Lithium Zincate-Enabled Divergent Synthesis: Regioselective One-Pot Formation of Heteroaryl Compounds

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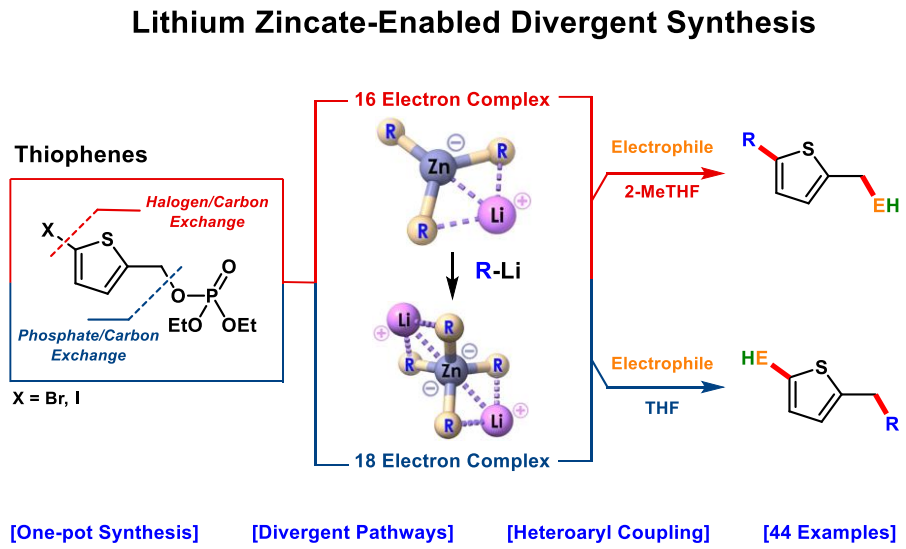
GRAPHICAL ABSTRACT



ABSTRACT

We present a lithium zincate-enabled, divergent one-pot synthesis for regioselective C–C bond formation in heteroaryl compounds. By modifying the zinc coordination environment, a single set of reagents ($ZnCl_2$, organolithium R^1Li, and diethyl (5-halo)thenylphosphate) was found to generate two distinct products through either a consecutive reaction sequence or two-independent intermolecular steps. 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 moeity. With a broad substrate scope and reliance on zinc and lithium—abundant, non-toxic metals—this approach offers a sustainable route to complex molecules with relevance for pharmaceuticals and materials science.

KEYWORDS

Lithium zincate; One-pot synthesis; Divergent pathways; Heteroaryl coupling; PAIRiodic table

INTRODUCTION

Recent outbreaks of epidemic and pandemic diseases, such as those caused by Ebola, SARS-CoV-2, and the Mpox virus, emphasize 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.

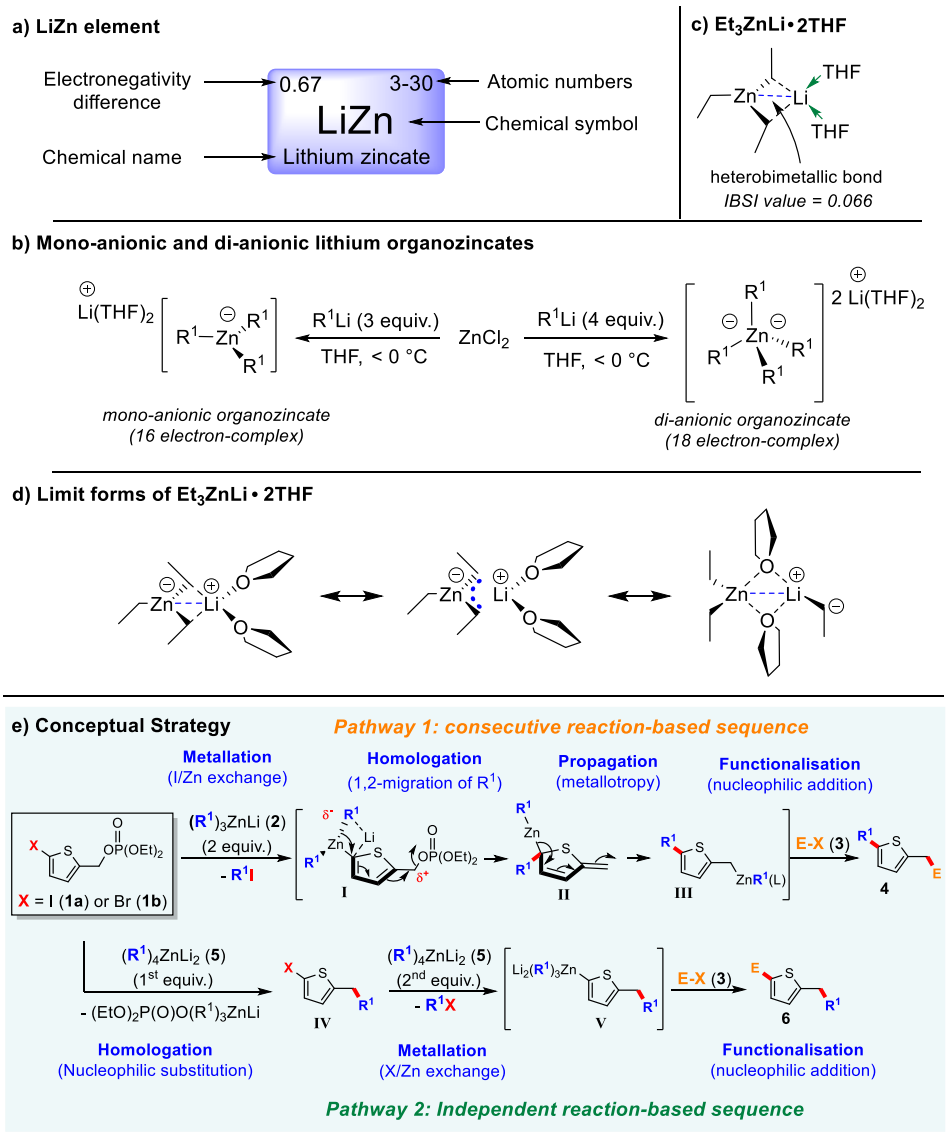
Synthetic strategies that quickly produce diverse, yet structurally related molecules are critical in this process. "One-pot synthesis" is particularly advantageous for such demands, as it enables multiple bond-forming reactions within a single reaction vessel.[3] This strategy encompasses domino, consecutive, 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 hypothesized that lithium zincate (LiZn) of the PAIRiodic table,[6] —a synergistic complex combining group 1 and group 12 elements—could fulfill 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 conceptualized two lithium zincate-mediated pathways as a framework for achieving regioselective functionalization 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, *Pathway 1*), 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 center and a potentially cationic center at the thenyl position could drive a homologation reaction *via* a 1,2-migration of an R^1 ligand, yielding intermediate **II** with temporary dearomatization. A formally [1,5] metallotropic rearrangement 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, *Pathway 2*) 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 emphasizes controlled sequential reactivity, requiring homologation to occur faster than metallation to maintain pathway fidelity.



Scheme 1: LiZn element and related synthetic strategy.

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 intermediates **III** and **V** with electrophile **3** (transfer of the thenyl or thienyl ligand rather than the alkyl ligand R^1).

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)thenylphosphate **1** to explore regioselective functionalization strategies.

RESULTS AND DISCUSSIONS

As an initial step, we identified optimal conditions to carry out the consecutive reaction sequence in *Pathway 1* (Scheme 2). Treating **1a** with $(n\text{-Bu})_3\text{ZnLi}$ 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 byproducts (**7**, **8**, and **9**), in a favorable **4aa**/(**7**+**8**+**9**) ratio of 90/10 (see Table in Section 3a, S7 in the Supporting Information (SI) for optimization details).

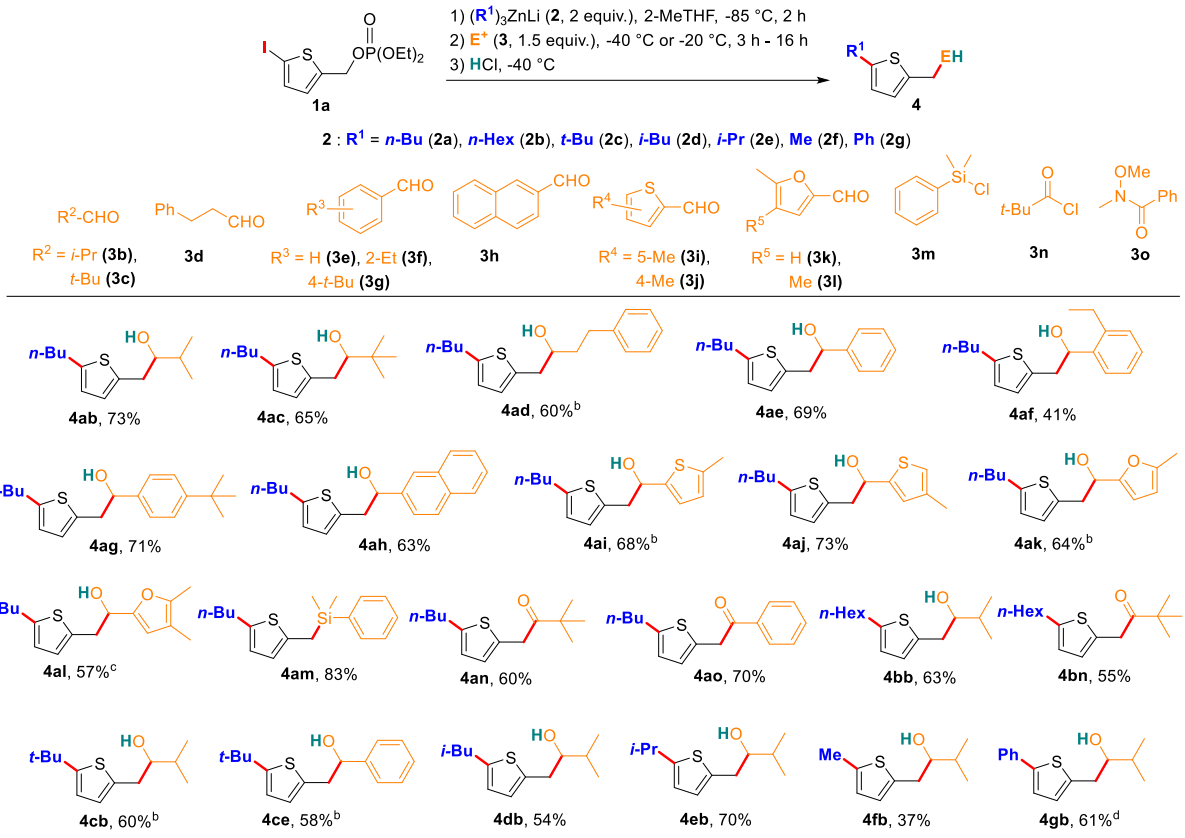
These results align with prior lithium zincate-assisted functionalization studies on 4-iodobenzyl derivatives, where 2-MeTHF served as a bio-solvent that promoted sequential steps and minimized Wurtz-type byproducts.[22] Notably, using THF instead of 2-MeTHF reversed the product ratio, giving a 20/80 distribution of **4aa** to byproducts, 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 optimized conditions (Scheme 2). 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 synthesized by reacting intermediate **III** with a range of aldehydes, including tertiary (**4ac**), enolizable primary (**4ad**), aromatic (**4ae–4ah**), and heteroaromatic (**4ai–4ak**) 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.



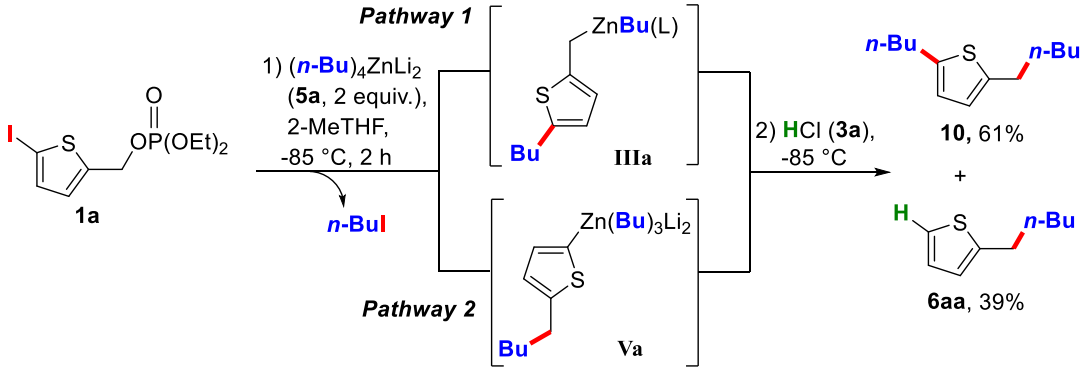
Scheme 2: Scope of substrates under optimized conditions for Pathway 1. [a]Conditions: 1) **1a** (0.6 mmol), **2** (1.2 mmol), 2-MeTHF (10 mL), -85 °C, 2 h; 2) **3** (0.9 mmol), -40 °C, 3 h; 3) HCl 1M (8 mL), -40 °C; isolated yield. [b]**3** added at -40 °C and mixture stirred at -20 °C for 3 h. [c]**3** 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, 1h30; 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 1M (8 mL), -20 °C.

Our approach was further validated for synthesizing sterically hindered (**4an**, 60%) and less hindered (**4ao**, 70%) homothenyl carbonyl compounds. Sterically hindered products were selectively synthesized 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 byproducts (see section 3c, S8 for details).

Beyond $(n\text{-Bu})_3ZnLi$, 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 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 $(n\text{-Bu})_4ZnLi_2$ (**5a**) in 2-MeTHF at -85 °C yielded a mixture of **6aa** and **10** in a 39/61 ratio after hydrolysis (Scheme 3), with *Pathway 1* favored. 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).



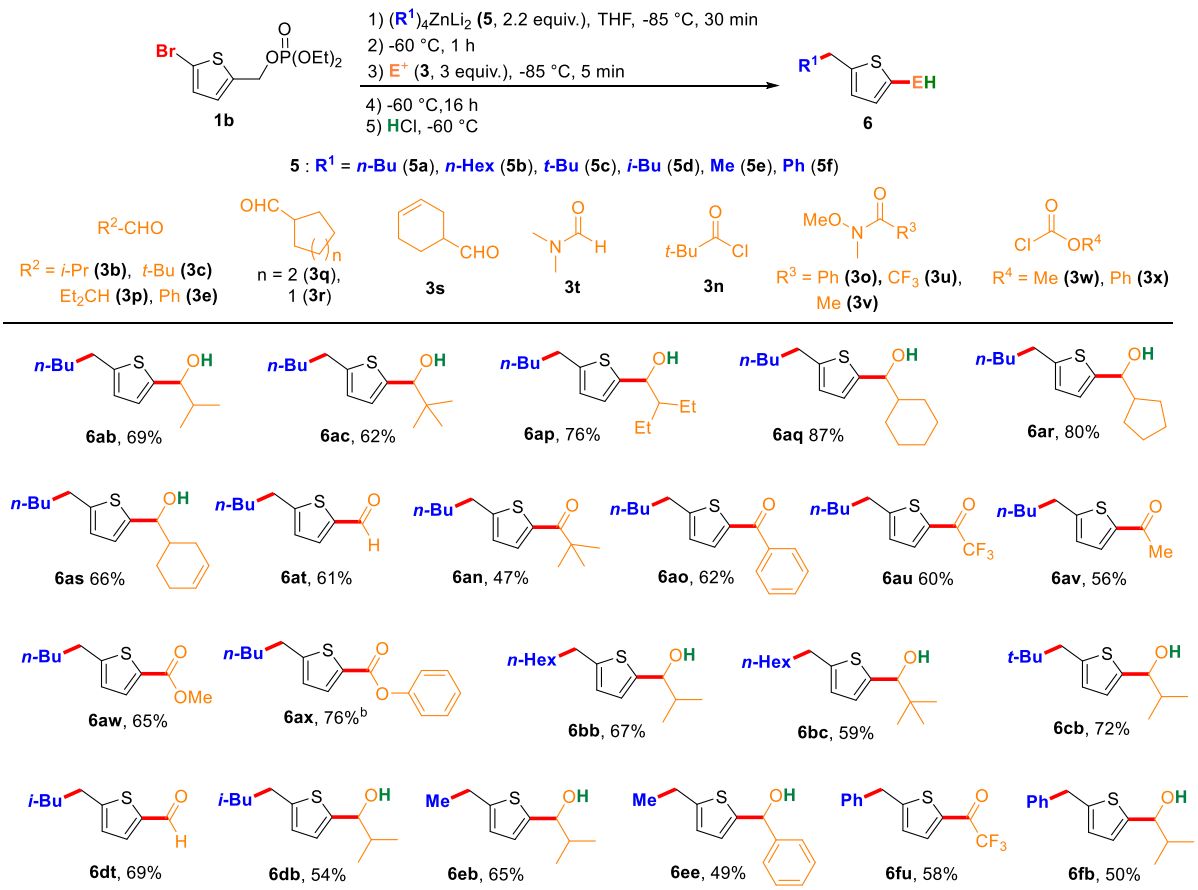
Scheme 3: Preliminary results supporting *pathway 2*.

Given the limited data on the reactivity of **Va**,[24] we investigated its reactions with aldehydes (Scheme 4). **Va** reacted successfully with secondary and tertiary aliphatic acyclic aldehydes (**6ab**, **6ac**, **6ap**) and cyclic aliphatic aldehydes (**6aq**, **6ar**, **6as**), yielding thienyl alcohols in 61% 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 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**, **6dp**, 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 an unprecedented C(sp^3)-C(sp^2) cross-coupling in the absence of a boronic acid[25] and/or transition metal catalyst.[26] In total, nine constitutional isomers of the products shown in Scheme 2 were successfully synthesized, underscoring the broad applicability of this approach.



Scheme 4: Scope of substrates under optimized conditions for Pathway 2 **.** [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 1M (10 mL), -60 °C; Isolated yields. [b]Product purified by HPLC.

CONCLUSION

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 functionalization approach[22] to heterocycles and *Pathway 2* representing a new methodology.

A critical factor was solvent choice: bio-solvent 2-MeTHF promoted *Pathway 1*, while THF favored *Pathway 2*. Across 44 examples, this method enabled heteroaryl-aryl couplings without transition metal and/or boronic acid activation, highlighting its synthetic versatility. Further exploration could expand this approach to other heterocycles or polyfunctional substrates, and mechanistic studies on solvent effects may improve control over selectivity. Additionally, asymmetric or catalytic applications of lithium organozincates could enhance the sustainability and utility of this approach for complex molecule synthesis in pharmaceutical and materials science.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study (*e.g.*, general considerations, experimental methods, synthetic details, copies of NMR spectra) are available in the Supporting Information of this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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, G. S. Sittampalam, *Nat. Rev. Drug Discovery* **2011**, *10*, 188–195.

[3] Yujiro Hayashi, *Acc. Chem. Res.* **2021**, *54*, 1385−1398.

[4] N. J. Green, M. S. Sherburn, *Aust. J. Chem.* **2013**, *66*, 267–283.

[5] Y. Wang, J. Feng, E.-Q. Li, Z. Jia, T.-P. Loh, *Org. Biomol. Chem.* **2024**, *22*, 37–54.

[6] S. D. Robertson, M. Uzelac, R. E. Mulvey, *Chem. Rev.* **2019**, *119*, 8332−8405.

[7] A. Pierret, C. Lefebvre, P. C. Gros, C. Denhez, A. Vasseur, *Eur. J. Org. Chem.* **2023**, *26*, e202300954.

[8] a) K. Hirano and M. Uchiyama, in *Polar Organometallic Reagents* (Eds.: A. E. H. Wheatley, M. Uchiyama), John Wiley and Sons, New York, **2022**, pp. 337–364; b) M. Uchiyama, C. Wang, *Top. Organomet. Chem.* **2014**, *47*, 159–202.

[9] M. Balkenhohl, P. Knochel, *Chem. Eur. J.* **2020**, *26*, 3688–3697.

[10] a) D. K. Wanic, Rebecca Melvin, G. Barker, *Synthesis* **2023**, *55*, 3487–3501; b) R. E. Mulvey, F. Mongin, M. Uchiyama, Y. Kondo, *Angew. Chem. Int. Ed.*, **2007**, *46*, 3802–3824; *Angew. Chem.* 2007, *119*, 3876–3899.

[11] I. Marek, *Tetrahedron* **2002**, *58*, 9463–9475.

[12] Selected papers on reactivity of zincate reagents with electrophiles: a) S. Cho, E. J. McLaren, Q. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 26332–26336; *Angew. Chem.* **2021**, *133*, 26536–26540; b) S. Cho, Q. Wang, *Org. Lett.* **2020**, *22*, 1670–1674; c) K. Shibata, M. Kimura, K. Kojima, S. Tanaka, Y. Tamaru, *J. Organomet. Chem.* **2001**, *624*, 348–353.

[13] a) S. E. Baillie, V. L. Blair, D. C. Blakemore, D. Hay, A. R. Kennedy, D. C. Prydeb, E. Hevia, *Chem. Commun.* **2012**, *48*, 1985–1987; b) T. Imahori, M. Uchiyama, T. Sakamoto, Y. Kondo, *Chem. Commun.* **2001**, 2450–2451.

[14] a) T. Harada, T. Katsuhira, A. Osada, K. Iwazaki, K. Maejima, A. Oku, *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390; b) T. Harada, T. Kaneko, T. Fujiwara, A. Oku, *J. Org. Chem.* **1997**, *62*, 8966–8967.

[15] a) M. Uchiyama, Y. Kondo, *J. Synth. Org. Chem., Jpn.* **2006**, *64*, 1180–1190; b) M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, T. Sakamoto, *J. Am. Chem. Soc.* **1998**, *120*, 4934–4946.

[16] C. Wang, T. Ozaki, R. Takita, M. Uchiyama, *Chem. Eur. J.* **2012**, *18*, 3482–3485.

[17] R. Murata, K. Hirano, M. Uchiyama, *Chem. Asian J.* **2015**, *10*, 1286–1290.

[18] a) M. Dell'Aera, F. M. Perna, P. Vitale, A. Altomare, E. Hevia, 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, V. Capriati, *Chem. Eur. J.* **2020**, *26*, 8742–8748.

[19] Dearomatization / rearomatization processes involving thenyl substrates have already been reported, but only under palladium-catalyzed conditions, see: S. Zhang, X. Yu, X. Feng, Y. Yamamoto, Ming 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, R. O. de Moura, *Pharmaceuticals* **2021**, *14*, 692; b) Archna, S. Pathania, P. A. Chawla, *Bioorg. Chem.* **2020**, *101*, 104026; (*c*) D. Gramec, L. P. Mašič, M. S. Dolenc, *Chem. Res. Toxicol.* **2014**, *27*, 1344−1358.

[21] Selected recent studies: a) L. Li, J. Li, L. Guo, Y. Xu, Y. Bi, Y. Pu, P. Zheng, X.-K. Chen, Y. Wang, C. Li, *Chem. Sci.* **2024**, *15*, 11435–11443; b) X. Yuan, K. Yang, C. Grazon, C. Wang, L. Vallan, J.-D. Isasa, P. M. Resende, F. Li, C. Brochon, H. Remita, G. Hadziioannou, E. Cloutet, J. Li, *Angew. Chem. Int. Ed.* **2024**, *63*, e202315333; *Angew. Chem.* **2024**, *136*, e202315333; c) X. Han, Y. Zhang, Y. Dong, J. Zhao, S. Ming, J. Zhang, *RSC Adv.* **2022**, *12*, 708–718; d) C. Yang, S. Zhang and J. Hou, *Aggregate* **2022**, *3*, e111.

[22] A. Pierret, C. Denhez, P. C. Gros, A. Vasseur, *Adv. Synth. Catal.* **2022**, *364*, 3805–3816.

[23] Two other examples without transition metal: a) H. J. Jeong, S. Chae, K. Jeong, S. K. Namgoong, *Eur. J. Org. Chem.* **2018**, *2018*, 6343–6349; b) A. Hernán-Gómez, E. Herd, M. Uzelac, T. Cadenbach, A. R. Kennedy, I. Borilovic, G. Aromí, E. Hevia, *Organometallics* **2015**, *34*, 2614–2623; Selected examples with transition metal: c) F. Trauner, B. Boutet, F. Rambaud, V. N. Ngo, D. Didier, *ChemRxiv preprint* **2024**, DOI: 10.26434/chemrxiv-2024-52hq3; d) S. Sase, M. Jaric, A. Metzger, V. Malakhov, P. Knochel, *J. Org. Chem.* **2008**, *73*, 7380–7382.

[24] In contrast, the hybrid zincate $Bu_3PhZnLi_2$ is well known for reacting non-selectively with aldehydes, favoring the 1,2-addition of the butyl ligand to the electrophile over the aryl ligand, see: Y. Kondo, M. Fujinami, M. Uchiyama, 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, 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, R. F. Sankey, *Angew. Chem. Int. Ed.* **2012**, *51*, 5435–5438; *Angew. Chem.* **2012**, *124*, 5531–5534.

[26] For cross coupling involving arylboronic acids in the presence of a transition metal, see: K. A. C. Bastick, A. J. B. Watson, *Synlett* **2023**, *34*, 2097–2102.