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(Citation)

Chemistry-A European Journal, 27(40):10267-10273

(Issue Date)

2021-07-16

(Resource Type)

journal article

(Version)

Accepted Manuscript

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“Snapshot” Trapping of Multiple Transient Azolylithiums in Batch

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Supporting information for this article is given via a link at the end of the document.

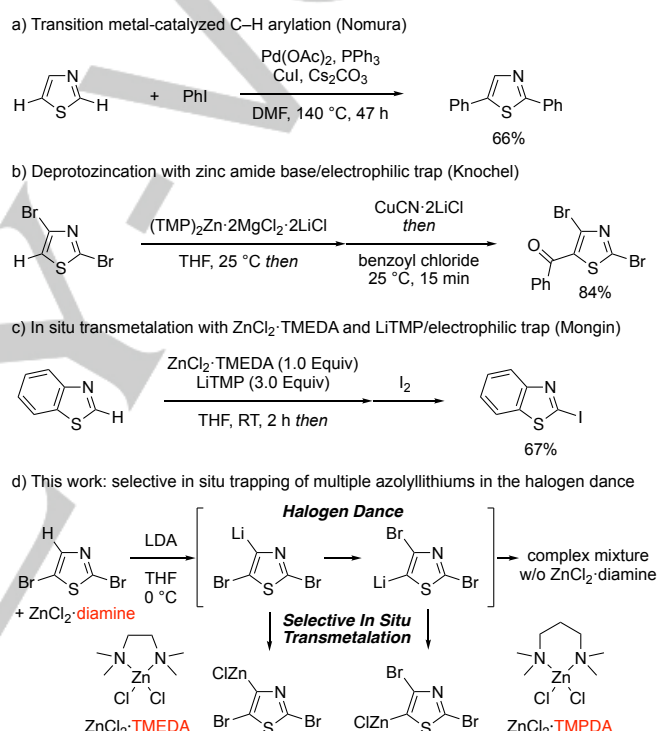
Abstract: Recent developments in flow microreactor technology have allowed the use of transient organolithium compounds that cannot be realized in a batch reactor. However, trapping of the transient aryllithiums in a “halogen dance” is still challenging. We report trapping of such short-lived azolylithiums in a batch reactor by developing a finely tuned *in situ* zincation using zinc halide diamine complexes, whose reaction rate is controlled by the appropriate choice of the diamine ligand. The reaction is operationally simple and can be performed at 0 °C with high reproducibility on a multi-gram scale. This method was applicable to a wide range of brominated azoles allowing for deprotonative functionalization, which was used for the concise divergent syntheses of both constitutional isomers of biologically active azoles.

Introduction

Multiply substituted azoles are one of the most common structural motifs in pharmaceuticals, agrochemicals, and functional organic materials.^[1] Their physical properties depend on the functional groups and their substitution patterns.^[2] Regioselective functionalization of an azole ring is still required^[3] as a complementary method to the established cyclization strategy.^[4] Azoles are categorized as electron-deficient aromatic rings; however, the azole nitrogen acts as a base, which limits the range of functional groups able to be installed by electrophilic aromatic substitution.^[5] Recently developed flow chemistry can generate organolithium species by halogen–lithium exchange rather than deprotonation,^[6] which requires the corresponding halogenated arene as the substrate.

In this context, a transition metal-catalyzed C–H arylation of thiazole has been developed (Scheme 1a).^[7,8] Halogen atoms such as a bromo group can be easily introduced onto azoles, and then converted through a halogen–metal exchange, cross coupling reaction, and S_NAr reaction. Knochel reported deprotonation of the dibromothiazole with a zinc amide base with the bromo groups intact (Scheme 1b).^[9,10] The generated organozinc species was used for benzoylation with copper cyanide. Instead of using the zinc amide base, *in situ* transmetalation of benzothiazole was achieved with a combination of LiTMP (lithium 2,2,6,6-tetramethylpiperidide) and ZnCl₂·TMEDA by Mongin and co-workers (Scheme 1c).^[11] Subsequent iodination provided 2-iodobenzothiazole.

Recently, our laboratory reported the functionalization of bromothiophenes, bromofurans, and bromopyrroles via a base-

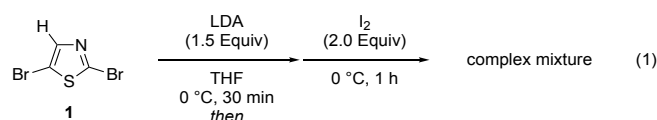


Scheme 1. Synthetic methods for functionalized azoles.

promoted halogen dance.^[12] This reaction has been used for synthesizing multiply brominated heteroaromatic compounds; however, several azoles have been reported to deteriorate by ring opening reaction after deprotonation.^[13] Furthermore, only the thermodynamically most stable organolithiums can be used in the halogen dance.^[14,15] Herein, we present the first examples of selective *in situ* trapping of transient thiazolylithiums in a halogen dance, which led to a complex mixture at 0 °C in the absence of a zinc chloride diamine complex (Scheme 1d). This method provides each constitutional isomer simply by changing the diamine ligand and can be applied to other brominated azoles.

Results and Discussion

First, we began with the deprotonation of 2,5-dibromothiazole (**1**) with LDA (lithium diisopropylamide) to obtain a fully substituted thiazole. Treatment of 2,5-dibromothiazole with LDA at 0 °C and subsequent addition of iodine provided a complex mixture without any iodinated thiazoles (Eq 1). This result implies that the thiazolylithium intermediate decomposes at 0 °C.



We then explored a suitable ZnX_2 -diamine to prevent the decomposition of the transient thiazolylithium by in situ zincation. The efficacy of the ZnX_2 -diamine was evaluated by subsequent iodination (Table 1). Following the report by Knochel,^[16] a mixture of 2,5-dibromothiazole (**1**) and ZnCl_2 in THF was treated with LDA and iodine to afford a mixture of 4-iodothiazole **2a** and 5-iodothiazole **2b** in 13% and 57% yields, respectively (entry 1). Because this mixture proved very difficult to separate by column chromatography, the yields were determined by a quantitative ^{13}C NMR spectroscopy.^[17] Structures of both products **2a** and **2b** were identified by X-ray crystallography using the pure compounds that were obtained under the optimal conditions described later.^[18] We next examined a variety of zinc halide diamine complexes (Figure 1).^[19] The use of ZnCl_2 -TMEDA^[20] resulted in the exclusive formation of **2a** in 89% isolated yield (entry 2). This result indicates transmetalation is slower with ZnCl_2 , compared to ZnCl_2 -TMEDA. In contrast, ZnBr_2 -TMEDA and ZnI_2 -TMEDA provided **2b** as the major product (entries 3 and 4).

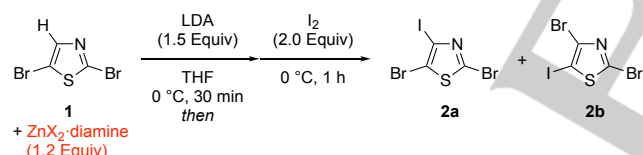


Table 1. Effects of ZnX_2 -diamine complexes on the in situ zincation of thiazolylithiums^[a]

| Entry | ZnX_2 -diamine | 2a [%] ^[b] | 2b [%] ^[b] |
|-------------------|--------------------------|--|--|
| 1 ^[c] | ZnCl_2 | 13 | 57 |
| 2 | ZnCl_2 -TMEDA | 89 ^[d] (91 ^[d,f]) | — ^[e] |
| 3 | ZnBr_2 -TMEDA | 23 | 61 |
| 4 ^[g] | ZnI_2 -TMEDA | 4 | 65 |
| 5 | ZnCl_2 -TMEDA | 44 | 30 |
| 6 | ZnCl_2 -TEEDA | 13 | 54 |
| 7 | ZnCl_2 -BuMeEDA | 12 | 71 |
| 8 | ZnCl_2 -TMPDA | — ^[e] | 72 ^[d] (87 ^[d,h]) |
| 9 | ZnCl_2 -DMP | 16 | 69 |
| 10 | ZnBr_2 -TMPDA | — ^[e] | 39 |
| 11 ^[g] | ZnI_2 -TMPDA | 5 | 78 |

[a] Reaction conditions: 2,5-dibromothiazole (**1**) (1.0 equiv, 0.30 mmol), ZnX_2 -diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then I_2 (2.0 equiv, 0.60 mmol), 0 °C, 1 h. [b] The yield was determined by a quantitative ^{13}C NMR technique. [c] Recovery of 3% of **1**. [d] Isolated yield. [e] Not observed in the ^{13}C NMR spectrum of the crude product. [f] The reaction was performed using 10 mmol of 2,5-dibromothiazole (**1**). [g] The products involved a minute amount (<10%) of an inseparable

byproduct. [h] The reaction was performed using 7.5 mmol of 2,5-dibromothiazole (**1**).

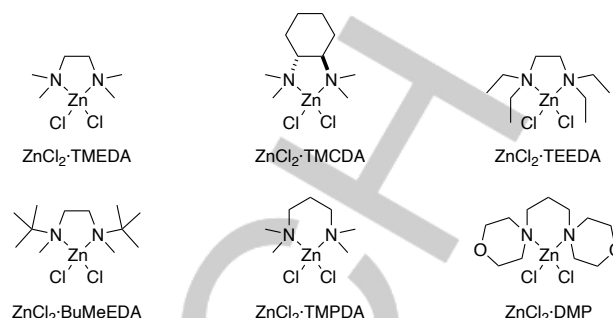
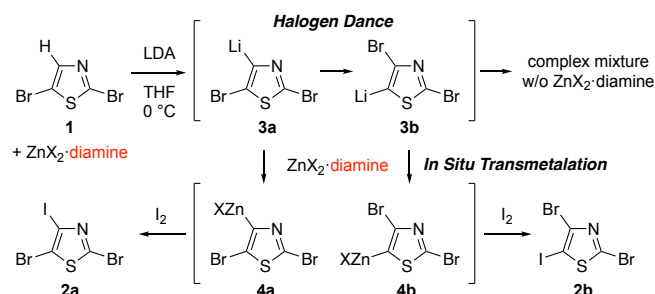


Figure 1. Structures of zinc halide diamine complexes.

These results indicate that the rate of transmetalation with ZnCl_2 -TMEDA was much faster than that with ZnBr_2 -TMEDA or ZnI_2 -TMEDA. We next investigated a suitable diamine ligand for the selective formation of **2b**. ZnCl_2 -TMCDA bearing *trans*-1,2-bis(dimethylamino)cyclohexane provided **2a** and **2b** in 44% and 30% yields, respectively (entry 5). ZnCl_2 -TEEDA, with four ethyl groups on the two nitrogen atoms, provided a better product ratio (entry 6), which suggests that the larger alkyl group reduced the rate of the transmetalation. ZnCl_2 -BuMeEDA, with a sterically more demanding ethylene diamine group, improved the yield of **2b**, albeit with 12% of the undesired isomer **2a** (entry 7). After intensive optimization, the newly prepared ZnCl_2 -TMPDA, where the dimethylamino groups are tethered with a propylene unit, proved effective for the exclusive formation of 5-iodothiazole **2b** in 72% yield (entry 8). When both dimethylamino groups were replaced with the morpholino groups, the undesired isomer **2a** was observed (entry 9). ZnBr_2 -TMPDA was also effective for the selective preparation of **2b**, albeit in lower yield than that with ZnCl_2 -TMPDA (entry 10). ZnI_2 -TMPDA provided a comparable yield of **2b**; however, isomer **2a** (5%) and another inseparable byproduct (<10%) were also observed (entry 11). The optimal conditions were robust and were performed on a gram scale to provide compounds **2a** or **2b** exclusively.

These results indicate that the rate of the in situ transmetalation can be controlled by choosing an appropriate diamine ligand (Scheme 2). The initially generated thiazolylithium **3a** was selectively trapped with ZnCl_2 -TMEDA to yield the corresponding organozinc reagent **4a**, which was treated with iodine to give thiazolyl iodide **2a**. On the basis of the experimental results, bulkier substituents on the nitrogen or homologation of the alkyl tether between the two nitrogen atoms led to a slower transmetalation rate. Transmetalation with ZnCl_2 -TMPDA was sufficiently sluggish to trap thiazolylithium **3b** which was generated after a halogen dance, leading to the formation of organozinc reagent **4b**. Although, the different relative reaction rates of the halogen dance and in situ transmetalation is a plausible explanation for the observed outcomes of the reaction, some uncertainty remains. Thus, relative transmetalation rates of thiazolylithiums **3a** and **3b** should be considered, if both thiazolylithiums **3a** and **3b** exist. This result does not exclude the possibility that transmetalation of **3b** with ZnCl_2 -TMPDA is faster than that of **3a**; however, this complex can selectively trap the azolylithiums after the halogen

dance, which is described later. This means that a zinc halide diamine complex with a slower transmetalation rate is preferred to trap the thiazolylithium **3b**. Preformed $i\text{-Pr}_2\text{NZnCl}\cdot\text{TMEDA}$ from LDA and $\text{ZnCl}_2\cdot\text{TMEDA}$ led to the formation of trace amount (<10%) of thiazoles **2a** and **2b** with 59% recovery of **1**. Similarly, preformed $i\text{-Pr}_2\text{NZnCl}\cdot\text{TMPDA}$ from LDA and $\text{ZnCl}_2\cdot\text{TMPDA}$ did not provide thiazoles **2a** and **2b** with 62% recovery of **1**. These control experiments exclude the possibility that thiazolylzinc species **4a** undergoes the halogen dance to afford **4b**.



Scheme 2. Rationale for the selective trapping of transient thiazolylithiums.

The findings from the reaction of dibromothiazole **1** were also applicable for trapping the three resulting imidazolylithiums from the halogen dance of metalated dibromoimidazole **5** (Table 2). The structures of the products were identified by X-ray crystallography.^[21] The initially generated organolithium intermediate was selectively trapped by $\text{ZnCl}_2\cdot\text{TMEDA}$ at 0 °C to provide **6a** after iodination, whereas ZnCl_2 led to a significant reduction in yield (entries 1–3). Among the ZnCl_2 -diamine complexes tested, $\text{ZnCl}_2\cdot\text{TMEDA}$ provided compound **6b** in the highest isolated yield (64%; entries 3–6). In the absence of a ZnCl_2 -diamine, lithiated bromoimidazole **5** underwent a halogen dance twice to provide the thermodynamically most stable organolithium, which was treated with iodine to provide **6c** in 67% isolated yield (entry 7), displaying different properties to dibromothiazole **1**.

In addition to dibromothiazole **1** and dibromoimidazole **5**, the combination of LDA and $\text{ZnCl}_2\cdot\text{TMEDA}/\text{ZnCl}_2\cdot\text{TMPDA}$ was

effective for mono-brominated azoles, providing each constitutional isomer after iodination (Table 3).^[22] Mono-brominated azoles **7–10** were subjected to LDA in the presence of $\text{ZnCl}_2\cdot\text{TMEDA}$, providing organozinc reagents from the initially

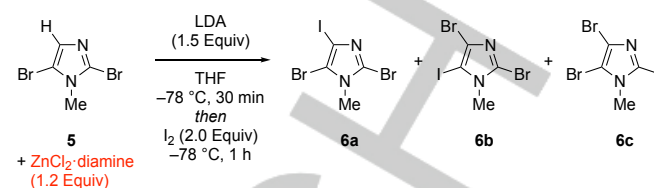


Table 2. Effects of ZnCl_2 -diamine complexes on the in situ zincation of imidazolylithiums^[a]

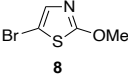
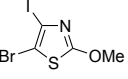


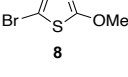
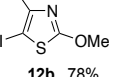


| Entry | ZnCl_2 diamine | 6a [%] ^[b] | 6b [%] ^[b] | 6c [%] ^[b] |
|------------------|----------------------------------|------------------------------|---|------------------------------|
| 1 ^[c] | ZnCl_2 | 17 | 2 | 3 |
| 2 | $\text{ZnCl}_2\cdot\text{TMEDA}$ | 30 | 37 | 16 |
| 3 ^[d] | $\text{ZnCl}_2\cdot\text{TMEDA}$ | 49 (58 ^[e]) | 4 | — ^[f] |
| 4 | $\text{ZnCl}_2\cdot\text{TMEDA}$ | — ^[f] | 50 (59 ^[e] , 64 ^[e,g]) | 24 |
| 5 | $\text{ZnCl}_2\cdot\text{TEEDA}$ | — ^[f] | 49 | 36 |
| 6 | $\text{ZnCl}_2\cdot\text{TMPDA}$ | — ^[f] | 38 | 49 |
| 7 | none | — ^[f] | 18 | 73 (67 ^[e]) |

[a] Reaction conditions: 2,5-dibromo-1-methyl-1H-imidazole (**5**) (1.0 equiv, 0.30 mmol), ZnCl_2 -diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), –78 °C, 30 min, then I_2 (2.0 equiv, 0.60 mmol), –78 °C, 1 h. [b] The yield was determined by ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c] Recovery of 51% of **5**. [d] The reaction was performed at 0 °C. [e] Isolated yield. [f] Not observed in the crude product. [g] The reaction was performed using 1.0 mmol of 2,5-dibromo-1-methyl-1H-imidazole (**5**).

generated organolithiums (entries 1, 3, 5, and 7). In contrast, the azolylithium species generated through the halogen dance were selectively transmetalated with $\text{ZnCl}_2\cdot\text{TMPDA}$ to provide the corresponding azolylzinc species, simply by changing the diamine ligand (entries 2, 4, and 6). In the case of the halogen dance of bromoimidazole **10**, $\text{ZnCl}_2\cdot\text{TMPDA}$ also provided **14a**, probably due to a slow halogen dance. Compound **14b** was obtained in 80% yield without the zinc halide diamine complex (entry 8).

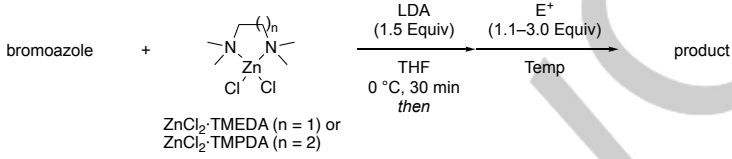
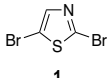
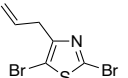
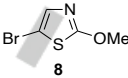
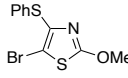
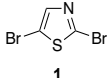
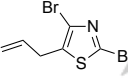
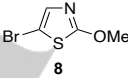
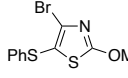
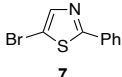
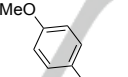

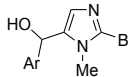
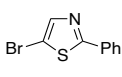
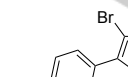

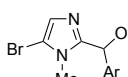
Table 3. Selective trapping of multiple azolylithiums by in situ transmetalation with $\text{ZnCl}_2\cdot\text{TMEDA}$ or $\text{ZnCl}_2\cdot\text{TMPDA}$ followed by iodination^[a]

| Entry | Bromoazole | ZnCl_2 -diamine | Product / Yield [%] ^[b] | Entry | Bromoazole | ZnCl_2 -diamine | Product / Yield [%] ^[b] |
|-------|------------|----------------------------------|------------------------------------|------------------|------------|----------------------------------|------------------------------------|
| 1 | | $\text{ZnCl}_2\cdot\text{TMEDA}$ | 11a 91% | 5 | | $\text{ZnCl}_2\cdot\text{TMEDA}$ | 13a 85% |
| 2 | | $\text{ZnCl}_2\cdot\text{TMPDA}$ | 11b 91% | 6 ^[c] | | $\text{ZnCl}_2\cdot\text{TMPDA}$ | 13b 91% |

| | | | | | | | | | |
|------------------|---|--------------------------|---|-----|------------------|---|--------------------------|---|-----|
| 3 |  | ZnCl ₂ ·TMEDA |  | 83% | 7 ^[c] |  | ZnCl ₂ ·TMEDA |  | 71% |
| 4 ^[c] |  | ZnCl ₂ ·TMPDA |  | 78% | 8 ^[c] |  | none |  | 80% |

[a] Reaction conditions: bromoazole (1.0 equiv, 0.30 mmol), ZnCl₂·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then I₂ (2.0 equiv, 0.60 mmol), 0 °C, 1 h. [b] Isolated yield. [c] Reaction temperature: –78 °C.

Table 4. Selective trapping of multiple azolylolithiums by in situ transmetalation with ZnCl₂·TMEDA or ZnCl₂·TMPDA followed by electrophilic trapping^[a]

|  | | | | | | | |
|--|---|--|---|------------------|--|---|---|
| Entry | Bromoazole | ZnCl ₂ ·diamine E ⁺ , Temp | Product / Yield [%] ^[b] | Entry | Bromoazole | ZnCl ₂ ·diamine E ⁺ , Temp | Product / Yield [%] ^[b] |
| 1 |  | ZnCl ₂ ·TMEDA CuCN·2LiCl RT |  15a 87% | 5 |  | ZnCl ₂ ·TMEDA Phth-SPh 7 mol% Cu(OAc) ₂ RT |  17a 47% |
| 2 |  | ZnCl ₂ ·TMPDA CuCN·2LiCl RT |  15b 65% | 6 ^[c] |  | ZnCl ₂ ·TMPDA Phth-SPh 5 mol% Cu(OAc) ₂ RT |  17b 27% |
| 3 |  | ZnCl ₂ ·TMEDA MeO-C ₆ H ₄ -I 3 mol% Pd ₂ (dba) ₃ 11 mol% P(C ₆ H ₅ CF ₃) ₃ 60 °C |  16a 65% | 7 ^[c] |  | ZnCl ₂ ·TMEDA MeO-C ₆ H ₄ -CHO <i>n</i> BuMgCl, 0 °C |  18a 32% |
| 4 |  | ZnCl ₂ ·TMPDA MeO-C ₆ H ₄ -I 3 mol% Pd ₂ (dba) ₃ 11 mol% P(C ₆ H ₅ CF ₃) ₃ 60 °C |  16b 78% | 8 ^[c] |  | None MeO-C ₆ H ₄ -CHO –78 °C |  18b 45% |

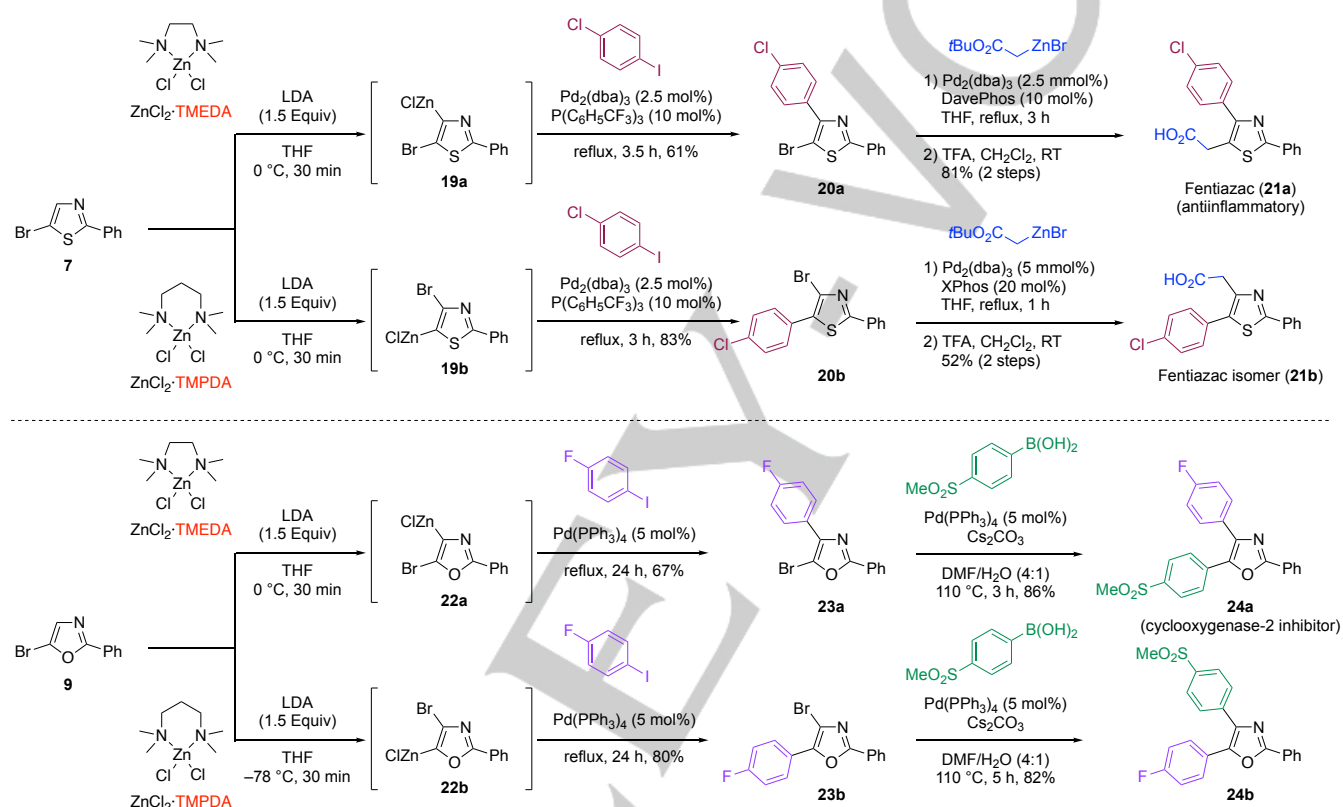
[a] Reaction conditions: bromoazole (1.0 equiv, 0.30 mmol), ZnCl₂·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), 0 °C, 30 min, then E⁺ (1.1–3.0 equiv). [b] Isolated yield. [c] Reaction temperature: –78 °C. Phth = phthalimide.

The scope of this reaction was investigated using a range of other electrophiles (Table 4). In the case of 2,5-dibromothiazole (**1**), both organozinc reagents were smoothly converted into the corresponding allylated products **15a** and **15b** through transmetalation with CuCN·2LiCl^[23] (entries 1 and 2). Neither **15a** nor **15b** was obtained at all in the absence of CuCN·2LiCl. The thiazolylzinc reagent from bromothiazole **7** and ZnCl₂·TMEDA was kinetically stable and did not undergo a halogen dance, even at 60 °C, compared with the corresponding organolithium, and was transformed into arylated thiazole **16a** by Negishi coupling in 65% yield^[24] (entry 3). In contrast, its constitutional isomer **16b** was obtained in 78% by using

ZnCl₂·TMPDA instead of ZnCl₂·TMEDA (entry 4). Copper-catalyzed thiolation^[25] proceeded to afford compounds **17a** and **17b** in moderate yields (entries 5 and 6). The organozinc reagent generated from bromimidazole **10** and ZnCl₂·TMEDA was not reactive toward *p*-anisaldehyde. Addition of 2 equivalents of *n*BuMgCl^[26] to the resulting organozinc proved effective for the nucleophilic addition to the aldehyde. During the reaction, a halogen dance was not observed to give adduct **18a** as the sole product with 40% recovery of imidazole **10** (entry 7). The other isomer (**18b**) was synthesized by reacting *p*-anisaldehyde to the corresponding imidazolylolithium species (entry 8).

The established method was applied to the divergent syntheses of biologically active azoles in a stereoselective manner (Scheme 3). Bromothiazole **7** was treated with the combination of LDA and $\text{ZnCl}_2 \cdot \text{TMEDA}$ to form organozinc **19a**, which underwent Negishi coupling to give arylated thiazole **20a** with the bromo group intact. Subsequent palladium-catalyzed installation of the acetate moiety and acidic removal of the *tert*-butyl group provided the anti-inflammatory fentiazac^[11,27] (**21a**). Its constitutional isomer **21b** was also synthesized through the same route using $\text{ZnCl}_2 \cdot \text{TMPDA}$.^[28] This method was applicable to the stereocontrolled syntheses of multiply arylated oxazoles. The use of $\text{ZnCl}_2 \cdot \text{TMEDA}$ or $\text{ZnCl}_2 \cdot \text{TMPDA}$ was effective for the selective generation of organozinc species **22a** and **22b** from a

single starting material, brominated oxazole **9**. Subsequent Negishi coupling in the presence of 5 mol% $\text{Pd}(\text{PPh}_3)_4$ smoothly afforded the corresponding products **23a** and **23b** in 67% and 80% yields, respectively.^[29] The remaining bromo group was converted to a 4-methanesulfonylphenyl group by Suzuki–Miyaura coupling^[30] to provide cyclooxygenase-2 inhibitor **24a**^[31] and its constitutional isomer **24b** in a stereocontrolled manner. Compared with conventional methods such as selective arylation of multiple halogen or pseudohalogen groups,^[32] this method provides two constitutional isomers via the selective in situ transmetalation. Furthermore, this method is superior from the perspective of atom economy.^[33]



Scheme 3. Divergent syntheses of biologically active azoles.

Conclusion

In summary, we have developed a divergent synthesis of multiply substituted azoles using selective trapping of multiple azolyllithiums via a halogen dance. The appropriate choice of diamine ligand provides the desired azolyllithium for the stereoselective synthesis. The protocol is robust, and the transformations can be performed using the combination of commercially available LDA and bench-stable zinc halide diamine complexes. In addition, these reactions can be performed in a batch reactor at 0 °C with high reproducibility and can be used for the synthesis of pharmaceutically important heteroaromatic compounds. The reaction not only enables direct functionalization of brominated heteroarenes while leaving the bromo group untouched; it also provides regioisomers from their transient organolithium species, which have been thought to

exist but have not been exploited synthetically until now. The development of additional functionalization methods involving this class of amine ligands and trapping principles will be reported in due course.

Acknowledgements

This work was financially supported by JSPS KAKENHI Grant Numbers JP16K05774 in Scientific Research (C), JP19H02717 in Scientific Research (B), JP16H01153 and JP18H04413 in the Middle Molecular Strategy, and The Kyoto Technoscience Center Research Fellowship. This work was performed under the Cooperative Research Program of "Network Joint Research Center for Materials and Devices. We thank Professor Shigeki Mori (Ehime University) and Ms. Rimi Konishi (Ehime University)

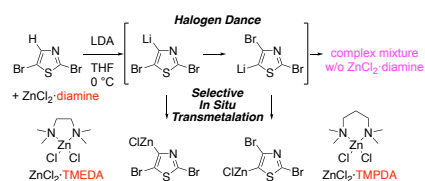
for the X-ray crystallographic analyses. We thank Alison McGonagle, PhD, from Edanz Group (<https://en-author-services.edanz.com/ac>) for editing a draft of this manuscript.

Keywords: Carbanions • Halogen dance • Heteroarenes • In situ transmetalation • Zinc

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Entry for the Table of Contents



- ✓ Selective trapping of multiple transient heteroarylolithiums
- ✓ Operationally simple and highly reproducible reaction
- ✓ Synthetic use of hitherto unexplored carbanions
- ✓ Scope: thiazole, oxazole, and imidazole

“Snapshot” trapping of multiple transient azolylolithiums via a halogen dance is realized in a batch reactor. This method allows selective generation of isomeric azolylzinc species from a single starting material using newly synthesized bench-stable zinc halide diamine complexes, leading to the divergent and stereoselective synthesis of functionalized azoles.