Tetrahedron Letters 52 (2011) 4590–4594

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Alkali-metal mediated zincation of *N*-heterocyclic substrates using the lithium zincate complex, (THF)Li(TMP)Zn(*t*Bu)$_2$ and applications in in situ cross coupling reactions

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ARTICLE INFO

Article history:
Received 22 April 2011
Revised 3 June 2011
Accepted 24 June 2011
Available online 1 July 2011

Keywords:
Metallation
Zincation
N-Heterocycles
Lithium
Mixed-metal reagents

ABSTRACT

This study investigates the ability of the mixed-metal reagent [Li(TMP)Zn(*t*Bu)$_2$] **1** to promote direct Zn–H exchange reactions (zincations) of a wide range of *N*-heterocyclic molecules. The generated metallated intermediates from these reactions are intercepted with I_2 and some of them are also employed as precursors in Pd-catalysed Negishi cross-coupling applications. A comparison with recent precedents in metallation chemistry reveals that for some of these heterocycles, **1** allows improved conversions, under milder conditions and in certain cases, even gives unique regioselectivities.

Nitrogen-containing heteroaromatic ring systems are key structural units present in a multitude of pharmaceuticals, natural products, agrochemicals and other biologically active molecules, making methods to enable their selective functionalization of great value in synthesis.[1–3] One of the most important methodologies which allows the incorporation of these important molecules into more complex molecular scaffolds is deprotonative metallation, traditionally using strong bases, such as alkyl lithiums and lithium diamides.[4,5] However, despite their extensive applications, the use of these reagents (which generate in situ highly reactive (hetero)aryllithiums) imposes severe limitations including the need for cryogenic temperatures, limited functional group tolerance, restricted regioselectivity and incompatibility with Pd cross-coupling methods.

Searching for more efficient reagents which can overcome these important drawbacks, a new generation of multimetallic reagents have been developed that allows the regioselective metallation of various functionalised aromatic and heteroaromatic substrates offering a wider functional group tolerance, and often requiring milder reaction conditions.[6–8] Pioneering work in this area includes Kondo and Uchiyama's TMP–zincate complex [Li(TMP)Zn(*t*Bu)$_2$],[9–11] (TMP = 2,2,6,6-tetramethylpiperidide), Mulvey's sodium related analogue [(TMEDA)Na(TMP)Zn(*t*Bu)$_2$][6,12] (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), and Knochel's Turbo-Grignard TMPMgCl·LiCl[13,14] and related salt-supported reagents such as lithium magnesiate Mg(TMP)$_2$·2LiCl when paired with the halide ZnCl$_2$.[15]

Within the context of TMP-dialkyl zincates, the isolation and structural characterization of key metallation intermediates (prior to any electrophilic interception) have demonstrated that these deprotonations are in fact direct zincations (alkali-metal mediated zincation, AMM*Zn*) as exemplified in Scheme 1 which feature the structural outcome of the AMM*Zn* of anisole by lithium-zincate [Li(TMP)Zn(*t*Bu)$_2$] **1**.[16]

Herein we report a reactivity study using the lithium-zincate base [Li(TMP)Zn(*t*Bu)$_2$] **1** (Scheme 1) with a range of *N*-containing heteroaromatic substrates. The intermediate zincated heterocycles were quenched with I_2 to determine the regioselectivity of the metallation, or cross-coupled with various electrophiles under Pd-catalysis. Our results are compared and contrasted to related reactions within the literature.

Zincate **1** was prepared in situ according to the reported literature procedure (by mixing LiTMP with *t*Bu$_2$Zn using THF as a solvent)[9] and reacted with several heteroarenes such as substituted pyridines, diazines and their benzo derivatives (Table 1).

Thus, 2-methoxypyridine (**2**) was zincated selectively at the 3-position with **1** (1 equiv, 25 °C, 2 h), and after I_2 addition gave the 3-iodo product **2a** in a 92% yield (entry 1). This metallation regioselectivity of **2** has been previously reported using the aluminate base [*i*Bu$_3$Al(TMP)Li][18] however, low temperatures (−78 °C) and an excess of base (2.2 equiv) were required to achieve 82% yield of **2a**.

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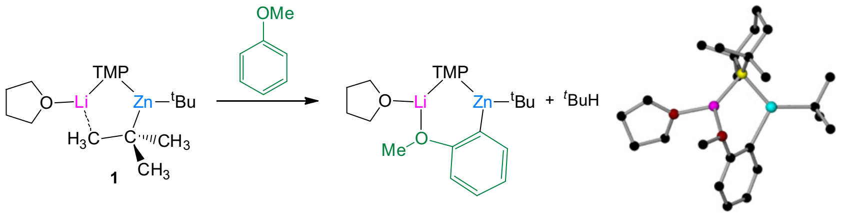
doi:10.1016/j.tetlet.2011.06.090



Scheme 1. AMM*Zn* of anisole and molecular structure of the metallated product $[(THF)LiZn(TMP)(C_6H_4\text{-}OMe)(tBu)]$[16] in the solid-state.

In a related reaction Knochel reported the selective acylation of **2** at the 3-position using the LiCl-complexed aluminate base $[(t\mathrm{Bu})NCH(i\mathrm{Pr})(t\mathrm{Bu})]_3Al{\cdot}3LiCl$[17] (25 °C, 2 h) in 68% yield.

Similarly the corresponding 3- and 4-methoxypyridines are also zincated selectively with **1** under mild conditions (0 °C, 2 h) to give **3a** and **4a** in 71% and 70% yields (entries 2 and 3), respectively, after I_2 quenching. The lithiation of these substrates has been previously investigated using mesityllithium (−23 °C, 3 h). Interestingly the lithiation promotes a different regioselectivity of substrate **3** which is metallated exclusively at the 2-position[19] to give the methylsulfanyl compound in 82% yield. Our results are more consistent with studies on 3-substituted pyridyl systems where the directing *ortho* group (DoG) is a carboxylate[27] or an *o*-tetrahydropyran-2-oxyl (O-THP)[28] group. In these cases, lithiation occurs at the 4-position of the pyridyl system rather than the 2-position (Scheme 2).

In pyridine itself, the relative acidities around the ring are 700:72:1 (4:3:2 positions).[29] The position next to the nitrogen is considered least acidic because the sp^2 lone pair on the nitrogen has an anti-bonding interaction with the C–Li bond. It is conceivable that our results reflect a similar unfavourable interaction with the C–Zn bond. Viewed in this light, the results of mesityllithium may be seen as more unusual (it may also be that the 2-position is the initial site of deprotonation in all cases but the resulting high energy species migrates to a lower energy 4-metallated species under our conditions).

Turning to pyridine (**5**), Kondo and Uchiyama[9] previously reported the *C*-2 zincation of **5** with **1** at room temperature, which gave the 2-iodopyridine product in 76% yield. In our studies, repeating this reaction at 0 °C with a shorter reaction time of 1 h gave a different regioselectivity, namely, the 4-iodopyridine (**5a**) product in 50% yield after I_2 addition, suggesting that the C-4 zincated species is the kinetic product of this deprotonation reaction. Closely related temperature-dependent regioselectivities have been reported for the metallation of trifluoromethylbenzene by the sodium zincate $[(TMEDA)Na(TMP)Zn(t\mathrm{Bu})_2]$.[30]

The next class of heteroaromatics we investigated was the diazines[31]: specifically, pyrazine (**6**), pyrimidine (**7**) and pyridazine (**8**). While metallation of diazines with lithium bases such as LiTMP[32] has been previously reported, very low temperatures, short reaction times and a large excess of base (4 equiv) were required resulting in low product yields. Using **1**, pyrazine could be twofold deprotonated selectively at positions 2 and 5 affording product **6a** after I_2 trapping in 68% yield (0 °C, 2 equiv, 1 h, entry 5). Interestingly, only products of dimetallation were observed even when 1 equiv of base **1** was used. In a previous metallation study of pyrazine[21,20,23] a less environmentally friendly lithium cadmate base was found to deprotonate **6** to give both the mono- and di-iodinated products after I_2 trapping in 63% and a lower 58% yield, respectively. A better alternative for the selective mono-metallation of pyrazine was recently achieved using $TMP_2Mg{\cdot}2LiCl$ in the presence of $ZnCl_2$ at room temperature to give the mono-iodinated product in 71% yield.

Deprotonation of pyrimidine (**7**) with **1** (entry 6) performed in THF at 0 °C provided mixtures of the 4-iodo and 5-iodo compounds in a 7:3 ratio after trapping with I_2. The selective 4-metallation of **7** was previously investigated using LiTMP in the presence of either $ZnCl_2$[23] or $CdCl_2$[21] to give exclusively the 4-iodo products in 57% and 71% yields, respectively. Contrasting with this, the use of the phosphazene base, *t*Bu-P4 and zinc iodide on pyrimidine gave the 5-metallated species exclusively (Scheme 3).[33]

We hypothesised that these observations could be rationalized by initial deprotonation at the position next to the nitrogens of the ring (either the 2- or 4-positions is possible but metallation at the 2-position would give a very high energy species) while subsequent migration to the less destabilized 5-position could then occur; how much of this is seen would depend on the rates of migration for the different species under the reaction conditions. This hypothesis will be investigated further.

The metallation of pyridazine (**8**) with **1** unfortunately failed as its reaction at 0 °C in THF gave a black solution with no recoverable products or starting materials (entry 7). However selective 3-metallation has been previously reported with LiTMP and $ZnCl_2$[23] to give the 3-iodo product in 66% yield. Alternatively, when reacted with LiTMP and $CdCl_2{\cdot}TMEDA$, mixtures of the 3-iodo and 4-iodo products were observed in an approximate 60:40 ratio.[21]

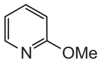
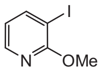
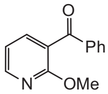
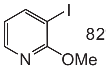
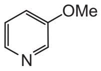
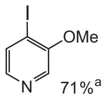
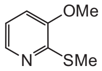
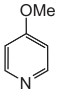
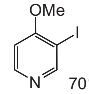
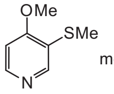
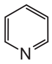
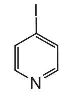
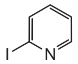
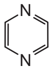
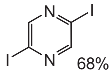
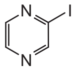
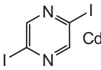
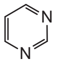
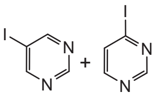
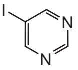
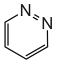
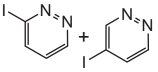
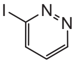
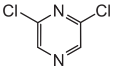
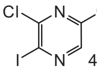
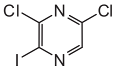
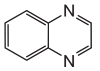
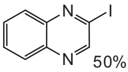
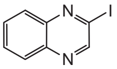
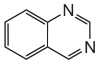
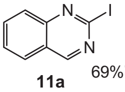
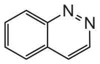
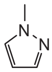
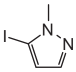
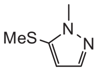
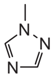
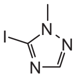
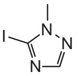
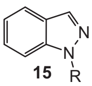
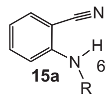
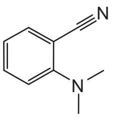
Reaction of **1** with the substituted pyrazine 2,6-dichloropyrazine (**9**) gave the expected 3-iodinated product (**9a**) in a moderate 46% yield after I_2 quenching. The yield of this reaction may have been adversely affected by a competing LiCl elimination reaction which has been noted before in a similar sodium zincate reaction with chlorobenzene.[34] Contrastingly, it is reported that **9** can be zincated quantitatively with $TMPZnCl{\cdot}LiCl$ and quenched with iodine to give **9a** in 90% yield.[24]

Direct zincation at the C2 position of quinoxaline (**10**) and quinazoline (**11**) can be accomplished by **1** (0 °C, 2 h, entries 9 and 10) which after trapping with I_2 gave the expected products **10a** and **11a** in 50% and 69% yields, respectively. This compares to the alternative precomplexation of **10** with $ZnCl_2$ followed by reaction with the lithium magnesiate, $TMP_2Mg{\cdot}2LiCl$, reported by Knochel[15] and Dong[22] which afforded **10a** in an almost quantitative 94% yield. However, we have found no other known alternative metallation procedures to access **11a**.

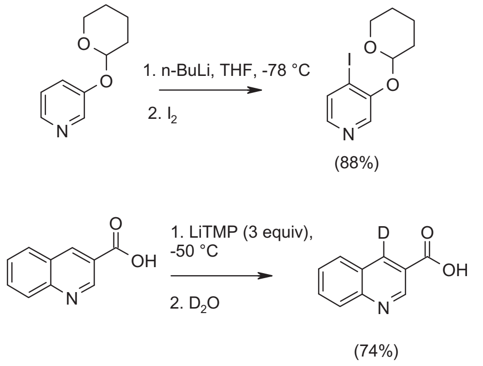
Significantly, like the attempted metallation of **8**, zincate **1** failed to metallate cinnoline (**12**). Reactions performed at low temperatures resulted in black solutions without recovery of the starting material or any iodinated products. ^1H NMR analysis of the metallated intermediates prior to iodine interception showed the presence of a complicated mixture of products in solution with several broad multiplets overlapping in the range 5.5– 4.5 ppm which suggests that decomposition of the metallated heterocycle with loss of aromaticity has likely taken place. It is interesting to contrast this with the use of $ZnCl_2$ and LiTMP which allows this deprotonation to occur in good yield; similarly, the use of the phosphazene base, *t*Bu-P4 and ZnI_2 with pyridazine did not lead to decomposition but gave the 4-metallated species. Again, this may suggest that initial deprotonation occurs at the 3-position and the resulting high energy metallated species may transform into the more stable 4-position metallated species (an α-effect is in operation between the two nitrogen lone pairs in this case and this may increase the destabilization of the metallated species).

Table 1

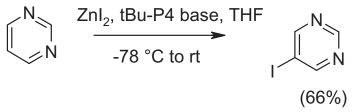
Range of *N*-heterocyclic substrate reactions with [Li(TMP)Zn(*t*Bu)$_2$] **1** and quenching with I$_2$, and the corresponding literature methods

Entry	Substrate	Product obtained using 'Li(TMP)Zn(*t*Bu)$_2$'	Comparative studies using alternative reagents	
1	 **2**	 **2a** 92%[a]	 68%[b] [(*t*Bu)NCH(*i*Pr)(*t*Bu)]$_3$Al.3LiCl	 82%[c] *i*Bu$_3$Al(TMP)Li
2	 **3**	 71%[a] **3a**	 mesityllithium 82%[d]	
3	 **4**	 70%[a] **4a**	 mesityllithium 84%[d]	
4	 **5**	 50%[e] **5a**	 Li(TMP)(*t*Bu)$_2$Zn 73%[f]	
5	 **6**	 68%[g] **6a**	 CdCl$_2$.TMEDA + LiTMP 63%[h] TMP$_2$Mg$_2$.LiCl + ZnCl$_2$ 71%[i]	 CdCl$_2$.TMEDA + LiTMP 58%[j]
6	 **7**	 30:70[e,k] mixture	 CdCl$_2$.TMEDA + LiTMP 71%[h] ZnCl$_2$.TMEDA + LiTMP 57%[l]	
7	 **8**	Decomposition products	 55% 41%[h] CdCl$_2$.TMEDA + LiTMP	 66%[m] ZnCl$_2$.TMEDA + LiTMP
8	 **9**	 46%[e] **9a**	 TMPZnCl.LiCl 90%[n]	
9	 **10**	 50%[e] **10a**	 TMP$_2$Mg.2LiCl + ZnCl$_2$ 94%[o]	
10	 **11**	 69%[e] **11a**		
11	 **12**	Decomposition products		
12	 **13**	 89%[p] **13a**	 TMPMgCl.LiCl 79%[q]	
13	 **14**	 98%[p] **14a**	 TMPZnCl.LiCl 98%[r]	
14	 **15** R = Me, CHO COOMe, Ph	 **15a** 60-80%[s] R = Me, CHO COOMe, Ph	 LDA 85%[t]	

(a) Li(TMP)Zn(*t*Bu)$_2$, 1 equiv, 25 °C, 1–2 h,(I$_2$). (b) TMPMgCl·LiCl + BF$_3$.OEt$_2$, 0 °C 60 h, (I$_2$).[17] (c) *i*Bu$_3$Al(TMP)Li, 2.2 equiv, −78 °C, 1 h, (I$_2$).[18] (d) Mesityllithium, −23 °C, 3 h, (MeSSMe 3 equiv).[19] (e) Li(TMP)(*t*Bu)$_2$Zn, 1 equiv, 0 °C, 1–2 h (I$_2$). (f) Li(TMP)Zn(*t*Bu)$_2$, 1 equiv, 25 °C, 3 h (I$_2$).[9] (g) Li(TMP)Zn(*t*Bu)$_2$, 2 equiv, 0 °C, 1 h (I$_2$). (h) CdCl$_2$.TMEDA + LiTMP, 25 °C, 2 h (I$_2$).[20,21] (i) TMP$_2$Mg·2LiCl + ZnCl$_2$, 25 °C, (I$_2$).[22] (j) CdCl$_2$·TMEDA + LiTMP, 2 equiv, 25 °C, 2 h (I$_2$).[21,20] (k) Determined by ^{1}H NMR spectroscopy. (l) ZnCl$_2$·TMEDA + LiTMP, 25 °C, 2 h, (I$_2$).[23] (m) ZnCl$_2$·TMEDA + LiTMP, reflux, 2 h, (I$_2$).[23] (n) TMPZnCl·LiCl, 1.1 equiv, 25 °C (I$_2$).[24] (o) TMP$_2$Mg·2LiCl + ZnCl$_2$, 25 °C, 2 h (I$_2$).[15] (p) Li(TMP)Zn(*t*Bu)$_2$, 2 equiv, 25 °C, 1 h (I$_2$). (q) TMPMgCl·LiCl, 25 °C, 1 h (MeSSMe).[25] (r) TMPZnCl·LiCl, 1.1 equiv, 25 °C, (I$_2$). (s) Li(TMP)Zn(*t*Bu)$_2$, 1 equiv, −78 °C to −40 °C 1–2 h. (t) LDA, 0–5 °C, MeI-78 °C.[26]



Scheme 2. Lithiation of 3-*O*-THP pyridine and quinoline-3-carboxylic acid.



Scheme 3. Reaction of *t*Bu-4P base and ZnI_2 with pyrimidine.

The literature precedent for this deprotonation clearly demonstrates that the generated metallated species are not too unstable to react without decomposition, so it is not clear to us why, under our conditions, decomposition occurs. It is possible that in this case the metallated species generated under our conditions falls apart rather than rearranging, but it may also be that our system is more prone to conjugate addition and subsequent further reaction.

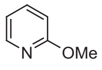
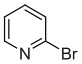
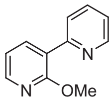
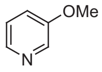
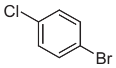
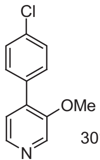
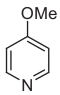
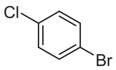
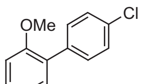
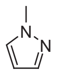
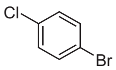
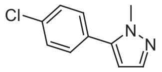
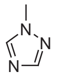
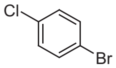
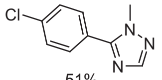
Moving on to five-membered heterocycles, both 1-methylpyrazole (**13**) and 1-methyl-1,2,4-triazole (**14**) were zincated selectively in the expected most acidic C5-position upon reaction with **1** under mild conditions (25 °C, 2 h, entries 12 and 13) to furnish the 5-iodo products **13a** and **14a** (89% and 98% yields, respectively) after I_2 trapping. Previously reported work using TMPMgCl·LiCl[25] has shown similar functionalisation of the C-5 position of **13** to give the methylsulfanyl product in 79% yield, while reacting **14** with TMPZnCl·LiCl (25 °C, 2 h) after I_2 quenching gives **14a** in excellent 98% yield. In summary for 5-membered heterocycles, α-lithiation is the preferred outcome of reaction with the lithiation occurring at the most acidic centre (typically next to the pyrrole-like nitrogen).

Finally, **1** was reacted with various 1-substituted indazoles in an attempt to furnish their 3-iodo derivatives (entry 14), however, instead we isolated the product of ring-opening, the 2-alkylbenzonitrile compounds **15a** in 60–80% yields. This result demonstrates the instability of the metallated intermediate that even at low temperatures (−78 °C) undergoes ring-opening to the more energetically stable compound **15a**. Precedent exists in the literature for a similar reaction with 1-methylindazole and LDA that after MeI quench gave the similar 2-dimethylaminobenzonitrile compound in 85% yield.[26]

Overall zincate **1** offers an alternative deprotonation method that in some cases is more practical (see typical procedure) and higher yielding than precedented literature methods (Table 1, entries 1, 5, 12 and 13). In most instances the quenched products show the same regioselectivity as the reported alternative bases; however, in a few select occasions a different metallation pattern is observed (Table 1, entries 2, 4 and 10).

In order to evaluate the full synthetic utility of these zincated intermediates as precursors in Negishi cross-coupling reactions to generate unsymmetrical bis-aryls, we carried out test reactions on five of the metallated substrates. Reactions of 2-, 3- and 4-methoxypyridine were attempted under palladium catalysis using $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) and 2-bromopyridine or 1-bromo-4-chlorobenzene as coupling partners. The reactions were heated to 100 °C in THF with microwave irradiation to give the bis-aryl compounds **2b**, **3b** and **4b** (Table 2, entries

Table 2
Metallation/cross-coupling results of selected substrates with base **1**

Entry	Substrate	Coupling partner	Catalyst/conditions	Product/yield[a]
1	 **2**		$PdCl_2$(dppf), 2.5 mol %, 100 °C, 10 min	 75% **2b**
2	 **3**		$PdCl_2$(dppf), 10 mol %, 110 °C, 10 min	 30% **3b**
3	 **4**		$PdCl_2$(dppf), 10 mol %, 110 °C, 10 min	 41% **4b**
4	 **13**		$PdCl_2$(dppf), 2.5 mol %, 100 °C, 10 min	 67% **13b**
5	 **14**		Pd[P(*t*Bu)$_3$]$_2$, 2.5 mol %, 100 °C, 10 min	 51% **14b**

[a] Isolated, analytically pure product.

1, 2 and 3) in isolated yields of 75%, 30% and 41%, respectively. Similarly the two five-membered ring heterocycles **13** and **14** (Table 2 entries 4 and 5) were also subjected to palladium-catalysed cross-coupling reactions under similar conditions to give the corresponding bis-aryl products **13b** and **14b** in 67% and 51% yields, respectively.

In summary, we have quantified the chemoselective deprotonative zincation reactions of a range of *N*-based heteroaromatic compounds using the known lithium zincate base [Li(TMP)Zn(*t*Bu)$_2$] **1**. In interesting cases it offers routes to different regioselectivity and higher yielding reactions compared with previous metallation methods described in the literature (whether using conventional organolithium reagents or mixed-metal bases). We have also demonstrated that the relative stability of the organometallic intermediates formed allows palladium-catalysed cross-coupling reactions to be performed successfully, without the need for an additional transmetallation step enabling the synthesis of unsymmetrical bis-aryl products.

Preparation of [Li(TMP)Zn(*t*Bu)$_2$] 1

In a vial under a N_2 atmosphere $ZnCl_2$ (54 mg, 0.4 mmol) was dissolved in THF (1 mL) and cooled to −50 °C. Next *t*BuLi (0.56 mL of a 1.7 M solution in pentane, 0.8 mmol) was added dropwise and the solution was allowed to stir at −50 °C for 40 min. In a separate vial containing TMPH (0.68 mL, 0.4 mmol) and THF (1 mL), *n*BuLi (0.25 mL of a 1.6 M solution in hexane, 0.4 mmol) was added dropwise at −50 °C and the solution was allowed to stir for 40 min reaching room temperature. Next the LiTMP solution was introduced to the in situ *t*Bu$_2$Zn solution at −50 °C and the reaction was allowed to stir for 30 min and warmed gradually to 0 °C.[35] The resultant light yellow solution was further reacted with various heterocyclic substrates.[36]

Typical iodination procedure

[Li(TMP)Zn(*t*Bu)$_2$] **1** was prepared on a 0.4 mmol scale in THF. To this solution 2-methoxypyridine (0.042 mL, 0.4 mmol) was added and the resultant light orange reaction allowed to stir at room temperature for 2 h. Next, the solution was cooled to 0 °C and quenched with I_2 (508 mg, in 1 mL THF) and allowed to stir for 1 h. A 10% solution of $Na_2S_2O_3$ was added until bleaching and the product extracted with CH_2Cl_2 (3×1 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by SiO_2 chromatography using heptane/CH_2Cl_2 as eluent (20:80 → 40:60) to give 3-iodo-2-methoxypyridine (**2a**) as a colourless oil (87.1 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.00 (s, 3H) 6.65 (dd, *J* = 7.61, 4.88 Hz, 1H) 8.03 (dd, *J* = 7.61, 1.76 Hz, 1H) 8.13 (dd, *J* = 4.88, 1.76 Hz, 1H).

Typical cross-coupling procedure

[Li(TMP)Zn(*t*Bu)$_2$] **1** was prepared on a 0.4 mmol scale in THF. To this, 1-methylpyrazole (**13**) (0.017 mL, 0.2 mmol) was added and the resultant light yellow solution was allowed to stir at room temperature for 2 h. This solution was then transferred to a THF (1 mL) solution of $PdCl_2$(dppf) (7.3 mg, 2.5 mol%) and 1-bromo-4-chlorobenzene (38.3 mg, 0.2 mmol) to give a heterogeneous orange solution. The mixture was then reacted in a Biotage initiator 8 microwave reactor at 100 °C for 10 min. The reaction was quenched with saturated NH_4Cl solution (2 mL) and extracted with CH_2Cl_2 (3×1 mL). The organic fractions were combined and dried by passing through a phase separator cartridge with a hydrophobic frit and the solvent removed under reduced pressure. The residue was purified by column chromatography using a 4 g silica cartridge and EtOAc/heptane 40:60 as eluent to give 5-(4-chlorophenyl)-1-methylpyrazole (**13b**) as a light yellow oil (25.9 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.88 (s, 3H) 6.30 (d, *J* = 1.95 Hz, 1H) 7.33–7.38 (m, 2H) 7.42–7.47 (m, 2 H) 7.51 (d, *J* = 1.95 Hz, 1H).

Acknowledgements

We thank the EPSRC and the University of Strathclyde for the generous sponsorship of this research (through the award of a Strathclyde Knowledge Transfer Account Research Exploitation Partnership).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.090.

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35. Low temperatures (−50 °C) are required during the preparation of 1 in order to avoid decomposition of the reactive organolithium reagents employed (*t*BuLi, *n*BuLi and LiTMP) with polar solvent THF.
36. Following the same experimental procedure described for **1**, the related *n*-butyl lithium zincate [Li(TMP)Zn(*n*Bu)$_2$] was prepared, however, it showed a much weaker metalating ability than **1**.