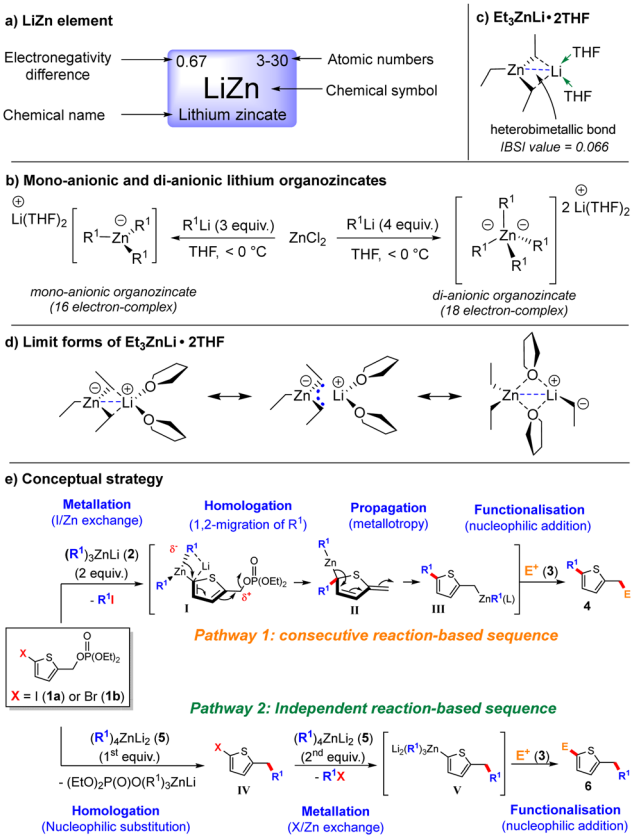


Scheme 1 Development of a lithium-zincate system for divergent bond formation. (a) Conceptual representation of the "LiZn element" as a synergistic assembly. (b) Structures of mono- and di-anionic zincates. (c) Representation of Li–Zn bonding. (d) Structural equilibria in THF. (e) Conceptual strategy.

would then restore aromaticity, producing the homologated thenylzinc intermediate **III**, which would react with an electrophile **3** to yield the final product (**4**).

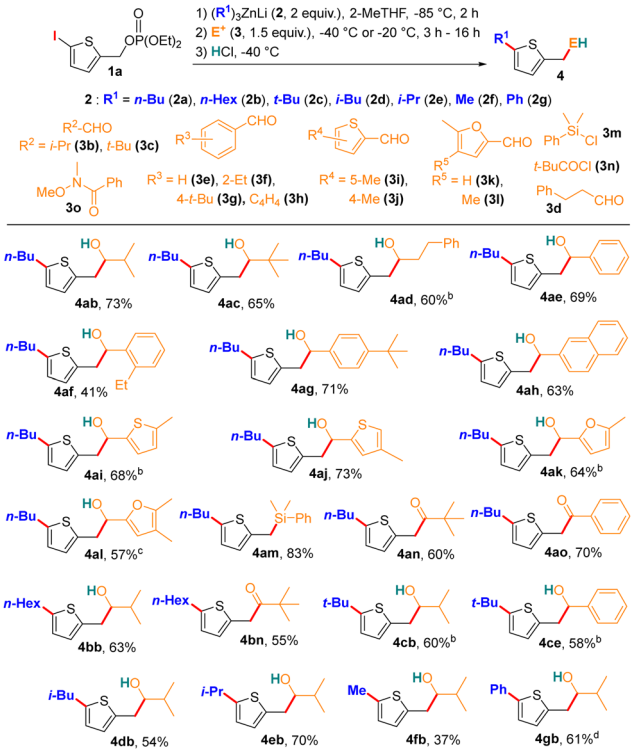
In contrast, the second pathway (Scheme 1e) employs two equivalents of di-anionic tetraorganonzincate (**5**), where homologation proceeds *via* nucleophilic substitution on **1a** or **1b** (X = Br). This generates an isomeric product (**6**) through an X/Zn exchange followed by electrophilic trapping. This pathway emphasises controlled sequential reactivity, requiring homologation to occur faster than metallation to maintain pathway fidelity. Directing each pathway enables access to a diverse array of heterocycles, highlighting the versatility of the lithium zincate-mediated approach. However, several challenges need to be addressed to ensure successful implementation. These include maintaining the stability of the thiophene framework under the polar organometallic conditions required for pathway 1,[19] managing the competition between halogen/metal exchange and nucleophilic substitution that determines entry into either pathway 1 or 2, and achieving selective reactivity of **III** and **V** with electrophile **3** (transfer of the thenyl or thienyl ligand rather than the alkyl R^1 ligand).

To overcome these challenges, we developed a LiZn element-promoted divergent process that regioselectively forms two carbon–carbon bonds five atoms apart in a single reaction vessel. By modifying the Zn coordination environment, we achieved significant structural transformations through the distinct reaction pathways. Given the widespread applications of thiophenes in pharmaceuticals[20] and materials science,[21] this investigation focuses on leveraging diethyl (5-halo)thenyl-phosphate **1** to explore regioselective functionalisation strategies.

As an initial step, we identified optimal conditions to carry out the consecutive reaction sequence in pathway 1 (Scheme 1e). Treating **1a** with $(n\text{-Bu})_3$ZnLi at −85 °C in 2-MeTHF for two hours, followed by the addition of 1 M HCl (**3a**), afforded the desired product **4aa** along with three minor Wurtz-type homocoupling by-products (**7**, **8**, and **9**), in a favourable **4aa**/(7+8+9) ratio of 90/10 (see table in Section 3a, S7 in the ESI† for optimisation details). These results align with prior lithium zincate-assisted functionalisation studies on 4-iodobenzyl derivatives, where 2-MeTHF served as a bio-solvent that promoted sequential steps and minimised Wurtz-type by-products.[22] Notably, using THF instead of 2-MeTHF reversed the product ratio, giving a 20/80 distribution of **4aa** to by-products, underscoring the role of the solvent in selectively driving the transformation sequence. A key difference in this reaction sequence compared to previous reports is the temperature requirement for the 1,2-migration homologation step. With **1a**, the homologation was completed at −85 °C, whereas a warmer environment (−40 °C) was necessary for similar transformations with 4-iodobenzyl mesylate substrates. The synthetic scope of the reaction was next examined under the optimised conditions (Table 1).

Various electrophiles were tested to achieve a second C–C bond formation five atoms away from the homologation site in a single operation. We found that the intermediate **III** (Scheme 1e), formed after the metallotropic rearrangement, was generally less reactive than its counterpart derived from 4-iodobenzyl mesylate.[22] Nevertheless, it reacted readily with secondary aldehyde **3b** at −40 °C over three hours to afford homothenyl alcohol **4ab** in an isolated yield of 73%. Notably, this transformation proceeded with complete selectivity, as no transfer of the butyl ligand to **3b** was observed. Several homothenyl alcohols were synthesised by reacting intermediate **III** with a range of aldehydes, including tertiary (**4ac**), enolisable primary (**4ad**), aromatic (**4ae–4ah**), and heteroaromatic (**4ai–4al**) aldehydes, with isolated yields generally exceeding 60%, except for **4af** (41%). In some cases, warming the reaction mixture from −40 °C to −20 °C after adding the electrophile improved yields. We also observed efficient C–Si bond formation with electrophile **3m**, yielding **4am** in 83% yield. Our approach was further validated for synthesising sterically hindered (**4an**, 60%) and less hindered (**4ao**, 70%) homothenyl carbonyl compounds. Sterically hindered products were selectively synthesised using the corresponding acid chlorides (*e.g.*, **3n** for **4an**), while Weinreb amides proved essential for less hindered compounds, as PhCOCl mainly led to double addition by-products (see Section 3c, S8 for details, ESI†). Beyond $(n\text{-Bu})_3$ZnLi, other lithium trialkylzincates with more nucleophilic (**4bb**, **4bn**) or bulkier ligands (**4cb**, **4ce**, **4db**, **4eb**) were also compatible, demonstrating the versatility of this methodology. Additionally, methyl ligands, traditionally considered less nucleophilic, could participate in the 1,2-migration, as seen with Me_3ZnLi (**2f**), yielding **4fb** in fair yield (37%). This contrasts with earlier findings where only the hybrid zincate Me_2PhZnLi facilitated similar migrations.[22] A major challenge in expanding the substrate scope

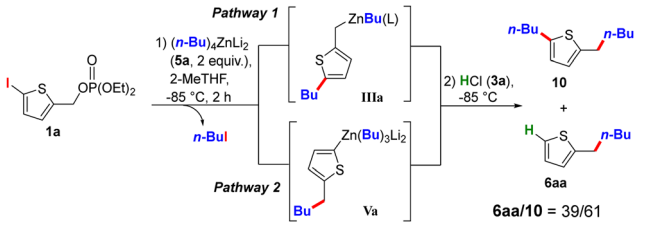
Table 1 Scope of substrates under optimised conditions for pathway 1[a]



[a] Conditions: (1) **1a** (0.6 mmol), **2** (1.2 mmol), 2-MeTHF (10 mL), −85 °C, 2 h; (2) **3** (0.9 mmol), −40 °C, 3 h; (3) HCl 1 M (8 mL), −40 °C; isolated yield. [b] **3** added at −40 °C and mixture stirred at −20 °C for 3 h. [c] **3** added at −40 °C and mixture stirred at −20 °C for 16 h. [d] (1) **1a** (0.6 mmol), **2** (1.2 mmol), 2-MeTHF (10 mL), −85 °C, 30 min; (2) −40 °C, 1 h 30; (3) PhLi (0.6 mmol), −40 °C, 20 min; (4) **3** (0.9 mmol), −40 °C and then −20 °C for 16 h; (5) HCl 1 M (8 mL), −20 °C.

involved achieving C(sp^2)–C(sp^2) bond formation *via* a 1,2-migration of an aryl ligand. Notably, reacting **1a** with Ph_3ZnLi (**2g**) at −85 °C followed by −40 °C produced the intermediate **III**, which gave **4gb** in a 61% yield when activated by one equivalent of PhLi before adding **3b**. Notably, **4gb** exemplifies a rare aryl-heteroaryl coupling *via* 1,2-migration of a Ph ligand without a transition metal[23] and highlights the potential of metallotropic rearrangement to facilitate one-pot remote formation of a second C–C bond.

The next objective was to develop a ligand-enabled divergent pathway relying on two independent reactions in a precise order: homologation *via* nucleophilic substitution of the phosphate by the zinc R^1 ligand, followed by Zn/X exchange metallation. Treating **1a** with 2 equivalents of the di-anionic reagent (n-Bu)$_4$ZnLi$_2$ (**5a**) in 2-MeTHF at −85 °C yielded a mixture of **6aa** and **10** in a 39/61 ratio after hydrolysis (Scheme 2), with pathway 1 favoured. The product **6aa** arises from hydrolysis of **Va** (pathway 2), while **10** results from the reaction of **IIIa** with n-BuI released during the I/Zn exchange (pathway 1). This result indicates that metallation proceeds faster than nucleophilic substitution, a finding further supported by solvent effects: replacing 2-MeTHF with THF reversed the **6aa**/**10** ratio, while using substrate **1b** (X = Br) delayed metallation, providing only **6aa** (see table in Section 3b, S7, for further details, ESI†).

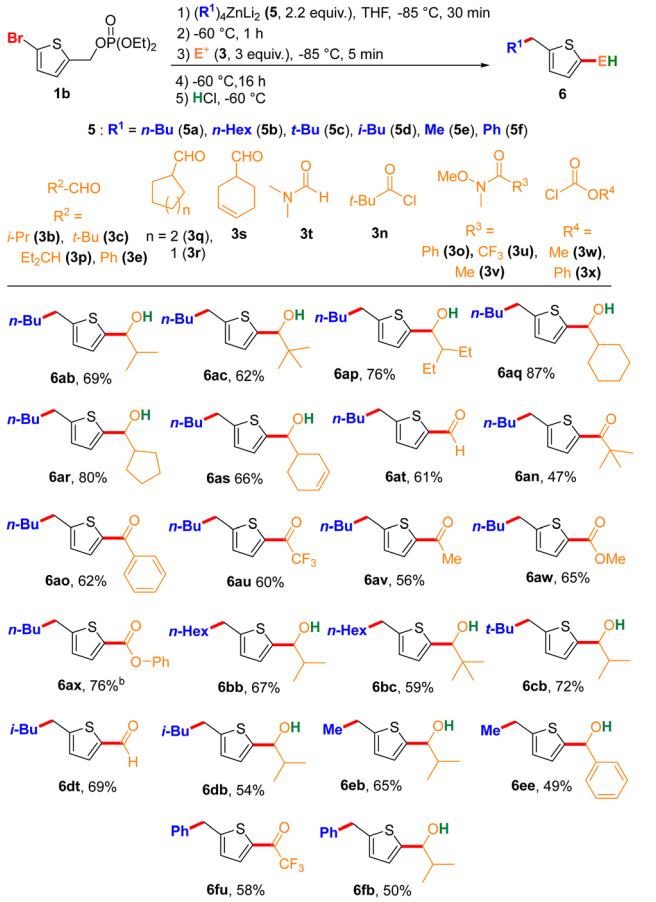


Scheme 2 Preliminary results supporting pathway 2.

Given the limited data on the reactivity of **Va**,[24] we investigated its reactions with aldehydes (Table 2). **Va** reacted successfully with secondary and tertiary aliphatic acyclic aldehydes (**6ab**, **6ac**, **6ap**) and cyclic aliphatic aldehydes (**6aq**, **6ar**, **6as**), yielding thienyl alcohols in 62% to 87%. This approach also enabled the synthesis of thienyl aldehyde **6at** (61%) and several ketones (**6an**, **6ao**, **6au**, **6av**), with Weinreb amides (**3o**, **3u**, **3v**) delivering higher yields than acid chlorides (**3n**). **Va** could also be successfully converted into ester compounds, as shown by the isolation of **6aw** and **6ax** in 65% and 76%, respectively.

Our method's versatility extends to zinc ligands beyond n-Bu. For instance, reagent **5b**, with n-hexyl ligands, yielded

Table 2 Scope of substrates under optimised conditions for pathway 2[a]



[a] Conditions: (1) **1b** (0.6 mmol), **5** (1.32 mmol), THF (10 mL), −85 °C, 30 min; (2) −60 °C, 1 h; (3) **3** (1.8 mmol), −85 °C, 5 min; (4) −60 °C, 16 h; (5) HCl 1 M (10 mL), −60 °C; isolated yields. [b] Product purified by HPLC.

products **6bb** and **6bc** in over 59% yield. Even bulkier ligands, such as those in **5c** (*t*-Bu) and **5d** (i-Bu), proved effective, as shown by products **6cb**, **6dt**, and **6db**, with yields between 54% and 72%. Notably, **5e**, containing less transferable ligands than *n*-Bu, afforded products **6eb** and **6ee** in fair yields (49–53%).

Finally, the presented one-pot strategy also supports $C(sp^3)$–$C(sp^2)$ cross-coupling. This was demonstrated by the synthesis of **6fu** and **6fb**, with yields of 58% and 50%, respectively. To our knowledge, this achievement represents a rare $C(sp^3)$–$C(sp^2)$ cross-coupling in the absence of a boronic acid and/or transition metal catalyst.[25] In total, nine constitutional isomers of the products shown in Table 2 were successfully synthesised, underscoring the broad applicability of this approach.

In summary, we developed a divergent, one-pot synthetic method for regioselective formation of two carbon–carbon bonds five atoms apart, leveraging the reactivity of lithium zincate (LiZn) element. By adjusting zinc's coordination environment, a single set of starting materials ($ZnCl_2$, organolithium R^1Li, and diethyl (5-halo)thenylphosphate) yielded distinct products: pathway 1 forms product **4** *via* a consecutive reaction sequence, while pathway 2 produces its constitutional isomer **6** through independent sequential reactions. This outcome underscores the versatility of lithium organozincates, with pathway 1 adapting our remote functionalisation approach[22] to heterocycles for the first time and pathway 2 representing a new methodology. A critical factor was the solvent choice: bio-solvent 2-MeTHF promoted pathway 1, while THF favoured pathway 2. Across 44 examples, this method enabled heteroaryl-aryl couplings without transition metal and/or boronic acid activation, highlighting its synthetic versatility. Other heterocycles are currently under study, and the role of the bio-solvent is also being examined. The results will be disclosed in due course.

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Data availability

The data supporting this article are included in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 Y. Hayashi, *J. Org. Chem.*, 2021, **86**, 1–23.
2 R. Macarron, M. N. Banks, D. Bojanic, D. J. Burns, D. A. Cirovic, T. Garyantes, D. V. S. Green, R. P. Hertzberg, W. P. Janzen, J. W. Paslay, U. Schopfer and G. S. Sittampalam, *Nat. Rev. Drug Discovery*, 2011, **10**, 188–195.
3 Y. Hayashi, *Acc. Chem. Res.*, 2021, **54**, 1385–1398.
4 N. J. Green and M. S. Sherburn, *Aust. J. Chem.*, 2013, **66**, 267–283.
5 Y. Wang, J. Feng, E.-Q. Li, Z. Jia and T.-P. Loh, *Org. Biomol. Chem.*, 2024, **22**, 37–54.
6 S. D. Robertson, M. Uzelac and R. E. Mulvey, *Chem. Rev.*, 2019, **119**, 8332–8405.
7 A. Pierret, C. Lefebvre, P. C. Gros, C. Denhez and A. Vasseur, *Eur. J. Org. Chem.*, 2023, e202300954.
8 M. Uchiyama and C. Wang, *Top. Organomet. Chem.*, 2014, **47**, 159–202.
9 M. Balkenhohl and P. Knochel, *Chem. – Eur. J.*, 2020, **26**, 3688–3697.
10 (*a*) D. K. Wanic, R. Melvin and G. Barker, *Synthesis*, 2023, 3487–3501; (*b*) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802–3824.
11 I. Marek, *Tetrahedron*, 2002, **58**, 9463–9475.
12 Selected papers on reactivity of zincate reagents with electrophiles: (*a*) S. Cho, E. J. McLaren and Q. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 26332–26336; (*b*) S. Cho and Q. Wang, *Org. Lett.*, 2020, **22**, 1670–1674.
13 (*a*) S. E. Baillie, V. L. Blair, D. C. Blakemore, D. Hay, A. R. Kennedy, D. C. Prydeb and E. Hevia, *Chem. Commun.*, 2012, **48**, 1985–1987; (*b*) T. Imahori, M. Uchiyama, T. Sakamoto and Y. Kondo, *Chem. Commun.*, 2001, 2450–2451.
14 (*a*) T. Harada, T. Katsuhira, A. Osada, K. Iwazaki, K. Maejima and A. Oku, *J. Am. Chem. Soc.*, 1996, **118**, 11377–11390; (*b*) T. Harada, T. Kaneko, T. Fujiwara and A. Oku, *J. Org. Chem.*, 1997, **62**, 8966–8967.
15 M. Uchiyama and Y. Kondo, *J. Synth. Org. Chem., Jpn.*, 2006, **64**, 1180–1190.
16 C. Wang, T. Ozaki, R. Takita and M. Uchiyama, *Chem. – Eur. J.*, 2012, **18**, 3482–3485.
17 R. Murata, K. Hirano and M. Uchiyama, *Chem. – Asian J.*, 2015, **10**, 1286–1290.
18 (*a*) M. Dell'Aera, F. M. Perna, P. Vitale, A. Altomare, E. Hevia and V. Capriati, *Eur. J. Inorg. Chem.*, 2024, e202400505; (*b*) M. Dell'Aera, F. M. Perna, P. Vitale, A. Altomare, A. Palmieri, L. C. H. Maddock, L. J. Bole, A. R. Kennedy, E. Hevia and V. Capriati, *Chem. – Eur. J.*, 2020, **26**, 8742–8748.
19 Dearomatisation/rearomatisation processes involving thenyl substrates are reported only under Pd-catalysed conditions, see: S. Zhang, X. Yu, X. Feng, Y. Yamamoto and M. Bao, *Chem. Commun.*, 2015, **51**, 3842–3845.
20 (*a*) R. M. D. da Cruz, F. J. B. Mendonça-Junior, N. B. de Mélo, L. Scotti, R. S. A. de Araújo, R. N. de Almeida and R. O. de Moura, *Pharmaceuticals*, 2021, **14**, 692; (*b*) Archna, S. Pathania and P. A. Chawla, *Bioorg. Chem.*, 2020, **101**, 104026.
21 L. Li, J. Li, L. Guo, Y. Xu, Y. Bi, Y. Pu, P. Zheng, X.-K. Chen, Y. Wang and C. Li, *Chem. Sci.*, 2024, **15**, 11435–11443.
22 A. Pierret, C. Denhez, P. C. Gros and A. Vasseur, *Adv. Synth. Catal.*, 2022, **364**, 3805–3816.
23 Two other examples without transition metal: (*a*) H. J. Jeong, S. Chae, K. Jeong and S. K. Namgoong, *Eur. J. Org. Chem.*, 2018, 6343–6349; (*b*) A. Hernán-Gómez, E. Herd, M. Uzelac, T. Cadenbach, A. R. Kennedy, I. Borilovic, G. Aromı and E. Hevia, *Organometallics*, 2015, **34**, 2614–2623.
24 In contrast, the hybrid zincate $Bu_3PhZnLi_2$ is well known for reacting non-selectively with aldehydes, favouring the 1,2-addition of the butyl ligand to the electrophile over the aryl ligand, see: Y. Kondo, M. Fujinami, M. Uchiyama and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1997, 799–800.
25 For rare examples of cross coupling involving arylboronic acids or arylboronic acid pinacol esters in the absence of transition metal, see: (*a*) J. Procter, J. J. Dunsford, P. J. Rushworth, D. G. Hulcoop, R. A. Layfield and M. J. Ingleson, *Chem. – Eur. J.*, 2017, **23**, 15889–15893; (*b*) R. B. Bedford, N. J. Gower, M. F. Haddow, J. N. Harvey, J. Nunn, R. A. Okopie and R. F. Sankey, *Angew. Chem., Int. Ed.*, 2012, **51**, 5435–5438. For examples in the presence of a transition metal, see: (*c*) K. A. C. Bastick and A. J. B. Watson, *Synlett*, 2023, 2097–2102; (*d*) F. Trauner, B. Boutet, F. Rambaud, V. N. Ngo and D. Didier, *ChemRxiv*, 2024, preprint, DOI: **10.26434/chemrxiv-2024-52hq3**.