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"Snapshot" Trapping of Multiple Transient Azolyllithiums in Batch

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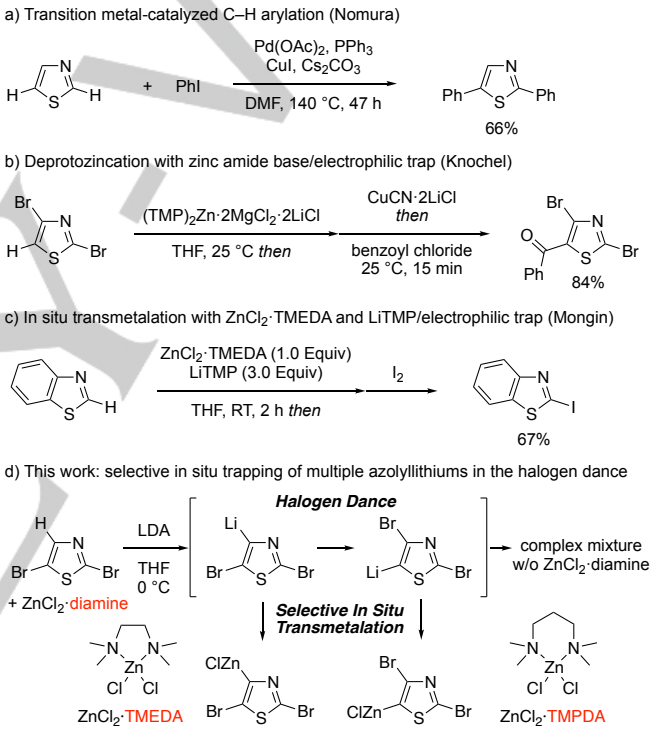
Abstract: Recent developments in flow microreactor technology have allowed the use of transient organolithium compounds that cannot be realized in a batch reactor. However, trapping of the transient aryllithiums in a "halogen dance" is still challenging. We report trapping of such short-lived azolyllithiums 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 deprotolithiation,[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 deprotozincation 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 $ZnCl_2$·TMEDA by Mongin and co-workers (Scheme 1c).[11] Subsequent iodination provided 2-iodobenzothiazole.

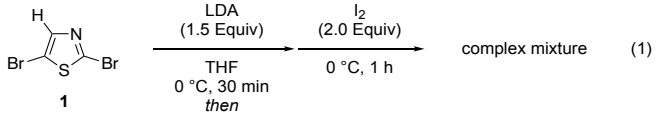
Recently, our laboratory reported the functionalization of bromothiophenes, bromofurans, and bromopyrroles via a base-promoted halogen dance.[12] This reaction has been used for synthesizing multiply brominated heteroaromatic compounds; however, several azoles have been reported to deteriorate by ring opening reaction after deprotolithiation.[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 thiazolyllithiums 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.



Scheme 1. Synthetic methods for functionalized azoles.

Results and Discussion

First, we began with the deprotolithiation 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 thiazolyllithium intermediate decomposes at 0 °C.



We then explored a suitable ZnX_2·diamine to prevent the decomposition of the transient thiazolyllithium 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).

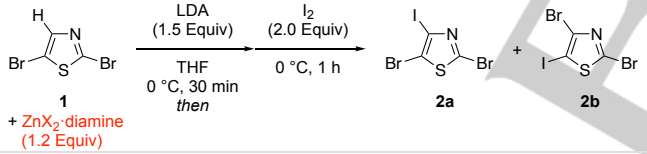


Table 1. Effects of ZnX_2·diamine complexes on the in situ zincation of thiazolyllithiums[a]

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	$ZnCl_2$·TMCDA	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**).

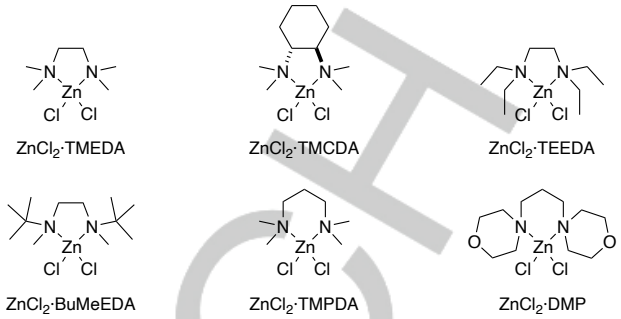
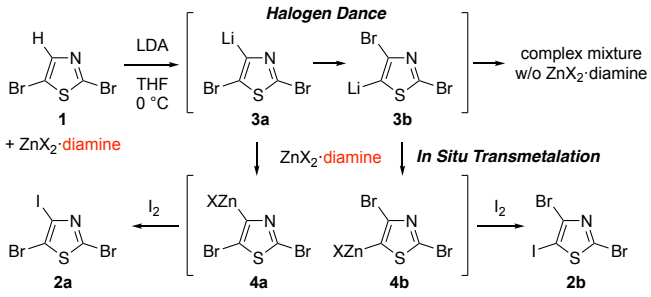


Figure 1. Structures of zinc halide diamine complexes.

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 thiazolyllithium **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 thiazolyllithium **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 thiazolyllithiums **3a** and **3b** should be considered, if both thiazolyllithiums **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 azolyllithiums 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 thiazolyllithium **3b**. Preformed *i*-Pr_2NZnCl·TMEDA from LDA and $ZnCl_2$·TMEDA led to the formation of trace amount (<10%) of thiazoles **2a** and **2b** with 59% recovery of **1**. Similarly, preformed *i*-Pr_2NZnCl·TMPDA from LDA and $ZnCl_2$·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 thiazolyllithiums.

The findings from the reaction of dibromothiazole **1** were also applicable for trapping the three resulting imidazolyllithiums 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 $ZnCl_2$·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, $ZnCl_2$·TMCDA 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 $ZnCl_2$·TMEDA/$ZnCl_2$·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 $ZnCl_2$·TMEDA, providing organozinc reagents from the initially

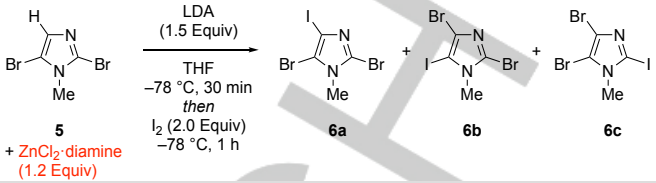


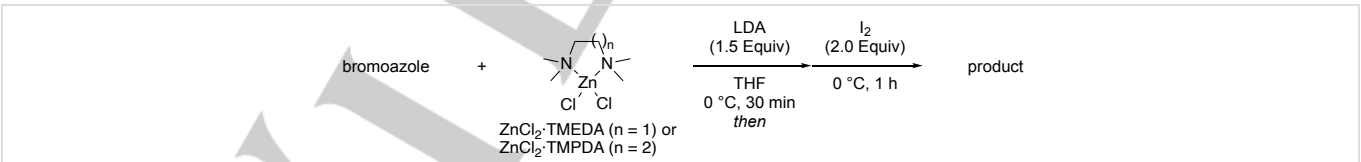
Table 2. Effects of $ZnCl_2$·diamine complexes on the in situ zincation of imidazolyllithiums[a]

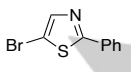
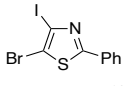
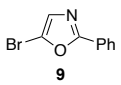
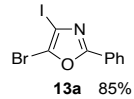
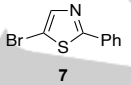
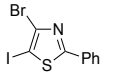
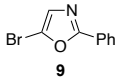
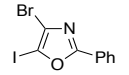
Entry	$ZnCl_2$·diamine	**6a** [%][b]	**6b** [%][b]	**6c** [%][b]
1[c]	$ZnCl_2$	17	2	3
2	$ZnCl_2$·TMEDA	30	37	16
3[d]	$ZnCl_2$·TMEDA	49 (58[e])	4	–[f]
4	$ZnCl_2$·TMCDA	–[f]	50 (59[e], 64[e,g])	24
5	$ZnCl_2$·TEEDA	–[f]	49	36
6	$ZnCl_2$·TMPDA	–[f]	38	49
7	none	–[f]	18	73 (67[e])

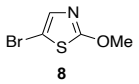
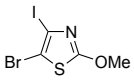
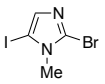
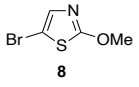
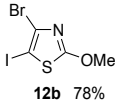
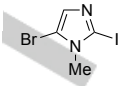
[a] Reaction conditions: 2,5-dibromo-1-methyl-1*H*-imidazole (**5**) (1.0 equiv, 0.30 mmol), $ZnCl_2$·diamine (1.2 equiv, 0.36 mmol), THF (3.0 mL), then LDA (1.5 equiv, 0.45 mmol), –78 °C, 30 min, then I_2 (2.0 equiv, 0.60 mmol), –78 °C, 1 h. [b] The yield was determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane 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-1*H*-imidazole (**5**).

generated organolithiums (entries 1, 3, 5, and 7). In contrast, the azolyllithium species generated through the halogen dance were selectively transmetalated with $ZnCl_2$·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**, $ZnCl_2$·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 azolyllithiums by in situ transmetalation with $ZnCl_2$·TMEDA or $ZnCl_2$·TMPDA followed by iodination[a]

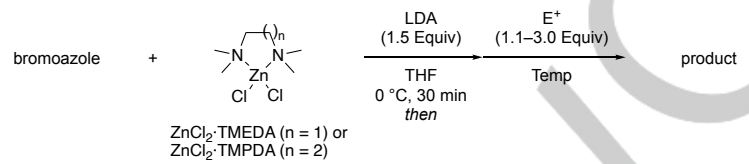


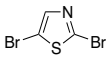
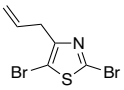
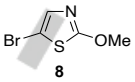
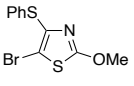
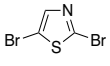
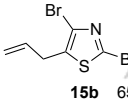
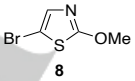
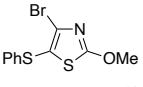
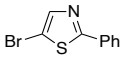
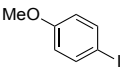
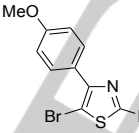
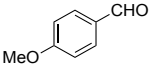
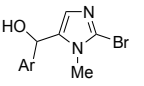
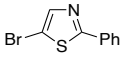
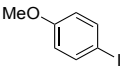
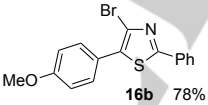
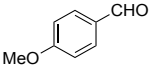
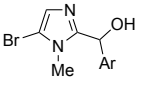
Entry	Bromoazole	$ZnCl_2$·diamine	Product / Yield [%][b]	Entry	Bromoazole	$ZnCl_2$·diamine	Product / Yield [%][b]
1	 **7**	$ZnCl_2$·TMEDA	 **11a** 91%	5	 **9**	$ZnCl_2$·TMEDA	 **13a** 85%
2	 **7**	$ZnCl_2$·TMPDA	 **11b** 91%	6[c]	 **9**	$ZnCl_2$·TMPDA	 **13b** 91%

3	 **8**	$ZnCl_2$·TMEDA	 **12a** 83%	7[c]	 **10**	$ZnCl_2$·TMEDA	 **14a** 71%
4[c]	 **8**	$ZnCl_2$·TMPDA	 **12b** 78%	8[c]	 **10**	none	 **14b** 80%

[a] Reaction conditions: bromoazole (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), 0 °C, 30 min, then I_2 (2.0 equiv, 0.60 mmol), 0 °C, 1 h. [b] Isolated yield. [c] Reaction temperature: –78 °C.

Table 4. Selective trapping of multiple azolyllithiums by in situ transmetalation with $ZnCl_2$·TMEDA or $ZnCl_2$·TMPDA followed by electrophilic trapping[a]

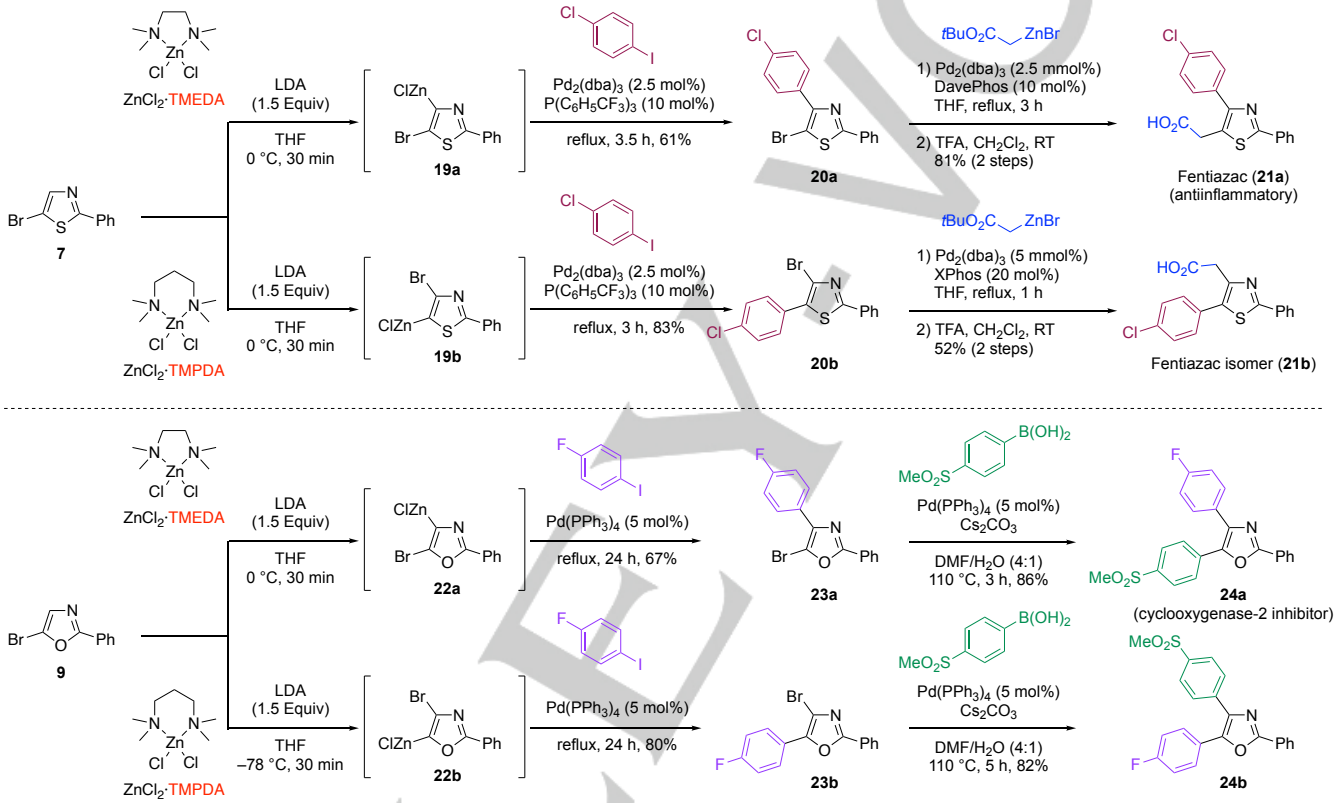


Entry	Bromoazole	$ZnCl_2$·diamine E^+, Temp	Product / Yield [%][b]	Entry	Bromoazole	$ZnCl_2$·diamine E^+, Temp	Product / Yield [%][b]
1	 **1**	$ZnCl_2$·TMEDA  CuCN·2LiCl RT	 **15a** 87%	5	 **8**	$ZnCl_2$·TMEDA Phth–SPh 7 mol% $Cu(OAc)_2$ RT	 **17a** 47%
2	 **1**	$ZnCl_2$·TMPDA  CuCN·2LiCl RT	 **15b** 65%	6[c]	 **8**	$ZnCl_2$·TMPDA Phth–SPh 5 mol% $Cu(OAc)_2$ RT	 **17b** 27%
3	 **7**	$ZnCl_2$·TMEDA  3 mol% $Pd_2(dba)_3$ 11 mol% $P(C_6H_5CF_3)_3$ 60 °C	 **16a** 65%	7[c]	 **10**	$ZnCl_2$·TMEDA  *n*BuMgCl, 0 °C	 **18a** 32%
4	 **7**	$ZnCl_2$·TMPDA  3 mol% $Pd_2(dba)_3$ 11 mol% $P(C_6H_5CF_3)_3$ 60 °C	 **16b** 78%	8[c]	 **10**	None  –78 °C	 **18b** 45%

[a] Reaction conditions: bromoazole (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), 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 $ZnCl_2$·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 $ZnCl_2$·TMPDA instead of $ZnCl_2$·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 bromoimidazole **10** and $ZnCl_2$·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 imidazolyllithium 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 $ZnCl_2$·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[1f,27] (**21a**). Its constitutional isomer **21b** was also synthesized through the same route using $ZnCl_2$·TMPDA.[28] This method was applicable to the stereocontrolled syntheses of multiply arylated oxazoles. The use of $ZnCl_2$·TMEDA or $ZnCl_2$·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% $Pd(PPh_3)_4$ 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 azolylzinc 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.

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

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[19] Deposition numbers^^<url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202101256">2073487 (for $ZnCl_2$·TMEDA), 2073489 (for $ZnBr_2$·TMEDA), 2073507 (for ZnI_2·TMEDA), 2073576 (for $ZnCl_2$·TEEDA), 2073715 (for $ZnCl_2$·TMPDA), and 2073647 (for $ZnCl_2$·DMP)</url> contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href=" http://www.ccdc.cam.ac.uk/structures ">Access Structures service</url>.

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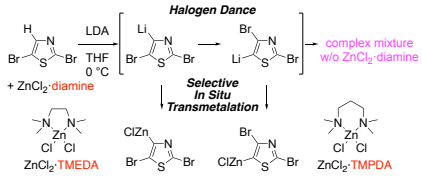

✓ Selective trapping of multiple transient heteroaryllithiums
✓ Operationally simple and highly reproducible reaction
✓ Synthetic use of hitherto unexplored carbanions
✓ Scope: thiazole, oxazole, and imidazole

"Snapshot" trapping of multiple transient azolyllithiums 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.