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Deprotonative Metalation of Substituted Benzenes and Heteroaromatics Using Amino/Alkyl Mixed Lithium–Zinc Combinations

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Abstract: Different homoleptic and heteroleptic lithium–zinc combinations were prepared, and structural elements obtained on the basis of NMR spectroscopic experiments and DFT calculations. In light of their ability to metalate anisole, pathways were proposed to justify the synergy observed for some mixtures. The best basic mixtures were obtained either by combining $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) with [Li(tmp)] (tmp = 2,2,6,6-tetramethylpiperidino; 3 equiv) or by replacing one of the tmp in the precedent mixture with an alkyl group. The reactivity of the aromatic lithium zincates supposedly formed was next studied, and proved to be substrate-, base-, and electrophile-dependent. The aromatic lithium zincates were finally involved in palladium-catalyzed cross-coupling reactions with aromatic chlorides and bromides.

Keywords: cross-coupling · density functional calculations · lithium · metalation · zinc

Introduction

Alkyllithiums and hindered lithium dialkylamides such as [Li(tmp)] (tmp = 2,2,6,6-tetramethylpiperidino) have been largely employed for the deprotonative metalation of aromatic rings.[1] Even if the less nucleophilic second category is more suitable for the metalation of sensitive aromatic compounds, either extremely low reaction temperatures or in situ electrophilic trapping are required due to the high reactivity of the corresponding aryllithiums.

The use of bimetallic combinations to reach enhanced reactivities and selectivities is a challenging field. Well-known examples are LIC–KOR (LIC = butyllithium, KOR = potassium *tert*-butoxide) first described by Schlosser[2] and Lochmann,[3] and BuLi–Li(DMAE) (DMAE = 2-dimethylaminoethoxide) developed in the pyridine series by Gros and Fort.[4] These species of [RR′MLi] type (R = alkyl, M = alkali metal) react as superbases since they exhibit behaviors that cannot be reproduced by the monometallic compounds on their own.

More recently, $[(R)_n(R')_{n'}MLi]$-type compounds in which M is not an alkali metal have also been described by different groups for their metalation ability.[5] Among them, lithium zincates of $[R_2(tmp)ZnLi]$ type described by different groups,[6] as well as salt-activated amidozincs developed by Knochel,[7] have been used to chemoselectively functionalize aromatic compounds.

The studies reported by Mulvey and co-workers on the lithium-mediated zincation of anisole using tmp–dialkyl zincates are of particular interest.[6f,h] Concerning the reaction of anisole using $[tBu_2(tmp)ZnLi]$ in tetrahydrofuran (THF), the authors obtained experimental evidence for a two-step mechanism, as previously predicted from theoretical studies,[8] in which the lithium zincate first acts as an amino base and thus generates 2,2,6,6-tetramethylpiperidine, then re-

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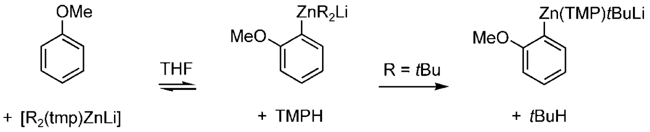
turns back to zinc through 2-anisyl- or *t*Bu-mediated proton abstraction (Scheme 1).



Scheme 1. Pathway proposed in the literature for the metalation of anisole using [*t*Bu$_2$(tmp)ZnLi].[6f,h,8]

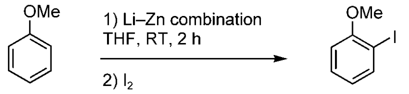
We recently accomplished the deproto-metalation of different aromatic compounds using a basic mixture obtained from ZnCl$_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and [Li(tmp)] (3 equiv), which proved to be 1:1 [Li(tmp)]/[(tmp)$_2$Zn].[9] It seemed that the synergy observed in these reactions was not due to the catalytic formation of a lithium zincate from the lithium and zinc amides, but to in situ trapping of generated lithio species with zinc compounds.

Herein, a complete study is described. Different lithium–zinc combinations have been prepared from ZnCl$_2$·TMEDA and lithium compounds, and their structures have been examined on the basis of NMR spectroscopic studies and DFT calculations. Their abilities to metalate aromatic compounds have been compared. In addition, different electrophilic trappings have been considered for the aromatic metalated species as well as palladium-catalyzed cross-couplings.

Results and Discussion

Combinations from ZnCl$_2$·TMEDA and lithium amides: The 1:1 [Li(tmp)]/[(tmp)$_2$Zn] mixture **A** (Table 1, entry 1) obtained from ZnCl$_2$·TMEDA[9] and [Li(tmp)] has been reported to allow efficient and chemoselective metalation reactions of aromatic substrates.[10] The synergy of the reaction has, for example, been demonstrated using benzo[*b*]furan as substrate: whereas the basic mixture (0.5 equiv of each metal amide) prepared in situ furnishes after subsequent trapping with iodine the 2-iodo derivative in 69 % yield, lower 20 and 10 % conversions are obtained, respectively, using separate [Li(tmp)] (1 equiv) and [(tmp)$_2$Zn] (1 equiv; see Table 2, entry 1).[10a,11] Similar results were obtained using anisole (**1a**) as substrate, the 2-iodo derivative being isolated in 9, 2, and 84 % yield by employing [Li(tmp)] (1 equiv),[12] [(tmp)$_2$Zn] (1 equiv), and 1:1 [Li(tmp)]/[(tmp)$_2$Zn] (0.5 equiv of each metal amide),[12] respectively (Table 2, entry 2).

Table 1. Metalation of anisole (**1a**) using different in situ prepared Li–Zn combinations (from ZnCl$_2$·TMEDA and lithium amides) followed by trapping with I$_2$.



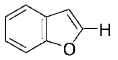
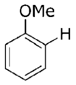
1a **1b**

Entry	Li–Zn combination **X**: lithium amide(s) added to ZnCl$_2$·TMEDA (1 equiv)	Yield [%][a]
1	**A**:[b] [Li(tmp)] (1.5 equiv)	84
2	**B**: [Li(p)] (3 equiv)	0
3	**C**: [Li(da)] (3 equiv)	16
4	**D**: [Li(p)] (2 equiv) then [Li(tmp)] (1 equiv)	2
5	**E**: [Li(da)] (2 equiv) then [Li(tmp)] (1 equiv)	38
6	**F**: [Li(tmp)] (2 equiv) then [Li(p)] (1 equiv)	35 (48)[c]
7	**G**: [Li(tmp)] (2 equiv) then [Li(da)] (1 equiv)	55 (73)[d]

[a] The rest is recovered anisole. [b] Prepared from 0.5 equiv ZnCl$_2$·TMEDA. [c] When the mixture of [Li(p)] (1 equiv) and [Li(tmp)] (2 equiv) was treated with ZnCl$_2$·TMEDA (1 equiv). [d] When the mixture of [Li(da)] (1 equiv) and [Li(tmp)] (2 equiv) was treated with ZnCl$_2$·TMEDA (1 equiv).

Table 2. Metalation of benzo[*b*]furan and anisole using [Li(tmp)], 1:1 [Li(tmp)]/[(tmp)$_2$Zn], or [(tmp)$_2$Zn] followed by trapping with I$_2$.

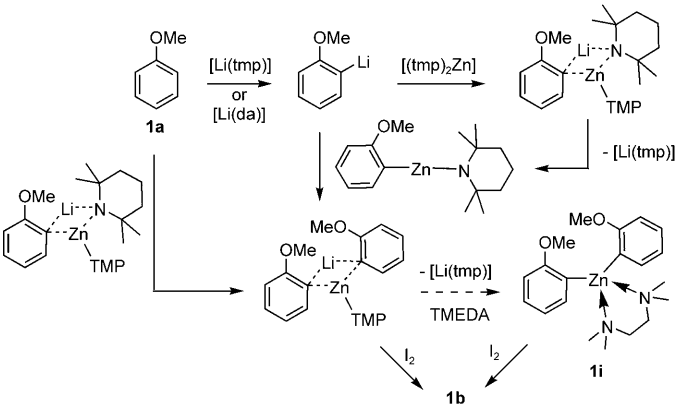
$$\text{Ar-H} \xrightarrow[\text{2) I}_2]{\text{1) base, THF, RT, 2 h}} \text{Ar-I}$$

Entry	Ar–H	Yields [%] using the following bases:[a] [Li(tmp)] (1 equiv)	1:1 [Li(tmp)]/[(tmp)$_2$Zn] (0.5 equiv each)	[(tmp)$_2$Zn] (1 equiv)
1[10a]		20	69	10
2		9[12]	84[12]	2

[a] The rest is recovered Ar–H.

The absence of LiCl or TMEDA can have an impact on the result of the experiments performed using [Li(tmp)] (since [(tmp)$_2$Zn] was prepared by adding 2 equiv of [Li(tmp)] to ZnCl$_2$·TMEDA, TMEDA and LiCl were present in this case). To take them into account, the reactions performed from anisole (**1a**) using [Li(tmp)] were repeated in the presence of LiCl (2 equiv) or TMEDA (1 equiv) or both, but without significant changes (14 % yield in the presence of TMEDA alone after interception with iodine, but only traces in the presence of LiCl).[12]

A reaction pathway through which the proton abstraction first proceeds with [Li(tmp)] and the resultant aryllithium intermediate converts by in situ trapping with a zinc compound to a more stabilized species was assumed to explain the synergy observed.[10a] Such a possibility applied to anisole (**1a**) is depicted in Scheme 2.[13] Elucidation of the structure of the intermediate formed in the metalation process was attempted. To this end, the solid that precipitated from the reaction mixture after storage for six weeks at −15 °C was characterized by X-ray diffraction crystallography.[14] Although the quality of the crystals, and consequently the quality of the X-ray diffraction data, were not good enough to perform a satisfactory structure refinement, the



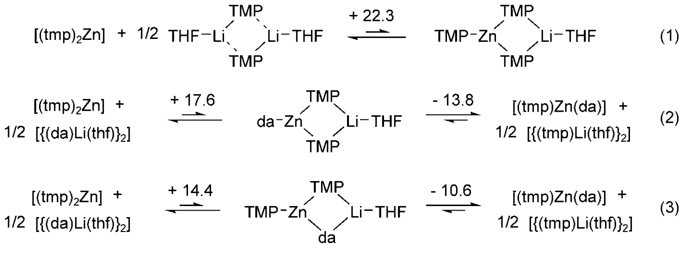
Scheme 2. Proposed pathway for the metalation of anisole (**1a**) using mixture **A** and **G** (THF, TMEDA, and LiCl have been omitted, except for compound **1i** for which we have structural evidence).

structure resolution revealed unambiguously the existence of the lithium-free neutral TMEDA-chelated dianisylzinc complex **1i** instead of a lithium zincate, as previously observed from *N*-phenylpyrrole using mixture **A**.[8b] Its formation from an intermediate zincate could be explained either by the loss of [Li(tmp)] during the long period storage, or by a disproportionation process.[6h]

To extend this possibility to other basic systems, other lithium–zinc combinations have been prepared and their ability to metalate anisole has been studied. Homoleptic mixtures were first studied by replacing [Li(tmp)] with other amides such as the less hindered/basic [Li(p)] (p = piperidino) (**B**, Table 1, entry 2) or [Li(da)] (da = diisopropylamino) (**C**, entry 3). The systems were prepared in situ from $ZnCl_2$•TMEDA and the lithium amide (3 equiv), and the metalation reactions were performed in THF at room temperature. Anisole remained unchanged after 2 h contact with mixture **B** (1 equiv of zinc source; entry 2). The reaction took place when [Li(p)] was replaced with more hindered/basic [Li(da)], albeit to give the iodide **1b** in a low 16 % yield (entry 3). These results clearly show that it is not possible to replace all three of the tmp groups of mixture **A** (84 % yield using 0.5 equiv of zinc source, entry 1) with three da or three p groups ($p < da < tmp$). The replacement of two or one tmp group(s) of mixture **A** was thus considered.

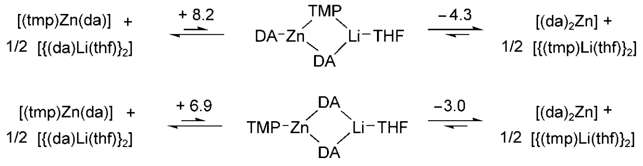
Heteroleptic mixtures were prepared from $ZnCl_2$•TMEDA and two different lithium amides (Table 1, entries 4–7). A mixture **D** prepared in situ from $[(p)_2Zn]$, generated from $ZnCl_2$•TMEDA and [Li(p)] (2 equiv), and [Li(tmp)] (1 equiv) led to traces of compound **1b** (entry 4). As observed above, the yield increased when [Li(p)] was replaced with [Li(da)] (mixture **E**) to reach 38 % (entry 5). Similarly, a mixture **F** prepared in situ from $[(tmp)_2Zn]$, generated from $ZnCl_2$•TMEDA and [Li(tmp)] (2 equiv), and [Li(p)] (1 equiv) led to compound **1b** in 35 % yield (entry 6), whereas the replacement of [Li(p)] with [Li(da)] (mixture **G**) furnished **1b** in 55 % yield (entry 7). The yields were still improved (to reach 48 and 73 %, respectively) when the lithium–zinc combinations were simply generated by treating a mixture of [Li(p)] or [Li(da)] (1 equiv) and [Li(tmp)] (2 equiv) with $ZnCl_2$•TMEDA (1 equiv).

It has been observed in the literature that sterically hindered diamido zinc and lithium dialkylamide (e.g., $[\{(tms)_2N\}_2Zn]$ (tms = trimethylsilyl) and $[LiN(tms)_2]$) rarely stabilize as a lithium triorganozincate.[15] The study of the corresponding equilibrium between $[(tmp)_2Zn]$ and [Li(tmp)] on the one side, and $[(tmp)_3ZnLi]$ on the other side, had led to a similar conclusion [Scheme 3, Eq. (1)].[10] To obtain information about the active species of the new basic mixtures, ^{13}C NMR spectroscopy[16] and DFT studies were carried out. By recording the ^{13}C NMR spectrum of mixture **F** (see Table 1, entry 6) after addition of C_6D_6 to the mixture, no [Li(tmp)] signals were detected ($\delta = 37.1$, 37.4, and 43.4 ppm), thus suggesting the presence of either $[(tmp)_2Zn]$/[Li(p)] or $[(p)(tmp)_2ZnLi]$. When [Li(p)] was replaced with [Li(da)] (mixture **G**, see entry 7), the absence of [Li(tmp)] was similarly observed, thereby supporting the possible formation of either $[(tmp)_2Zn]$/[Li(da)] or $[(da)(tmp)_2ZnLi]$. Similar NMR spectra were obtained in both cases when the lithium–zinc combinations were simply generated by treating a mixture of [Li(p)] or [Li(da)] (1 equiv) and [Li(tmp)] (2 equiv) with $ZnCl_2$•TMEDA (1 equiv).



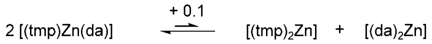
Scheme 3. $\Delta E = E$+ZPE (kcal mol^{-1}; ZPE = zero point energy) at B3LYP/6-31G* (SVP = split valence polarization for Zn).[17]

On account of the mixed tmp–da mixtures **G** and, to a lesser extent, **E** being more promising bases (higher yields), recourse to B3LYP calculations to know more about their structures was considered. Concerning mixture **G**, the calculated equilibria between $[(tmp)_2Zn]$/[Li(da)], $[(da)(tmp)_2ZnLi]$, and [(tmp)Zn(da)]/[Li(tmp)] [Scheme 3, Eqs. (2) and (3)] showed that the formation of a lithium zincate is unlikely (+14.4 kcal mol^{-1}). In addition, as inferred from the ^{13}C NMR spectrum, $[(tmp)_2Zn]$/[Li(da)] seemed to be more likely than [(tmp)Zn(da)]/[Li(tmp)] (3.8 kcal mol^{-1} in favor of the former). As far as mixture **E** was concerned, the calculated equilibria between [(tmp)Zn(da)]/[Li(da)], $[(tmp)(da)_2ZnLi]$, and $[(da)_2Zn]$/[Li(tmp)] (Scheme 4) also proved to be rather in favor of free [Li(da)] instead of free more-hindered and more-basic [Li(tmp)]. In addition, even if it was not possible to come to a decision using ^{15}N NMR



Scheme 4. $\Delta E = E$+ZPE (kcal mol^{-1}) at B3LYP/6-31G* (SVP for Zn).[17]

spectroscopy, it is pertinent to mention that [(tmp)Zn(da)] can be in equilibrium with [$(tmp)_2Zn$] and [$(da)_2Zn$] (Scheme 5).



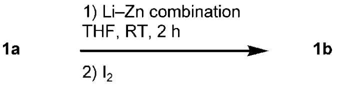
Scheme 5. $\Delta E = E$+ZPE (kcal mol^{-1}) at B3LYP/6-31G* (SVP for Zn).[17]

The synergy observed for the metalation using mixture **G** (see Table 1, entry 7) can be rationalized using the reaction pathway depicted in Scheme 2, but where the lithiation proceeds first with [Li(da)]. Indeed, [Li(da)] is capable of generating traces of 2-lithioanisole under the same conditions.

If a similar pathway can be proposed to explain the metalation of anisole using mixture **E** (see Table 1, entry 5), it can hardly be applied to mixture **F** (entry 6). Indeed, [Li(p)] is unable to metalate anisole by itself when used under the same reaction conditions. Pathways in which in situ generated lithium zincates act as catalytic metalating species could be alternatively proposed in these cases.

Combinations from $ZnCl_2$·TMEDA and alkyllithiums and lithium amides: Since lithium zincates that bear both alkyl and amino groups are efficient bases,[5,6] other kinds of combinations prepared from $ZnCl_2$·TMEDA were studied (Table 3). [Bu_3ZnLi] (**H**) allowed the expected iodide **1b** to be obtained in 28 % yield (Table 3, entry 1). By replacing one and two butyl groups with tmp groups (mixtures **I** and **J**), the iodide **1b** was isolated in 20 and 79 % yield, respectively (entries 2 and 3). A similar behavior was noticed using *sec*-butyllithium (mixtures **K** and **L**, entries 4 and 5) and *tert*-butyllithium (mixtures **M** and **N**, entries 6 and 7) instead of *n*-butyllithium. With (trimethylsilyl)methyllithium (mixtures **O**–**Q**, entries 8–10), the situation proved different since iodide **1b** was only obtained after replacement of two (trimethylsilyl)methyl groups of [{(tms)CH_2}$_3$ZnLi] with tmp groups (mixture **Q**, entry 10).

Table 3. Metalation of anisole (**1a**) using different in situ prepared Li–Zn combinations (from $ZnCl_2$·TMEDA and lithium compounds) followed by trapping with I_2.

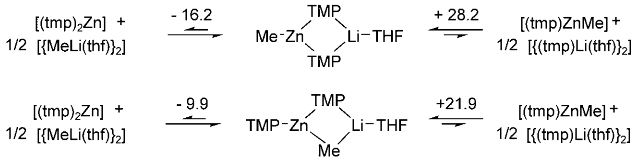


Entry	Li–Zn combination **X**: lithium compound(s) added to $ZnCl_2$·TMEDA (1 equiv)	Yield [%][a]
1	**H**: BuLi (3 equiv)	28
2	**I**: [Li(tmp)] (1 equiv) then BuLi (2 equiv)	20
3	**J**: [Li(tmp)] (2 equiv) then BuLi (1 equiv)	79
4	**K**: [Li(tmp)] (1 equiv) then *s*BuLi (2 equiv)	5
5	**L**: [Li(tmp)] (2 equiv) then *s*BuLi (1 equiv)	73
6	**M**: [Li(tmp)] (2 equiv) then *t*BuLi (1 equiv)	44
7	**N**: [Li(tmp)] (1 equiv) then *t*BuLi (1 equiv)	65
8	**O**: (TMS)CH_2Li (3 equiv)	0
9	**P**: [Li(tmp)] (1 equiv) then (TMS)CH_2Li (2 equiv)	0
10	**Q**: [Li(tmp)] (2 equiv) then (TMS)CH_2Li (1 equiv)	74

[a] The rest is recovered anisole.

Mulvey and co-workers showed that unlike [*t*Bu_2(tmp)ZnLi], [Me_2(tmp)ZnLi] is not capable of metalating anisole, and that 2-$MeOC_6H_4ZnMe_2Li$ can react with 2,2,6,6-tetramethylpiperidine, but to furnish anisole and [Me_2(tmp)ZnLi], and not 2-$MeOC_6H_4$ZnMe(TMP)Li.[6h] The efficiency of the process thus depends on the nature of the alkyl groups. Since the base prepared by successive addition of 2 equiv of *tert*-butyllithium and 1 equiv of [Li(tmp)] to a solution of $ZnCl_2$ in THF proved to be [*t*Bu_2(tmp)ZnLi],[6d,8] we assumed that the bases **I**, **K**, **M**, and **P** prepared from 2 equiv of an alkyllithium and 1 equiv of a lithium amide were lithium zincates (entries 2, 4, 6, and 9). When able to metalate, these lithium–zinc compounds provided the iodide **1b** in moderate yields. The ability of 2-$MeOC_6H_4ZnR_2Li$ to metalate 2,2,6,6-tetramethylpiperidine could follow the order *t*Bu > Bu > *s*Bu > (TMS)CH_2.

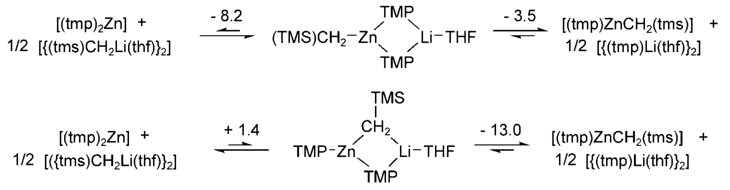
To get more information about the highest relative efficiency exhibited by the bases prepared from 1 equiv of an alkyllithium and 2 equiv of a lithium amide, NMR spectroscopy and DFT studies were performed. Recording the ^{13}C NMR spectrum of mixture **J** (Table 3, see entry 3) showed that [Li(tmp)] ($\delta = 37.1$, 37.4, and 43.4 ppm), butyllithium ($\delta = 12.0$ ppm), and dibutylzinc ($\delta = 11.3$ ppm) were not present, thereby suggesting the formation of [Bu(tmp)$_2$ZnLi]. Methyllithium was employed as a chemical model for butyllithium to carry out the theoretical study. The B3LYP-calculated equilibria between [$(tmp)_2Zn$]/MeLi, [Me$(tmp)_2$ZnLi], and [(tmp)ZnMe]/[Li(tmp)] (Scheme 6) indicate that the formation of a lithium zincate is greatly favored (−16.2 kcal mol^{-1}). We can assume a similar situation by replacing butyllithium with *sec*-butyllithium (mixture **L**, see entry 5) and *tert*-butyllithium (mixture **N**, see entry 7). The mechanism of the metalation reaction using these supposed ate bases could be as described for dialkyl–tmp mixtures.[6h,8,18] Nevertheless, what is striking in the reactions using these putative [R$(tmp)_2$ZnLi] is that, in contrast to re-



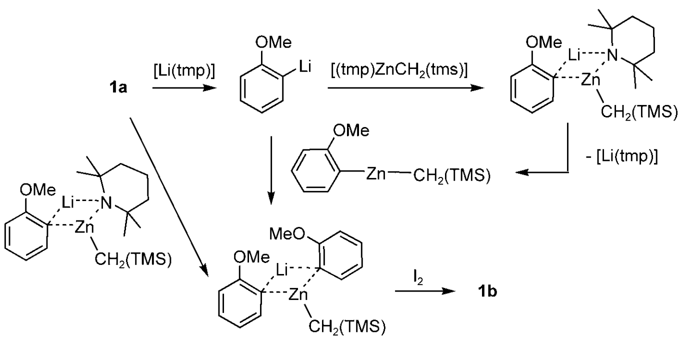
Scheme 6. $\Delta E = E$+ZPE (kcal mol^{-1}) at B3LYP/6-31G* (SVP for Zn).[17]

actions using [R_2(tmp)ZnLi], the nature of the R group has a moderate effect on the efficiency of the reaction, as if the formation of 2-$MeOC_6H_4ZnR$(TMP)Li (see Scheme 1, first step) was more favored.

When (trimethylsilyl)methyllithium was used instead (mixture **Q**, see entry 10), the B3LYP-mediated calculations showed that the formation of a lithium zincate became unlikely. Indeed, as depicted in Scheme 7, if ate compounds can be formed, they are rapidly converted to a [(tmp)$ZnCH_2$(tms)]/[Li(tmp)] mixture. In such a case, the mechanism for the metalation of anisole could rather follow the pathway proposed in Scheme 8. However, the ^{13}C NMR spectroscopic data of mixture **Q** revealed the absence of [Li(tmp)]; due to solubility problems, only 2,2,6,6-tetramethylpiperidine was clearly identified.

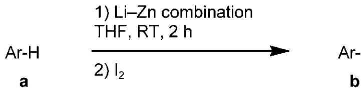


Scheme 7. $\Delta E = E + \text{ZPE}$ (kcal mol^{-1}) at B3LYP/6-31G* (SVP for Zn).[17]

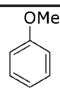
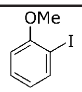
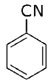
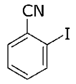
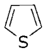
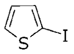
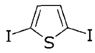
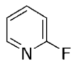
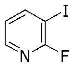
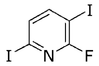
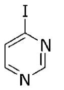
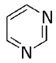
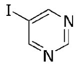


Scheme 8. Proposed pathway for the metalation of anisole (**1a**) using mixture **Q** (THF, TMEDA, and LiCl have been omitted due to lack of structural evidence).

Table 4. Metalation of the substrates **1a**–**5a** using different in situ prepared Li–Zn combinations followed by trapping with I_2.



$$\underset{\mathbf{a}}{\text{Ar-H}} \xrightarrow[\text{2) I}_2]{\text{1) Li–Zn combination, THF, RT, 2 h}} \underset{\mathbf{b}}{\text{Ar-I}}$$

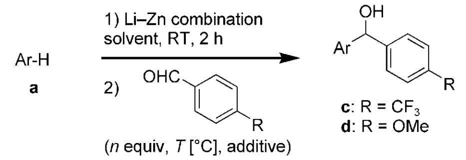
Entry	Ar–H (**a**)		Li–Zn combination **X**	Ar–I (**b**)		Yield [%]
1		**1a**	**A**[a]		**1b**	84
			J			79
			Q			74
2		**2a**	**A**[a]		**2b**	52[b]
			J			100
			Q			90
3		**3a**	**A**[a]		**3b**	54
					**3b′**	32
4		**4a**	**A**[a]		**4b**	81
					**4b′**	6
			A[a]		**5b**	36[b]
5		**5a**		**5b**		58[c]
			J		**5b′**	10[c]

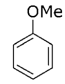
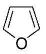
[a] Prepared from 0.5 equiv $ZnCl_2$•TMEDA. [b] The low yield is due to degradation. [c] The compounds **5b** and **5b′** could not be separated by column chromatography.

Metalation–iodination of different aromatic substrates: The metalation–iodination sequence using the most efficient bases was then extended to other aromatic substrates (Table 4). Due to their electrophilic functional groups or their ring prone to nucleophilic attacks, benzonitrile (**2a**),[6a] 2-fluoropyridine (**4a**),[19] and pyrimidine (**5a**)[20] have rarely been metalated at room temperature. Benzonitrile (**2a**) was efficiently converted to iodide **2b** using mixtures **J** and **Q**, whereas a lower 52% yield was obtained using the homoleptic tmp combination **A** (Table 4, entry 2). Thiophene (**3a**) and 2-fluoropyridine (**4a**) were efficiently metalated using **A**, but competitive dimetalation was evidenced in both cases (entries 3 and 4). Pyrimidine (**5a**) was regioselectively converted to iodide **5b** under the same reaction conditions, albeit in a lower yield probably in relation with the incompatibility of this substrate with free [Li(tmp)].[20] Indeed, the yield could be improved using mixture **J** (entry 5).

Trapping of the metalated aromatics with different electrophiles: Aromatic aldehydes, which are known to react with alkali and alkali-earth organometallic compounds, were then employed to trap the arylmetal species (Table 5). The yields obtained after trapping with 4-(trifluoromethyl)benzaldehyde and anisaldehyde largely depended on both the basic mixture employed and the substrate. From anisole (**1a**), using mixture **A** (0.5 equiv of zinc source) resulted in the formation of the expected alcohols **1c**,**d**, but in yields not exceeding 41% (Table 5, entry 1). With this basic mixture, the addition of the aryl species to the aromatic aldehyde hardly took place at room temperature, and recourse to BF_3•Et_2O (1 equiv/aldehyde) or to other solvents did not improve the trapping reaction. When putative [Bu(tmp)$_2$ZnLi] (**J**) was used instead, the reactivity of the metalated species toward the aromatic aldehydes was improved, and the com-

Table 5. Metalation of the substrates **1a** and **6a** using different in situ prepared Li–Zn combinations followed by trapping with aromatic aldehydes.



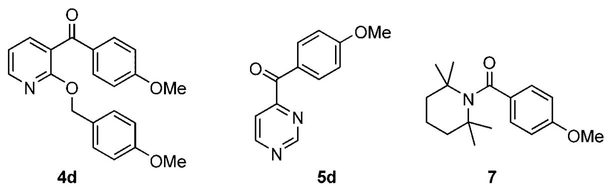
Entry	Substrate	Li–Zn combination X	Solvent, R, n, T [°C], additive	Product, yield [%][a]
1	 **1a**	A[b]	THF, CF_3, 1.5, RT, –	**1c**, traces
			THF, CF_3, 1.5, 60, –	**1c**, 35
			THF, CF_3, 1, 60, –	**1c**, 41
			THF, CF_3, 1, RT, $BF_3{\cdot}Et_2O$	**1c**, 22
			THF, CF_3, 1, 60, $BF_3{\cdot}Et_2O$	**1c**, 22
			hexane+TMEDA (5 equiv), CF_3, 1, 60, –	**1c**, 20
			THF/hexane 2:3, CF_3, 1, 60, –	**1c**, 36
			THF, OMe, 1.5, 60, –	**1d**, 36
2	**1a**	J	THF, CF_3, 3, RT, –	**1c**, 71
			THF, CF_3, 3, 60, –	**1c**, 81
			THF, OMe, 3, 60, –	**1d**, 63
3	**1a**	Q	THF, CF_3, 3, 60, –	**1c**, 11
			THF, OMe, 3, 60, –	**1d**, 4
4	**1a**	I	THF, CF_3, 3, 60, –	**1c**, 14
5	 **6a**	A[b]	THF, CF_3, 1.5, 60, –	**6c**, 34
			THF, OMe, 1.5, 60, –	**6d**, 65
6	**6a**	J	THF, CF_3, 3, 60, –	**6c**, 40
			THF, OMe, 3, 60, –	**6d**, 42
7	**6a**	Q	THF, CF_3, 3, 60, –	**6c**, 75
			THF, OMe, 3, 60, –	**6d**, 46

[a] The low yields are mainly due to competitive reactions (reduction, etc.) during the trapping step, and to difficulties encountered during the purification processes. [b] Prepared from 0.5 equiv $ZnCl_2$·TMEDA.

pounds **1c**,**d** were isolated in good yields (entry 2). In contrast, disappointing yields were obtained using mixture **Q** (entry 3). With [Bu_2(tmp)ZnLi] (**I**), the low yield obtained after trapping with 4-(trifluoromethyl)benzaldehyde was probably due to a less efficient metalation step (entry 4). Using furan (**6a**) as substrate, yields were less dependent on the nature of the basic mixture employed (entries 5–7).

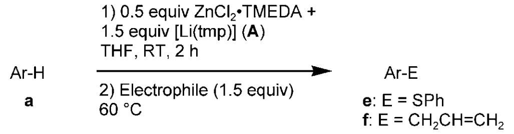
Unfortunately, starting from more stabilized metalated aromatics such as thiophene metalated at the 2-position resulted in low yields (about 10% yield after interception with anisaldehyde). For substrates that bear an electron-withdrawing group such as benzonitrile (**2a**), or that are π deficient such as 2-fluoropyridine (**4a**) and pyrimidine (**5a**), the aryl transfer to an aromatic aldehyde did not occur at all. Side reactions were evidenced instead by the isolation of compounds **4d** (about 7% yield from **4a**), **5d** (about 11% yield from **5a**), and **7** (traces to 10% yield, based on anisaldehyde; Scheme 9).

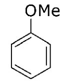
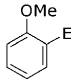
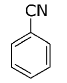
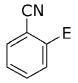
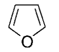
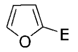
Reacting the metalated anisole, benzonitrile, and furan with phenyl disulfide and allyl bromide at 60 °C furnished the expected derivatives **1e**,**f**, **2e**,**f**, and **6e** in moderate yields (Table 6). Other electrophiles such as trimethylsilyl chloride and benzoyl chlorides were unable to trap the 2-metalated anisole. Starting from thiophene (**3a**) and 2-fluoropyridine (**4a**), the phenylthio and allyl derivatives were formed in low yields and, as also noted with benzonitrile (**2a**), in low purities due to important side reactions. Under the same reaction conditions, pyrimidine (**5a**) was not converted at all to the corresponding functionalized derivatives.



Scheme 9. Products isolated after reaction of 2-fluoropyridine and pyrimidine with mixture **A** or **J** followed by trapping by anisaldehyde.

Table 6. Metalation of the substrates **1a**, **2a**, and **6a** using mixture **A** followed by trapping by phenyl disulfide or allyl bromide.



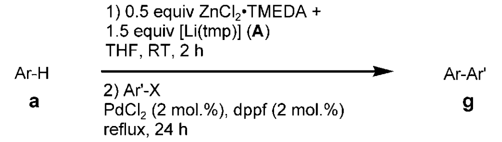
Entry	Substrate		Electrophile	Product	Yield [%]
1		**1a**	PhSSPh		**1e**, 45
			$BrCH_2CH{=}CH_2$		**1f**, 36
2		**2a**	PhSSPh		**2e**, 57[a]
			$BrCH_2CH{=}CH_2$		**2f**, 58[a]
3		**6a**	PhSSPh		**6e**, 36[b]

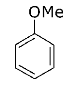
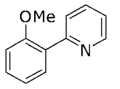
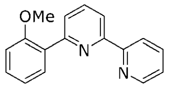
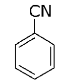
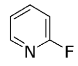
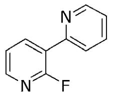
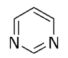
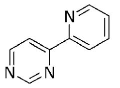
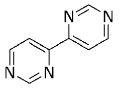
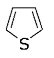
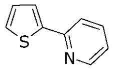
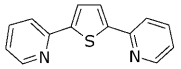
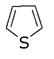
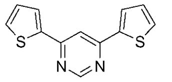
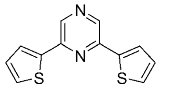
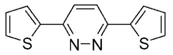
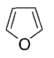
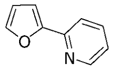
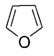
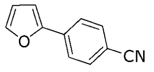
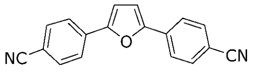
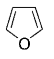
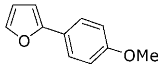
[a] Estimated yields, the compounds being contaminated by impurities. [b] Reaction of 2-metalated furan with allyl bromide also took place, but the product could not be isolated due to its volatility.

Pd-catalyzed cross-coupling from the metalated heterocycles: To extend the synthetic applications of the aryl- and heteroarylzincates supposedly formed from **1a**–**6a**, it was decided to involve them in catalyzed cross-coupling reactions with aryl and heteroaryl chlorides (Table 7). Such a possibility had previously been reported starting from benzo[*b*]furan and benzo[*b*]thiophene under palladium catalysis using 1,1′-bis(diphenylphosphino)ferrocene (dppf) as ligand.[10a]

When anisole was metalated and treated with 2-chloropyridine under these conditions, the starting materials were recovered. Using 2-bromopyridine instead of 2-chloropyridine, the expected coupling product was obtained but in a moderate yield due to the concomitant formation of the tris-heterocycle **1h** (Table 7, entry 1); the latter could result from a second metalation in the course of the coupling step. Using benzonitrile (**2a**) with 2-chloropyridine under the same con-

Table 7. Metalation of the substrates **1a**–**6a** using mixture **A** followed by palladium-catalyzed cross-coupling with aromatic halides.



Entry	Substrate		Product(s)		Yield(s) [%]
1		**1a**		**1g**	0,[a] (0),[a,b] (33)[c]
				**1h**	10[c]
2		**2a**	complex mixture[a]		
3		**4a**		**4g**	54[a]
4		**5a**		**5g**	11,[a] (traces)[a,b]
				**5h**	3,[a] 3[a,b]
5		**3a**		**3g**	83,[a] 55[d]
				**3h**	17,[a] 45[d]
6		**3a**		**3i**	40[e,f]
				**3j**	76[f,g]
				**3k**	17[f,h]
7		**6a**		**6g**	71[a]
8		**6a**		**6i**	3,[i] 39[j]
				**6j**	21[j]
9		**6a**		**6k**	0,[k,l] 48[m]

[a] Ar′−X = 2-chloropyridine. [b] Using mixture **J**. [c] Ar′−X = 2-bromopyridine. [d] The amount of thiophene was reduced by half. [e] Ar′−X = 4,6-dichloropyrimidine. [f] The amount of dichloride was reduced by half. [g] Ar′−X = 2,6-dichloropyrazine. [h] Ar′−X = 3,6-dichloropyridazine. [i] Ar′−X = 4-chlorobenzonitrile. [j] Ar′−X = 4-bromobenzonitrile. [k] Ar′−X = 4-chloroanisole. [l] 2,2′-Bifuran was isolated in 6% yield. [m] Ar′−X = 4-bromoanisole.

ditions, a complex mixture was obtained from which the expected product could not be isolated (entry 2).

Still using 2-chloropyridine, 2-fluoropyridine (**4a**) was in contrast converted to the functionalized derivative **4g** in 54% yield (Table 7, entry 3). Pyrimidine (**5a**) is not a substrate of choice for this reaction due to its incompatibility toward nucleophile compounds (notably evidenced by the presence of **5h**), thus leading to the expected coupled product in a low 11% yield (entry 4).

The metalation–coupling sequence proved particularly efficient using thiophene (**3a**) as starting material; it afforded both the bis- and tris-heterocycle **3g**,**h** in 83 and 17% yield, respectively, by reaction with 2-chloropyridine. The compound **3h**, which probably results from a dimetalation, was isolated in 45% yield when the amount of thiophene was reduced by half (Table 7, entry 5). Metalation–coupling sequences between thiophene (**3a**) and different dichlorodiazines were next considered. The amount of dichloride was reduced by half so as to favor the formation of tris-heterocycles **3i**–**k**; the latter were obtained in variable yields ranging from 17 to 76% (entry 6).

The procedure applied to furan (**6a**) and using 2-chloropyridine afforded compound **6g** in 71% yield (Table 7, entry 7). We next turned to reactions with phenyl halides. Using 4-chlorobenzonitrile under the conditions employed above only gave traces of the expected derivative **6i**. With 4-bromobenzonitrile, biaryl **6i** was isolated in 39% yield, a moderate result due to the competitive formation of the triaryl derivative **6j** in 21% yield (entry 8). If triaryl **3h** (entry 5) could come from the corresponding 2,5-dimetalated species, as thiophene (**3a**) is prone to dimetalation (Table 4, entry 3), a similar situation is less obvious with furan (**6a**), from which products that result from 2,5-dimetalation have not been isolated. A palladium-catalyzed direct arylation could be proposed instead to explain the formation of the derivative **6j** from the activated compound **6i**.[21] Maybe because compound **6k** is less prone to such a competitive reaction, it could be isolated in a higher albeit still moderate yield (entry 9).

Conclusion

Different homoleptic and heteroleptic lithium–zinc combinations have been explored in light of NMR spectroscopic experiments, ab initio calculations, and their ability to allow the functionalization of anisole. To draw conclusions about their efficiency, the deproto-metalation step and the subsequent trapping have to be considered separately.

Concerning the metalation step, the best combination proved to be the previously reported 1:1 [Li(tmp)]/[(tmp)$_2$Zn] mixture (**A**) prepared from ZnCl$_2$·TMEDA and [Li(tmp)] (3 equiv). It was nevertheless possible to replace one of the tmp equivalents with an alkyl to obtain putative [R(tmp)$_2$ZnLi] (R = Bu (**J**), *s*Bu (**L**), *t*Bu (**N**)). Mechanisms have been proposed for reactions using triamino and amino–dialkyl lithium–zinc combinations. The reason why the reactions using diamino–alkyl combinations give higher yields than the reactions employing amino–dialkyl combinations is still obscure.

If iodine can be used to quantitatively intercept the arylmetal derivatives whatever their nature, this proved to be wrong with other electrophiles. For instance, due to possible competitive reduction reactions, the efficiency of the quenching step using 4-(trifluoromethyl)benzaldehyde and anisaldehyde depends on the basic mixture used for the metalation step. Further studies would allow the potential of the method for organic synthesis to be evaluated.

Experimental Section

The reactions were performed in Schlenk tubes under an argon atmosphere. THF was freshly distilled over Na/Ph_2CO. Liquid chromatography separations were achieved on silica gel Merck-Geduran Si 60 (63–200 μm). NMR spectra were acquired using a Bruker AC-300 (300, 75, and 282 MHz for ^1H, ^{13}C, and ^{19}F, respectively) spectrometer. ^1H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts relative to the central peak of the solvent signal, and ^{19}F chemical shifts relative to CCl_3F.[22] High-resolution mass spectra measurements were performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes.

$ZnCl_2$·TMEDA:[9] $ZnCl_2$ (20 g, 147 mmol) was heated under vacuum with a heat gun for 30 min. After cooling, dry THF (400 mL) was added, and the solution was heated until complete dissolution of the salt. TMEDA (44 mL, 0.29 mol) was then added slowly, and the mixture was stirred for 2 h at room temperature. The solvents were evaporated, and the solid was recrystallized from THF (70 mL). Crystals were collected by filtration and washed with pentane. The complex was obtained in a quantitative yield (≈37 g) as white needles: M.p. 176 °C (ref. [9] 176–177 °C); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 2.62$ (s, 12 H), 2.75 ppm (s, 4 H).

Mixtures A, **B**, and **C**: BuLi (about 1.6 M hexane solution, 6.0 mmol) and, 15 min later, $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) were added to a stirred, cooled (0 °C) solution of the amine (6.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C.

Mixtures D and **E**: BuLi (about 1.6 M hexane solution, 6.0 mmol) and, 15 min later, $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) were added to a stirred, cooled (0 °C) solution of the amine (4.0 mmol) and of TMPH (0.34 mL, 2.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C.

Mixtures F and **G**: BuLi (about 1.6 M hexane solution, 6.0 mmol) and, 15 min later, $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) were added to a stirred, cooled (0 °C) solution of the amine (2.0 mmol) and of TMPH (0.68 mL, 4.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C.

Mixtures H and **O**: The alkyllithium (6.0 mmol) was added to a stirred, cooled (0 °C) solution of $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C.

Mixtures I, **K**, **M**, and **P**: BuLi (about 1.6 M hexane solution, 2.0 mmol) was added to a stirred, cooled (0 °C) solution of TMPH (0.34 mL, 2.0 mmol) in THF (5 mL). After 15 min at 0 °C, $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) was added, and the mixture was stirred for 15 min at this temperature before the addition of BuLi (4.0 mmol). The mixture was stirred for further 15 min at 0 °C.

Mixtures J, **L**, **N**, and **Q**: BuLi (about 1.6 M hexane solution, 4.0 mmol) was added to a stirred, cooled (0 °C) solution of TMPH (0.68 mL, 4.0 mmol) in THF (5 mL). After 15 min at 0 °C, $ZnCl_2$·TMEDA (504 mg, 2.0 mmol) was added, and the mixture was stirred for 15 min at this temperature before the addition of BuLi (2.0 mmol). The mixture was stirred for further 15 min at 0 °C.

General procedure for the metalation using A followed by iodination: After the substrate (4.0 mmol) had been added to the in situ prepared mixture **A** at 0 °C, the mixture was stirred for 2 h at room temperature before introduction of a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL). The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL) and extraction with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure before being purified by means of column chromatography on silica gel.

General procedure for the metalation using an in-situ-prepared mixture (≠A) followed by iodination: After the substrate (2.0 mmol) had been added to the in situ prepared mixture at 0 °C, the mixture was stirred for 2 h at room temperature before introduction of a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL). The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL) and extraction with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure before being purified by means of column chromatography on silica gel.

General procedure for the metalation with an in situ prepared mixture followed by trapping with an electrophile (≠I_2): After the substrate (4.0 mmol when mixture **A** was used, or 2.0 mmol otherwise) had been added to the in situ prepared mixture at 0 °C, the mixture was stirred for 2 h at room temperature before introduction of the electrophile (6.0 mmol). The mixture was stirred at 60 °C overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL) and extraction with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure before being purified by means of column chromatography on silica gel.

General procedure for the metalation with an in situ prepared mixture followed by cross-coupling with an aromatic halide: After the substrate (4.0 mmol when mixture **A** was used, or 2.0 mmol otherwise) had been added to the in situ prepared mixture at 0 °C, the mixture was stirred for 2 h at room temperature before introduction of the halide (4.8 mmol), palladium(II) chloride (14 mg, 80 μmol), and 1,1′-diphenylphosphinoferrocene (44 mg, 80 μmol). The mixture was heated at the reflux point of THF for 24 h. After the addition of water (0.5 mL) and EtOAc (50 mL), and drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the coupled product was isolated by purification by flash chromatography on silica gel.

Note that 1.8 mmol of 4,6-dichloropyrimidine, 2,6-dichloropyrazine, or 3,6-dichloropyrimidine was used to perform the bis-coupling reactions.

2-Iodothiophene (3b): Pale yellow liquid; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.81$ (dd, $J = 3.6$, 5.4 Hz, 1 H), 7.25 (dd, $J = 1.2$, 3.6 Hz, 1 H), 7.36 ppm (dd, $J = 1.2$, 5.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 73.1$, 128.9, 131.5, 136.9 ppm. These data are consistent with the literature[23] and with those obtained for a commercial sample.

2-Fluoro-3-iodopyridine (4b): White solid; m.p. < 50 °C (ref. [24] 42–43 °C); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 6.97$ (m, 1 H), 8.16 ppm (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 76.0$ (d, $J_F = 43$ Hz), 122.7 (d, $J_F = 129$ Hz), 147.2 (d, $J_F = 13$ Hz), 150.1 (d, $J_F = 3$ Hz), 162.0 ppm (d, $J_F = 235$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -54.5$ ppm. These data are consistent with the literature.[24]

2-Fluoro-3,6-diiodopyridine (4b′): White solid; m.p. 89 °C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.38$ (dd, $J = 7.9$ Hz, $J_F = 1.5$ Hz, 1 H), 7.75 ppm (dd, $J = 7.9$ Hz, $J_F = 7.9$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 75.5$ (d, $J_F = 42$ Hz), 112.2 (d, $J_F = 12$ Hz), 134.1 (d, $J_F = 5$ Hz), 150.7 (d, $J_F = 3$ Hz), 160.5 ppm (d, $J = 242$ Hz); ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -51.7$ ppm. The structure was identified unequivocally by X-ray structure analysis from crystals obtained by evaporating a CH_2Cl_2 solution.

(2-Methoxyphenyl)(4-methoxyphenyl)methanol (1d): Pale yellow liquid; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 3.02$ (d, $J = 5.2$ Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 6.02 (d, $J = 5.0$ Hz, 1 H), 6.88 (m, 3 H), 6.95 (td, $J = 1.0$, 7.5 Hz, 1 H), 7.28 ppm (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 55.2$, 55.4, 71.8, 110.7, 113.5 (2 C), 120.7, 127.6, 127.8 (2 C), 128.5, 132.1, 135.5, 156.6, 158.7 ppm. These data are consistent with the literature.[25]

(Furan-2-yl)[4-(trifluoromethyl)phenyl]methanol (6c): Yellow liquid; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 5.88$ (s, 1 H), 6.14 (br d, $J = 3.3$ Hz, 1 H), 6.33 (dd, $J = 1.9$, 3.3 Hz, 1 H), 7.40 (dd, $J = 0.8$, 1.8 Hz, 1 H), 7.56 (d, $J = 8.4$ Hz, 2 H), 7.63 ppm (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 63.4$, 107.8, 110.4, 122.1 (q, $J_F = 272$ Hz), 125.4 (q, $J_F = 3.8$ Hz, 2 C), 126.8, 130.2 (q, $J_F = 32.4$ Hz, 2 C), 142.9, 144.5, 155.0 ppm; ^{19}F NMR ($CDCl_3$, 282 MHz): $\delta = -62.6$ ppm; HRMS (ESI) calcd for $C_{12}H_9F_3O_2$ $[M+H-H_2O]^+$: 225.0527; found: 225.0525.

(Furan-2-yl)(4-methoxyphenyl)methanol (6d): Yellow liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=2.46 (d, J=4.3 Hz, 1H), 3.81 (s, 3H), 5.77 (d, J=3.9 Hz, 1H), 6.11 (td, J=0.8, 3.2 Hz, 1H), 6.32 (dd, J=1.8, 3.2 Hz, 1H), 6.90 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 7.39 ppm (dd, J=0.8, 1.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=55.3, 69.8, 107.2, 110.2, 113.8 (2C), 127.9 (2C), 133.1, 142.4, 156.2, 159.4 ppm. These data are consistent with the literature.[26]

[2-(4-Methoxybenzyloxy)pyridin-3-yl](4-methoxyphenyl)methanone (4d): Yellow liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=3.77 (s, 3H), 3.87 (s, 3H), 5.31 (s, 2H), 6.75 (d, J=8.8 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 7.00 (dd, J=5.0, 7.3 Hz, 1H), 7.08 (d, J=8.8 Hz, 2H), 7.72 (dd, J=2.0, 7.3 Hz, 1H), 7.74 (d, J=9.0 Hz, 2H), 8.30 ppm (dd, J=2.0, 5.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=55.2, 55.5, 67.2, 113.5 (2C), 113.6 (2C), 116.7, 123.3, 128.9 (2C), 129.0, 130.4 (2C), 132.1, 138.8, 148.9, 159.0, 160.4, 163.7, 193.5 ppm. HRMS (ESI) calcd for $C_{21}H_{19}NO_4$ $[M+Na]^+$: 372.1212; found: 372.1215.

(4-Methoxyphenyl)(pyrimidin-4-yl)methanone (5d): Inseparable mixture with reduced aldehyde. ^{1}H NMR (CDCl$_3$, 300 MHz): δ=3.91 (s, 3H), 7.00 (d, J=9.0 Hz, 2H), 7.88 (dd, J=1.4, 5.1 Hz, 1H), 8.15 (d, J=9.0 Hz, 2H), 9.00 (d, J=5.1 Hz, 1H), 9.38 ppm (d, J=1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=55.3, 113.9 (2C), 120.5, 127.6, 133.5 (2C), 157.9, 158.7, 162.0, 164.3, 190.4 ppm; HRMS (ESI) calcd for $C_{12}H_{11}N_2O_2$: 215.0821 $[M+H]^+$ and 237.0640 $[M+Na]^+$; found: 215.0833 $[M+H]^+$ and 237.0639 $[M+Na]^+$.

***N*-(4-Methoxybenzoyl)-2,2,6,6-tetramethylpiperidine (7)**: Inseparable mixture with aldehyde. ^{1}H NMR (CDCl$_3$, 300 MHz): δ=1.34 (s, 12H), 1.76 (s, 6H), 3.81 (s, 3H), 6.84 (d, J=8.8 Hz, 2H), 7.4 ppm (d, J=8.8 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=15.1, 30.5 (2C), 37.1 (2C), 55.2 (2C), 56.3, 113.0 (2C), 129.6 (2C), 135.8, 160.7, 177.1 ppm. These data are consistent with the literature.[27]

2-(Phenylthio)benzonitrile (2e): Yellow liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.13 (ddd, J=0.4, 1.1, 8.1 Hz, 1H), 7.26 (dt, J=1.2, 7.6 Hz, 1H), 7.39 (m, 2H), 7.40 (m, 2H), 7.48 (m, 2H), 7.64 ppm (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=112.9, 116.9, 126.4, 128.9, 129.7 (2C), 129.9, 131.8, 132.7, 133.5 (2C), 133.6, 142.3 ppm. These data are consistent with the literature.[28]

2-(Phenylthio)furan (6e): Colorless liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=6.57 (dd, J=2.0, 3.2 Hz, 1H), 6.84 (dd, J=0.8, 3.2 Hz, 1H), 7.23–7.28 (m, 3H), 7.33 (m, 2H), 7.67 ppm (dd, J=0.9, 2.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=111.9, 119.5, 126.3, 127.5 (2C), 129.0 (2C), 136.3, 143.1, 146.5 ppm. These data are consistent with the literature.[29]

2-(4-Methoxyphenyl)pyridine (1g): Colorless liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=3.86 (s, 3H), 7.00 (dd, J=0.9, 8.3 Hz, 1H), 7.08 (dt, J=1.1, 7.5 Hz, 1H), 7.21 (ddd, J=1.3, 4.9, 7.4 Hz, 1H), 7.38 (ddd, J=1.8, 7.4, 8.3 Hz, 1H), 7.71 (ddd, J=1.9, 7.4, 8.0 Hz, 1H), 7.76 (dd, J=1.8, 7.6 Hz, 1H), 7.81 (td, J=1.1, 8.0 Hz, 1H), 8.71 ppm (ddd, J=0.9, 1.8, 4.9 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=55.6, 111.3, 121.0, 121.7, 125.1, 129.0, 129.9, 131.1, 135.7, 149.3, 156.1, 156.9 ppm. These data are consistent with the literature.[30]

6-(2-Methoxyphenyl)-2,2′-bipyridine (1h):[31] Inseparable mixture with **1g**. ^{1}H NMR (CDCl$_3$, 300 MHz): δ=3.89 (s, 3H), 7.06 (d, J=1.1 Hz, 1H), 7.13 (ddd, J=1.1, 7.5, 7.5 Hz, 1H), 7.30 (ddd, J=1.2, 4.8, 7.5 Hz, 1H), 7.41 (dd, J=1.8, 8.2 Hz, 1H), 7.80–7.85 (m, 2H), 7.92 (dd, J=1.1, 7.9 Hz, 1H), 8.01 (dd, J=1.8, 7.6 Hz, 1H), 8.34 (dd, J=1.1, 7.6 Hz, 1H), 8.58 (ddd, J=1.1, 1.1, 8.0 Hz, 1H), 8.70 ppm (ddd, J=0.9, 1.8, 5.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=55.6, 111.5, 118.8, 121.3, 123.5, 125.2, 129.0, 129.1, 129.9, 131.4, 136.5, 136.8, 149.0, 155.0, 155.5, 156.5, 157.2 ppm.

2-(Furan-2-yl)pyridine (6g):[32] Colorless liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=6.53 (m, 1H), 7.06 (d, J=3.3 Hz, 1H), 7.15 (m, 1H), 7.53 (m, 1H), 7.70 (m, 2H), 8.60 ppm (d, J=3.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=108.5, 111.9, 118.5, 121.8, 136.5, 143.2, 149.2, 149.5, 153.4 ppm.

2,5-Di(pyridin-2-yl)thiophene (3h): Yellow solid; m.p. 140 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.17 (ddd, J=2.6, 4.9, 5.9 Hz, 2H), 7.63 (s, 2H), 7.66–7.70 (m, 4H), 7.60 ppm (dt, J=1.5, 4.9 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=119.0, 122.1, 125.6, 136.7, 145.9, 149.6, 152.3 ppm. These data are consistent with the literature.[33]

4,6-Di(thiophen-2-yl)pyrimidine (3i): Yellow solid; m.p. 142 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.19 (dd, J=3.8, 5.0 Hz, 2H), 7.55 (dd, J=1.1, 5.0 Hz, 2H), 7.81 (d, J=1.4 Hz, 1H), 7.84 (dd, J=1.1, 3.8 Hz, 2H), 9.05 ppm (d, J=1.4 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=109.0, 127.5 (2C), 128.6 (2C), 130.4 (2C), 142.3, 159.2, 159.3 ppm. These data are consistent with the literature.[34]

2,6-Di(thiophen-2-yl)pyrazine (3j): Yellow solid; m.p. 185 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.16 (dd, J=3.7, 5.1 Hz, 2H), 7.49 (dd, J=1.1, 5.1 Hz, 2H), 7.73 (dd, J=1.1, 3.7 Hz, 2H), 8.75 ppm (s, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=126.1 (2C), 128.4 (2C), 129.2 (2C), 137.9 (2C), 141.4, 147.5 ppm. These data are consistent with the literature.[35] The structure was identified unequivocally by X-ray structure analysis from crystals obtained by evaporating a CH_2Cl_2 solution.

3,6-Di(thiophen-2-yl)pyridazine (3k): Yellow solid; m.p. 172 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.15 (dd, J=3.7, 5.0 Hz, 2H), 7.48 (dd, J=1.1, 5.0 Hz, 2H), 7.65 (dd, J=1.1, 3.7 Hz, 2H), 7.74 ppm (s, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=122.6 (2C), 126.1 (2C), 128.2 (2C), 129.4 (2C), 140.8, 153.5 ppm. These data are consistent with the literature.[36]

4-(Pyridin-2-yl)pyrimidine (5g): White solid; m.p. 78–80 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=7.41 (ddd, J=1.2, 4.8, 7.6 Hz, 1H), 7.87 (td, J=1.8, 7.7 Hz, 1H), 8.36 (dd, J=1.4, 5.3 Hz, 1H), 8.48 (dt, J=1.1, 8.0 Hz, 1H), 8.72 (ddd, J=0.9, 1.7, 4.8 Hz, 1H), 8.86 (d, J=5.3 Hz, 1H), 9.28 ppm (d, J=1.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=117.4, 121.7, 125.5, 137.2, 149.6, 153.7, 158.0, 158.7, 162.7 ppm. These data are consistent with the literature.[37]

4,4′-Bipyrimidine (5h): Yellow liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=8.44 (dd, J=1.5, 5.0 Hz, 2H), 8.97 (d, J=5.0 Hz, 2H), 9.36 ppm (d, J=1.5 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=118.0, 158.9, 159.1, 160.8 ppm. These data are consistent with the literature.[37,38]

4-(Furan-2-yl)benzonitrile (6i): White solid; m.p. 54–56 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=6.53 (dd, J=1.8, 3.5 Hz, 1H), 6.81 (dd, J=0.7, 3.5 Hz, 1H), 7.54 (dd, J=0.7, 1.8 Hz, 1H), 7.65 (d, J=8.8 Hz, 2H), 7.74 ppm (d, J=8.8 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=108.1, 110.2, 112.2, 118.9, 123.9 (2C), 132.5 (2C), 134.6, 143.6, 151.9 ppm. These data are consistent with the literature.[39]

2,5-Di(4-cyanophenyl)furan (6j): Yellow solid; m.p. >250 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=6.95 (s, 2H), 7.71 (d, J=8.8 Hz, 4H), 7.83 ppm (d, J=8.8 Hz, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=110.6 (2C), 110.9 (2C), 118.7 (2C), 124.1 (4C), 132.7 (4C), 133.8 (2C), 152.8 ppm (2C). These data are consistent with the literature.[40]

2,2′-Bifuran: Colorless liquid; ^{1}H NMR (CDCl$_3$, 300 MHz): δ=6.45 (dd, J=1.8, 3.4 Hz, 2H), 7.55 (d, J=3.1 Hz, 2H), 7.41 ppm (d, J=1.8 Hz, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ=105.0 (2C), 111.3 (2C), 141.7 (2C), 146.6 ppm (2C). These data are consistent with the literature.[41]

The preparation of 2-iodoanisole (**1b**),[42] 2-iodobenzonitrile (**2b**),[42] 2,5-diiodothiophene (**3b′**),[42] 4-iodopyrimidine (**5b**),[42] 5-iodopyrimidine (**5b′**),[10c] (2-methoxyphenyl)[4-(trifluoromethyl)phenyl]methanol (**1c**),[12] 2-(phenylthio)anisole (**1e**),[12] 2-allylanisole (**1f**),[12] 2-allylbenzonitrile (**2f**),[12] 2-(thiophen-2-yl)pyridine (**3g**),[12] 2-fluoro-3-(pyridin-2-yl)pyridine (**4g**),[12] and 2-(4-methoxyphenyl)furan (**6k**)[43] has been previously described.

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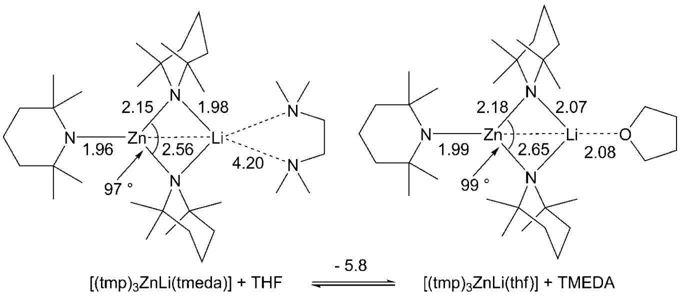
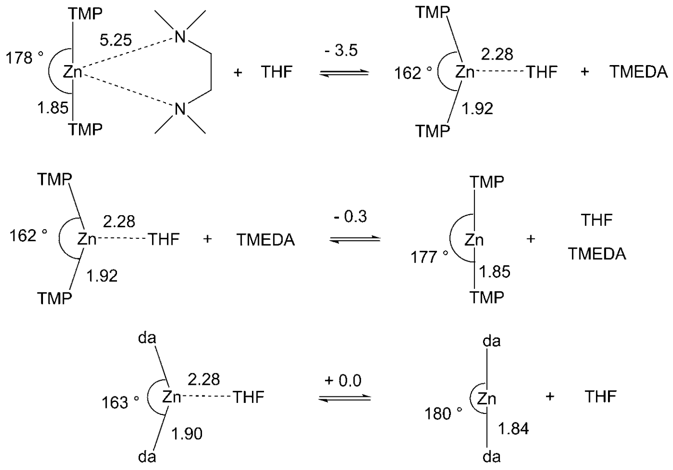
[17] A THF-coordinated lithium zincate seemed more likely than a TMEDA-chelated lithium zincate (B3LYP/6-31G* SVP for Zn, $\Delta E = E + ZPE$ (kcal mol^{-1}), bond lengths in Å):



A THF-coordinated zinc diamide seemed more likely than a TMEDA-chelated zinc diamide. The coordination of THF to the zinc diamide seemed to have a low impact on the stability of the metallic species (B3LYP/6-31G* SVP for Zn, $\Delta E = E + ZPE$ (kcal mol^{-1}), bond lengths in Å):



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