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Homoleptic Zincate-Promoted Room-Temperature Halogen–Metal Exchange of Bromopyridines

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Abstract: Homoleptic lithium tri- and tetraalkyl zincates were reacted with a set of bromopyridines. Efficient and chemoselective bromine–metal exchanges were realized at room temperature with a substoichiometric amount of nBu$_4$ZnLi$_2$·TMEDA reagent (1/3 equiv; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine). This reactivity contrasted with that of tBu$_4$ZnLi$_2$·TMEDA, which was inefficient below one equivalent. DFT calculations allowed us to rationalize the formation of N···Li stabilized polypyridyl zincates in the reaction. The one-pot difunctionalization of dibromopyridines was also realized using the reagent stoichiometrically. The direct creation of C–Zn bonds in bromopyridines enabled us to perform efficient Negishi-type cross-couplings.

Keywords: bromopyridines · cross-coupling · halogen–metal exchange · lithium · zinc

Introduction

Bromopyridines are highly important compounds due to their unique reactivity opening the way to numerous functionalizations. Indeed the C–Br bonds can be involved in metal-catalyzed cross-couplings and undergo bromine–lithium exchange reactions. Bromine–lithium exchange requires very low temperatures (typically −78 to −100 °C) to avoid side reactions, such as nucleophilic addition of the alkyllithium reagent, isomerization, dimerization, or pyridyne formation.[1] Among recently reported non-cryogenic alternatives,[2] organozincates are promising reagents allowing switchable selectivities by modifying substituents around the metal center and concomitant creation of a C–Zn bond immediately available for further Negishi-type cross-coupling reactions.[3]

Homoleptic polyalkylzincates (all substituents identical) are attractive reagents, since they can be easily prepared and should be able to transfer several reactive groups and consequently be used in substoichiometric amounts. The compound tBu$_4$ZnLi$_2$,[4] which has been reported by Uchiyama and co-workers to be highly chemoselective for iodine or bromine exchange in the aromatic series, was reacted only in stoichiometric amounts and its reactivity was not studied in the pyridine series. Curiously, nBu$_3$ZnLi and nBu$_4$ZnLi$_2$ generated from the safer nBuLi have been less studied, probably due to their strong propensity to transfer the butyl chain to the electrophile during the quenching step.[5] The search for more applicable metalation methodology in the pyridine series remains a challenge; hence we decided to investigate the reactivity of lithium alkylzincates toward a range of bromopyridines.

Results and Discussion

The lithium-zinc reagents were prepared following two procedures: by reacting the alkyllithium either with 1) commercially available nBu$_2$Zn [Eq. (1)] or 2) with weakly hygro-

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scopic $ZnCl_2$·TMEDA[6] (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) [Eq. (2)].

$$n\mathrm{Bu_2Zn} + n\mathrm{BuLi}\ (x\ \text{equiv}),\ x = 1,2 \xrightarrow[\text{then } 0^\circ\mathrm{C},\ 30\ \text{min}\ \text{then RT}]{\text{toluene}\ -15^\circ\mathrm{C},\ 5\ \text{min}} n\mathrm{Bu}_{(x+2)}\mathrm{ZnLi}_x \quad (1)$$

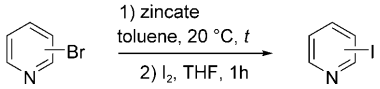
$$\mathrm{ZnCl_2}\cdot\mathrm{TMEDA} + \mathrm{RLi}\ (y\ \text{equiv}),\ \mathrm{R} = n\mathrm{Bu},\ t\mathrm{Bu},\ y = 3,4 \xrightarrow[0^\circ\mathrm{C}\ \text{then RT}]{\text{toluene}} \mathrm{R}_y\mathrm{ZnLi}_{(y-2)}\cdot\mathrm{TMEDA} + 2\ \mathrm{LiCl} \quad (2)$$

Before investigating the metalation ability of the reagents, the zincate nature of $n\mathrm{Bu_3ZnLi}$·TMEDA and $n\mathrm{Bu_4ZnLi_2}$·TMEDA was checked.[4b, 7] The reagents were thus prepared in C_6D_6/cyclohexane according to Equation (2) and studied by ^{1}H and ^{13}C NMR spectroscopy.[8] Relevant chemical shifts of the lithium–zinc mixtures and their components are collected in Table 1.

Compared with those of *n*BuLi (Table 1, entry 1) and TMEDA (entry 2), the ^{1}H NMR spectra of the zinc-containing reagents were profoundly modified. The formation of the *n*BuLi·TMEDA dimer resulted in a slight shielding of the TMEDA methylene proton signal (entry 3). When *n*BuLi was treated with $ZnCl_2$·TMEDA (1/3 equiv), the α-proton signal was downshifted from −0.94 to −0.18 ppm as a consequence of the metal electronegativity increase during the lithium–zinc transmetalation (entry 4). When $ZnCl_2$·TMEDA (1/4 equiv) was added, the *n*BuZn α proton signal was significantly upshifted (from −0.18 to −0.28 ppm), in agreement with a metal electronegativity decrease by reaction of the metal center with the additional butyl chain (entry 5). The TMEDA signals were found dramatically shielded in $n\mathrm{Bu_3ZnLi}$·TMEDA and $n\mathrm{Bu_4ZnLi_2}$·TMEDA, in particular the methylene protons (from 2.05 to 1.37 ppm). Such chemical shifts indicated a profound change in coordination and were characteristic of TMEDA-chelated metal[9] (entries 4 and 5). Taking into account the identical TMEDA shifts for both reagents, a similar coordination mode was likely. Although less sensitive, ^{13}C NMR spectra displayed signals matching the ^{1}H NMR spectra. Indeed the carbon linked to the metal was deshielded upon addition of $ZnCl_2$·TMEDA (entries 4 and 5). It is worth mentioning that no residual *n*BuLi or *n*BuLi-TMEDA signals were detected in the reactions with 1/3 and 1/4 equivalents of $ZnCl_2$·TMEDA (entries 4 and 5), indicating the complete consumption along the process and making likely single species instead of dissociated zinc and lithium compounds. Additionally, when *n*BuLi was treated with 1/5 equivalents of $ZnCl_2$·TMEDA, besides the signals obtained in for the reaction with 1/4 equivalents, signals corresponding to unreacted *n*BuLi appeared, indicating that the formed species could not accept another butyl chain. In summary, the NMR analyses supported the formation of zincate species $n\mathrm{Bu_3ZnLi}$·TMEDA and $n\mathrm{Bu_4ZnLi_2}$·TMEDA.

Zincation of bromopyridines: The reactivity of the reagents toward 2- and 3-bromopyridines was next investigated under various conditions (Table 2). In preliminary experiments with 3-bromopyridine (**1**), $n\mathrm{Bu_3ZnLi}$ was found unreactive at −78 °C in tetrahydrofuran (THF) whatever the stoichiometry, and increase of the temperature led to degradation. In contrast, the exchange proceeded chemoselectively in toluene at room temperature with $n\mathrm{Bu_3ZnLi}$ or $n\mathrm{Bu_3ZnLi}$·TMEDA, but incomplete conversions were obtained (Table 2, entries 1 and 2). The metalation with $n\mathrm{Bu_4ZnLi_2}$ or $n\mathrm{Bu_4ZnLi_2}$·TMEDA was found particularly efficient, even with 1/3 equiv of the reagents (entries 3 and 4).[10] The presence of TMEDA in the reagent significantly improved the exchange, exclusively affording compound **1a**

Table 2. Conditions screening for zincation–iodination of bromopyridines.[a]



1, 3-Br
2, 2-Br

1a, 3-I
2a, 2-I

	BrPy	Zincate (equiv)	*t* [h]	BrPy [%][b]	**1a** or **2a** [%][b]
1	**1**	$n\mathrm{Bu_3ZnLi}$ (1)	2	7	86
2	**1**	$n\mathrm{Bu_3ZnLi}$·TMEDA (1)	2	12	88
3	**1**	$n\mathrm{Bu_4ZnLi_2}$ (1/3)	1	8	72
4	**1**	$n\mathrm{Bu_4ZnLi_2}$·TMEDA (1/3)	0.5	0	>95 (75)
5	**2**	$n\mathrm{Bu_4ZnLi_2}$ (1/3)	1	0	>95 (78)
6	**2**	$n\mathrm{Bu_4ZnLi_2}$·TMEDA (1/3)	1	0	>95 (77)
7	**1**	$n\mathrm{Bu_4ZnLi_2}$·TMEDA (1/4)	3	50	50
8	**2**	$n\mathrm{Bu_4ZnLi_2}$·TMEDA (1/4)	3	6	75(60)
9	**1**	$t\mathrm{Bu_4ZnLi_2}$·TMEDA (1)	0.5	0	70
10	**2**	$t\mathrm{Bu_4ZnLi_2}$·TMEDA (1)	1	0	60[c]
11	**1**	$t\mathrm{Bu_4ZnLi_2}$·TMEDA (1/3)	0.5	23	50[c]
12	**2**	$t\mathrm{Bu_4ZnLi_2}$·TMEDA (1/3)	1	4	35[c]

[a] Reaction performed on 3 mmol of BrPy. [b] Conversions and yields estimated by ^{1}H NMR spectroscopy. Isolated yields in brackets. [c] Important material loss was observed due to degradation.

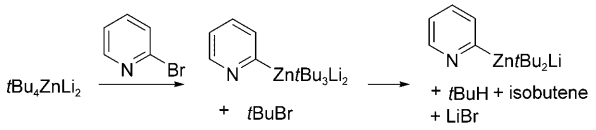
Table 1. ^{1}H and ^{13}C NMR chemical shifts of the lithium–zinc mixtures and their components.[a]

	Putative species	^{1}H NMR *n*Bu (H_α)	TMEDA (CH_3)	TMEDA (CH_2)	^{13}C NMR *n*Bu (C_α)	*n*Bu (C_β)	*n*Bu (C_δ)	*n*Bu (C_γ)	TMEDA (CH_3)	TMEDA (CH_2)
1	$(n\mathrm{BuLi})_6$	−0.91	–	–	12.2	31.6	32.0	13.8	–	–
2	TMEDA	–	2.10	2.27	–	–	–	–	46.0	58.6
3	$(n\mathrm{BuLi}\cdot\mathrm{TMEDA})_2$	−0.94	2.12	2.05	12.8	34.9	36.4	14.5	46.6	57.6
4	$n\mathrm{Bu_3ZnLi}$·TMEDA	−0.18	1.88	1.37	13.3	31.3	32.3	14.2	46.0	57.0
5	$n\mathrm{Bu_4ZnLi_2}$·TMEDA	−0.28	1.87	1.37	13.0	31.4	32.3	14.4	46.0	57.0

[a] Performed in C_6D_6–cyclohexane at 20 °C (300 and 75 MHz for ^{1}H and ^{13}C spectra, respectively).

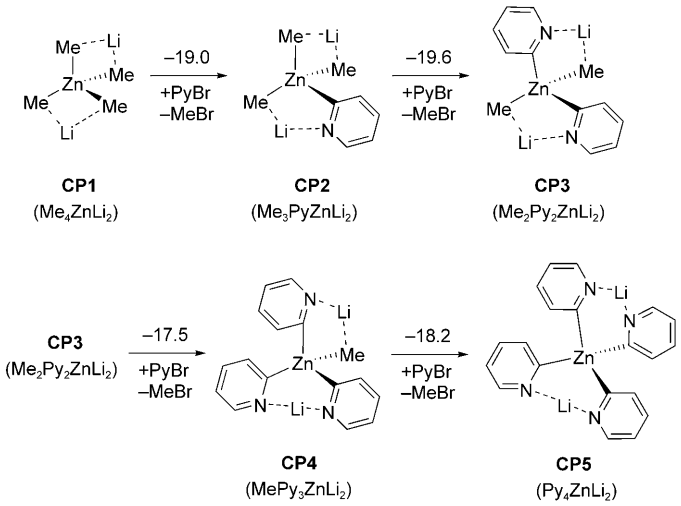
(75% isolated yield) in short reaction time (entry 4). In a separate experiment, LiCl-containing nBu$_4$ZnLi$_2$ was prepared from ZnCl$_2$ and experiment of from entry 3 was repeated. Similar conversion and yield were obtained indicating that LiCl had no effect on the reaction as expected from the low solubility of this salt in toluene. Excellent conversions and yields were also obtained with 2-bromopyridine (**2**) regardless of the presence of TMEDA in the reagent (entries 5 and 6).

An additional decrease of reagent amount (1/4 equiv) while not allowing to complete the reactions led to **1a** and **2a** in 50 and 75% yields, respectively (Table 2, entries 7 and 8). This is in agreement with the transfer of three butyl ligands from the tetrabutylzincate. The tBu$_4$ZnLi$_2$·TMEDA reagent was also used for comparison, and gave a complete exchange with notable amount of degradation products in contrast with nBu$_4$ZnLi$_2$·TMEDA when used stoichiometrically (entries 9 and 10). Another important discrepancy was the inability of tBu$_4$ZnLi$_2$·TMEDA to complete the reaction under substoichiometric conditions (entries 11 and 12). Such a sluggish reaction probably results of zincate tBu groups consumption by formed tBuBr to generate isobutene (a well-known reaction between tBuLi and tBuBr), making these ligands unavailable for the exchange reaction (Scheme 1).



Scheme 1. Plausible pathway for *tert*-butylzincate consumption.

To get a better understanding of the multiple zincation of 2-bromopyridine with Bu$_4$ZnLi$_2$, we carried out DFT calculations using Me$_4$ZnLi$_2$ as a model compound (Scheme 2). Coordination of lithium by TMEDA was not computed at this stage. An alkyl group on zincate (**CP1**) is exchanged to a pyridyl group to give a heteroleptic zincate (**CP2**) and alkyl bromide with considerable energy gain (alkyl = Me, 19.0 kcal mol^{-1} at the B3LYP/631SVPs level[11]). The calculation clearly showed that the pyridyl-coordinated zincate is thermodynamically much more stable than the (homo)alkyl-coordinated zincate thanks to creation of the stable N–Li bond favored in non-coordinating toluene. Therefore, the more pyridine coordinates to the zincate, the more the resultant zincate is stabilized. Based on these calculations, we consider that the zincation reactions of bromopyridines with a catalytic amount of tetraalkylzincate proceeds smoothly to produce tripyridyl (RPy$_3$ZnLi$_2$) or tetrapyridyl (Py$_4$ZnLi$_2$) zincates, depending on the character of the resultant zincates, such as solubility or reactivity (Table 2, entries 5, 6, and 8). The solubility issue is consistent with our observations since precipitation of the reaction medium occurred during the exchange process. From these calculations, the absence of reactivity in THF could be rationalized by a competitive coordination of lithium impeding N–Li interactions.

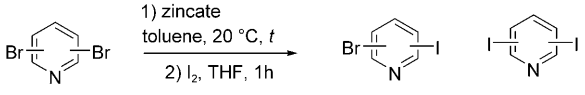


Scheme 2. Ligand exchange reaction of Me$_n$Py$_{4-n}$ZnLi$_2$. Energy changes (ΔE_0) in kcal mol^{-1} at the B3LYP/631SVPs level.[11]

Zincation of dibromopyridines: After having demonstrated the exchange chemoselectivity with tetrabutylzincates on **1** and **2** we investigated the possible scope extension with dibromopyridines. Thus substrates **3**, **4**, and **5** were reacted with zincates under various conditions with the aim to control both mono and dizincation at room temperature (Table 3). When 2,6-dibromopyridine (**3**) was treated with nBu$_4$ZnLi$_2$, a clean exchange occurred giving exclusively the monozincation product **3a** (entry 1). An extended reaction time (3.5 h) led reaction to completion with the quantitative formation of **3a** without any trace of diiodo compound **6a** (entry 2). In contrast, reaction with nBu$_4$ZnLi$_2$·TMEDA showed a notable effect of TMEDA that favored the formation of **6a**. An increase of base amount up to stoichiometry produced **6a** in high yield as a single product (entry 5). This exchange selectivity in **3** has been studied with nBuLi by Gilman,[1a] Newkome,[1b] and later by Cai.[1c] Cai et al. found that, even at low temperatures, the selectivity was hardly controlled leading to a mixture of 2-lithio-6-bromopyridine, 2,6-dilithiopyridine as well as pyridine deprotonation products. Control of monolithiation could be achieved by precipitation of the monolithiopyridine in diethylether at −78 °C. Thus our room-temperature zincation is a useful methodology, the reaction being driven easily toward mono- or dizincation by changing ligand and stoichiometry. The same set of conditions was applied to 3,5-dibromopyridine (**4**).

The use of nBu$_4$ZnLi$_2$, and nBu$_4$ZnLi$_2$·TMEDA favored the monozincation (Table 3, entries 6–8) when used in substoichiometric amount (1/3 equiv). By comparing with results obtained given in Table 3 entry 2 with **3**, the bromine at C-3 was less easily exchanged here, since reaction with nBu$_4$ZnLi$_2$ was incomplete after 4 h of reaction. This was in agreement with the weaker activation by the azomethine

Table 3. Zincation–iodination of dibromopyridines.[a]



3, 2,6-Br_2
4, 3,5-Br_2
5, 2,5-Br_2

3a, 2-Br-6-I
4a, 3-Br-5-I
5a, 2-Br-5-I
5b, 5-Br-2-I

6a, 2,6-I_2
7a, 3,5-I_2
8a, 2,5-I_2

	BrPy	Zincate (equiv)	t [h]	BrPy [%][b]	Monoiodo [%][b]	Diiodo [%][b]
1	**3**	nBu$_4$ZnLi$_2$ (1/3)	1	32	**3a**, 68	**6a**, 0
2	**3**	nBu$_4$ZnLi$_2$ (1/3)	3.5	0	**3a**, >95	**6a**, 0
3	**3**	nBu$_4$ZnLi$_2$·TMEDA (1/3)	1.5	0	**3a**, 75	**6a**, 25
4	**3**	nBu$_4$ZnLi$_2$·TMEDA (1/2)	1.5	0	**3a**, 45	**6a**, 55
5	**3**	nBu$_4$ZnLi$_2$·TMEDA (1)	1.5	0	**3a**, 0	**6a**, >95
6	**4**	nBu$_4$ZnLi$_2$ (1/3)	1	25	**4a**, 64	**7a**, 11
7	**4**	nBu$_4$ZnLi$_2$ (1/3)	4	25	**4a**, 61	**7a**, 15
8	**4**	nBu$_4$ZnLi$_2$·TMEDA (1/3)	1	0	**4a**, 87	**7a**, 13
9	**4**	nBu$_4$ZnLi$_2$·TMEDA (1.5)	1.5	0	**4a**, 17	**7a**, 83
10	**4**	nBu$_4$ZnLi$_2$·TMEDA (2)	1	–	**4a**, 0	**7a**, >98
11	**5**	nBu$_4$ZnLi$_2$ (1/3)	1	12	**5a**, 8 **5b**, 80	**8a**, 0
12	**5**	nBu$_4$ZnLi$_2$ (1/3)	3.5	12	**5a**, 21 **5b**, 63	**8a**, 4
13	**5**	nBu$_4$ZnLi$_2$·TMEDA (1/3)	1	23	**5a**, 41 **5b**, 23	**8a**, 13
14	**5**	nBu$_4$ZnLi$_2$·TMEDA (1/3) + TMEDA (1)	1	35	**5a**, 37 **5b**, 0	**8a**, 28
15	**5**	nBu$_4$ZnLi$_2$·TMEDA (1) + TMEDA (1.5)	1	0	**5a**, 2 **5b**, 0	**8a**, 98
16	**5**	nBu$_4$ZnLi$_2$·TMEDA (1.5)	1	0	**5a**, 0 **5b**, traces	**8a**, >98

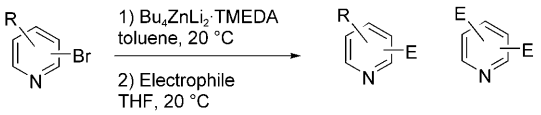
[a] Reaction performed on 3 mmol of BrPy. [b] Conversions and yields estimated by ^{1}H NMR spectroscopy.

bond of pyridine, which was more distant from the C–Br bond than in **3**. Completion was achieved by using nBu$_4$ZnLi$_2$·TMEDA. In contrast with **3**, TMEDA increased the mono/bis ratio leading to **4a** in 87% yield (entry 8). Dizincation was obtained cleanly thanks to an increase to two equivalents of nBu$_4$ZnLi$_2$·TMEDA, affording **7a** quantitatively (entry 10). The control of regioselectivity in 2,5-dibromopyridine (**5**) was more challenging due to the ease of migration of the halogen at C-5 to the C-2 position, leading to a more stable derivative, a well-known process with organolithium reagents.[1d,2d] Reaction with nBu$_4$ZnLi$_2$ (1/3 equiv) preferentially zincated the C-2 position (product **5b**, 80%) with 8% of zincation at C-5 (entry 11). Extension of the reaction time to 3.5 h to complete the reaction resulted in an increase of zincation at C-5 (entry 12). Attempts to optimize the formation of **5a** by additional increase of reaction time up to 12 h only gave unidentified degradation products. TMEDA also had an impact on the reaction pathway, since nBu$_4$ZnLi$_2$·TMEDA (1/3 equiv) reversed the C-2/C-5 ratio favoring zincation at C-5 with concomitant dizincation (entry 13). It was thought that TMEDA could help in a better control of C-5 zincation. Thus an additional amount (1 equiv) was added to the reagent and C-2 zincation was totally suppressed leading to **5a** and increased amount of dizincation product **8a** (entry 14). Although it was possible to control the C-2/C-5 ratio we were unable to avoid dizincation, and attempts were made to obtain it exclusively. Success was obtained by using two reagents: 1) nBu$_4$ZnLi$_2$·TMEDA (1 equiv) with TMEDA (1.5 equiv) (entry 15), and 2) 1.5 equivalents of nBu$_4$ZnLi$_2$·TMEDA (entry 16), the latter giving the best selectivity and producing **8a** quantitatively.

Reaction of pyridylzincates with electrophiles: As new tools were now available for room-temperature zincation of bromo- and dibromopyridines giving access to mono and bifunctional derivatives, we investigated further the scope of the methodology by reacting a set of bromopyridines and analogues and trapping the zincates with several electrophiles (Table 4).

The substrates were functionalized in moderate to excellent yields depending on the electrophile used. The iodine-trapping gave the best results and generally excellent yields of iodopyridines. Aldehydes were converted into the corresponding pyridylcarbinols in poor to acceptable yields. Alcohols resulting from the reduction of aldehydes were always isolated besides the target products. The pyridylzinc intermediates themselves or the in situ formed metal alkoxides could be responsible of such a reduction.[12] It is worth noting that no product arising from zincate nBu-ligand addition to the carbonyl bond was observed indicating that the pyridyl group was exclusively transferred. Dibromopyridines were monofunctionalized in moderate yields. The deuteration experiments gave exclusively compounds **3c** and **4b** with full deuterium content as an additional proof for quantitative zincation. The dizincated pyridines were trapped with anisaldehyde or PhSSPh giving the new diol **6b** and sulfide **7b**. All synthetically useful diiodopyridines **6a**, **7a**, and **8a** were isolated in excellent 85, 85 and 88% yields respectively. Bromopicolines **9** and **10** were metalated cleanly, leaving the acidic methyl group unaffected (entries 8 and 9). Bromomethoxypyridines **11** and **12** were also reacted efficiently (entries 10 and 11); no side deprotonation at the position adjacent to the methoxy group of the pyridine ring was observed. A good chemoselectivity was also obtained with 5-bromo-2-chloropyridine (**13**), since the C–Cl bond at C-2 was tolerated (entry 12). 3-Bromoquinoline (**14**) was also iodinated in acceptable yield (**14a**, 46%), but concomitant homocoupling occurred giving 3,3′-diquinoline (16%; entry 13). Our methodology is of interest, since very low temperatures are always needed for retention

Table 4. Zincation-functionalization of bromopyridines.[a]



R = H, Me, MeO, Cl, Ar, Br

	BrPy	Product	Yield [%]
1	**1**	**1a**: E = I[b]	75
		1b: E = PhCH(OH)[c]	25[d]
		1c: 4-MeOC$_6$H$_4$CH(OH)[e]	30[d]
2	**2**	**2a**: E = I[b]	78
		2b: E = Me$_3$Si[f]	60
		2c: E = 4-MeOC$_6$H$_4$CH(OH)[e]	50[d]
		2d: E = 4-CF$_3$C$_6$H$_4$CH(OH)[g]	25[d]
3	**3**	**3a**: E = I[b]	84
		3b: E = MeS	26
		3c: E = D[l]	31[m]
4	**4**	**4a**: E = I[b]	65
		4b: E = D[l]	50[m]
		4c: E = PhS[k]	40
5	**3**	**6a**, E = I[b]	85
		6b, 4-MeOC$_6$H$_4$CH(OH)[e]	20
6	**4**	**7a**, E = I[b]	85
		7b, E = PhS[k]	40
7	**5**	**8a**, E = I[b]	88
8	**9**	**9a**: E = I[b]	88
9	**10**	**10a**: E = I[b]	88
		10b: E = allyl[h]	25[i]
		10c: E = 4-MeOC$_6$H$_4$CH(OH)[e]	20[d]
10	**11**	**11a**: E = I[b]	60
11	**12**	**12a**: E = I[b]	80
		12b: E = MeS[j]	40
12	**13**	**13a**: E = I[b]	80
		13b: E = PhS[k]	20
13	**14**	**14a**: E = I[b]	46

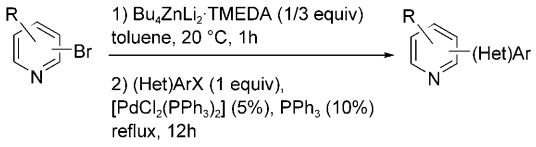
[a] Reaction performed on 3 mmol of bromopyridine. All zincations conducted with nBu$_4$ZnLi$_2$·TMEDA (1/3 equiv) for 1 h except for entries 5, 6, and 7 in which 1, 2, and 1.5 equiv of the reagent were used, respectively. [b] Electrophile = I$_2$. [c] Electrophile = PhCHO. [d] The aldehyde was partially consumed and the alcohol (reduction) was also observed. [e] Electrophile = 4-MeOC$_6$H$_4$CHO. [f] Electrophile = Me$_3$SiCl. [g] Electrophile = 4-F$_3$CC$_6$H$_4$CHO. [h] Electrophile = allyl bromide. [i] Volatile compound. [j] Electrophile = MeSSMe. [k] Electrophile = PhSSPh. [l] Electrophile = MeOD. [m] The crude ^{1}H NMR spectra showed exclusive formation of **3c** or **4b** with deuterium content > 98%.

of methyl side chains or C–Cl bonds using nBuLi as a metalating agent.[13]

Palladium-catalyzed cross-coupling of pyridylzincates: As mentioned in the introduction, besides applicability and chemoselectivity, the direct creation of a C–Zn bond on the heteroaromatic ring is of particular interest, since cross-couplings are possible avoiding the classical Li–Zn transmetalation.[14]

Several pyridylzincates prepared above were reacted with various aryl and heteroaryl halides under palladium catalysis (Table 5). As shown, the 2- and 3-*z*incated pyridines were coupled efficiently. Functional arylpyridines **10d**, **12c**, and **13c**, were obtained in good yields. The yield of **10d** was lowered by steric hindering effect of the methyl group at C-3. Bisheteroaromatic compounds were also obtained such as 2,2′-bipyridine **2f** and pyridylpyrimidine **13d**. The cross-coupling of 2,6-dizincated pyridine underwent the double cross-coupling affording dianisylpyridine **6c** in 41% yield. At this stage, the aim was to show the ability of pyridylzincates to give coupling products in a palladium catalyzed process, the reaction conditions (solvent, catalyst, ligands) have not been optimized yet.

Table 5. Palladium-catalyzed cross-coupling of zincated pyridines.[a]



BrPy	(Het)ArX	Product	(Het)Ar	Yield [%][b]
2			**2e** (3-MeOC$_6$H$_4$)	65
2			**2f** (6-MeO-2-Py)	58
10			**10d** (4-MeOC$_6$H$_4$)	46
12			**12c** (4-MeOC$_6$H$_4$)	63
13			**13c** (4-ClC$_6$H$_4$)	62
13			**13d** (5-pyrimidyl)	50
3[c]			**6c** (4-MeOC$_6$H$_4$)	41

[a] Reaction performed on 3 mmol of bromopyridine. [b] Isolated yields after column chromatography. [c] 1 equiv of nBu$_4$ZnLi$_2$·TMEDA was used.

Conclusion

In summary, we have shown the efficiency of nBu$_4$ZnLi$_2$·TMEDA for the chemoselective zincation of bromopyridines. The exchange was performed at room temperature using 1/3 equivalents of the reagent. DFT calculations clearly showed that, in the case of 2-bromopyridine, a stabilized tripyridyl zincate is involved in the process. This proved not possible with tBu$_4$ZnLi$_2$·TMEDA, owing to

probable consumption by *t*BuBr released during the exchange. This study also revealed a dramatic TMEDA effect on the selectivity of dibromopyridines zincation. While nBu$_4$ZnLi$_2$ gave mainly the monozincation, the use of 1–2 equivalents of nBu$_4$ZnLi$_2$·TMEDA promoted a clean dizincation. The efficiency of the zincation was assessed by quantitative trapping with iodine, giving useful iodopyridines in high yields, and palladium-catalyzed cross-couplings. This methodology is promising for the development of more applicable organometallic reagents (room temperature, low amount of reagents). Progress is still needed to optimize the interception yields with electrophilic reagents. This will be the subject of future work.

Experimental Section

Materials and methods: All reactions were performed under argon atmosphere. Toluene and THF were distilled over sodium/benzophenone and stored over sodium wire. TMEDA was distilled from CaH_2. Commercially available starting materials were used without further purification. Liquid chromatography separations were achieved on silica gel Merck-Geduran Si 60 (63–200 μm). NMR spectra were acquired on Bruker ARX-200 (200 and 50 MHz for ^{1}H and ^{13}C respectively), Bruker ARX-250 (250 and 62.5 MHz for ^{1}H and ^{13}C respectively) and Bruker AC-400 (400 and 100 MHz for ^{1}H and ^{13}C respectively) spectrometers. The chemical shifts (δ) are given in ppm relative to tetramethylsilane as an internal standard (for ^{1}H) or the central peak of the solvent signal (for ^{13}C). Coupling constants are given in Hz. NMR studies of the bases were performed on a Bruker AC-300 (300 and 75 MHz for ^{1}H and ^{13}C respectively) at 20 °C using *n*BuLi (2 mL of a 2 M solution in cyclohexane) with additional C_6D_6 (0.5 mL).

Preparation of ZnCl$_2$·TMEDA:[15] Anhydrous $ZnCl_2$ (20 g, 0.15 mol) was heated under vacuum with a heating 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, 0.30 mol) was then added slowly, and the mixture was stirred for 2 h at room temperature. The solvents were evaporated under vacuum, 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 ($\approx$37 g) as white needles. M.p. 176 °C (lit.[10] 176–177 °C); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.75 (s, 4H), 2.62 ppm (s, 12H).

Preparation of nBu$_3$ZnLi and nBu$_4$ZnLi$_2$: *n*BuLi (1.6 M hexanes solution, 0.63 mL, 1.0 mmol) (for nBu$_3$ZnLi) or *n*BuLi (1.6 M hexanes solution, 1.25 mL, 2.0 mmol) (for nBu$_4$ZnLi$_2$) was added to a stirred, cooled (−15 °C) solution of nBu$_2$Zn (1.0 M heptanes solution, 1.0 mL, 1.0 mmol) in dry toluene (3 mL). The mixture was stirred for 30 min at 0 °C before introduction of the bromopyridine substrate (*n* equiv) at 20 °C.

Preparation of nBu$_3$ZnLi·TMEDA and nBu$_4$ZnLi$_2$·TMEDA: *n*BuLi (1.6 M hexanes solution, 1.88 mL, 3.0 mmol) (for nBu$_3$ZnLi·TMEDA) or *n*BuLi (1.6 M hexanes solution, 2.5 mL, 4.0 mmol) (for nBu$_4$ZnLi$_2$·TMEDA) was added to a stirred, cooled (0 °C) solution of $ZnCl_2$·TMEDA (0.25 g, 1.0 mmol) in dry toluene (3 mL). The mixture was stirred for 30 min at 0 °C before introduction of the bromopyridine substrate (*n* equiv) at 20 °C.

Preparation of tBu$_4$ZnLi$_2$·TMEDA: *t*BuLi (1.7 M pentanes solution, 2.35 mL, 4.0 mmol) was added to a stirred, cooled (−15 °C) solution of $ZnCl_2$·TMEDA (0.25 g, 1.0 mmol) in dry toluene (3 mL). The mixture was stirred for 30 min at 0 °C before introduction of the bromopyridine substrate (*n* equiv) at 20 °C.

Typical procedure for monozincation of bromopyridines: The bromopyridine substrate (3.0 mmol) was added to a stirred suspension of nBu$_4$ZnLi$_2$·TMEDA (1.0 mmol) in toluene (3 mL) at 20 °C. After 0.5–3 h at room temperature, the reaction was quenched with an electrophile (I_2, PhCHO, 4-$CF_3C_6H_4CHO$, 4-$MeOC_6H_4CHO$, TMSCl, MeOD, MeSSMe, or PhSSPh) (4.0–8.0 mmol). The mixture was stirred for 1 h (for I_2) or 18 h (for the other electrophiles) before addition of an aqueous solution of ammonia (5 mL), aqueous saturated solution of $Na_2S_2O_3$ (5 mL) (if the electrophile was I_2) and extraction with EtOAc (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by chromatography on silica gel.

3-Iodopyridine (1a):[16] The standard protocol was applied to 3-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile: Yellow solid; m.p. 50–52 °C (lit.[16] 52–53 °C); yield: 0.46 g (75%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.85 (s, 1H) , 8.56 (d, J = 3.8 Hz, 1H) , 8.01 (d, J = 7.5 Hz, 1H), 7.07–7.13 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 155.8, 148.1, 144.2, 125.2, 93.6 ppm.

Phenyl(pyridin-3-yl)methanol (1b):[2a] The standard protocol was applied to 3-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and benzaldehyde (0.41 mL, 4.0 mmol) was used as electrophile. Beige solid; m.p. 65–67 °C (lit.[2a] 67–69 °C); yield: 0.14 g (25%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.41 (s, 1H), 8.28 (s, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.31 (m, 5H), 7.20 (dd, J = 7.6, 5.0 Hz, 1H), 5.78 (s, 1H), 5.03 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 147.8, 147.6, 143.2, 139.9, 135.4, 128.6, 127.5, 126.2, 123.4, 73.4 ppm.

(4-Methoxyphenyl)(pyridin-3-yl)methanol (1c):[17] The standard protocol was applied to 3-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and 4-methoxybenzaldehyde (0.50 mL, 4.0 mmol) was used as electrophile. Beige solid; m.p. 66–67 °C (lit.[17] 70 °C); yield: 0.19 g (30%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.38 (s, 1H), 8.23 (d, J = 4.1 Hz, 1H), 7.66 (dd, J = 7.9, 1.7 Hz, 1H), 7.13–7.24 (m, 3H), 6.82 (d, J = 8.7 Hz, 2H), 5.71 (s, 1H), 3.74 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 159.1, 147.8, 140.4, 135.8, 134.4, 127.9, 123.4, 114.0, 73.2, 55.2 ppm.

2-Iodopyridine (2a):[2a] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Yellow oil; yield: 0.47 g (77%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.37 (d, J = 1.7 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.24–7.38 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 150.6, 137.4, 134.8, 122.8, 118.0 ppm.

2-(Trimethylsilyl)pyridine (2b):[18] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and trimethylsilyl chloride (0.64 mL, 5.0 mmol) was used as electrophile. Yellow oil; yield: 0.27 g (60%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.70 (d, J = 4.2 Hz, 1H), 7.25–7.75 (m, 3H), 0.25 ppm (s, 9H); the ^{1}H NMR data are in accordance with those of the literature; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 168.2, 150.1, 133.8, 128.6, 122.6, −1.81 ppm.

(4-Methoxyphenyl)(pyridin-2-yl)methanol (2c):[19] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and 4-methoxybenzaldehyde (0.50 mL, 4.0 mmol) was used as electrophile. Yellowish solid; m.p. 124–126 °C; yield: 0.32 g (50%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.52 (d, J = 4.5 Hz, 1H), 7.59 (td, J = 7.7, 2.0 Hz, 1H), 7.24 (m, 2H), 7.13–7.18 (m, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.70 (s, 1H), 5.24 (br s, 1H), 3.76 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 161.4, 159.2, 147.9, 136.8, 135.5, 128.3, 122.3, 121.3, 113.9, 74.6, 55.2 ppm.

Pyridin-2-yl(4-(trifluoromethyl)phenyl)methanol (2d):[19] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h, and 4-trifluromethylbenzaldehyde (0.56 mL, 4.0 mmol) was used as electrophile. White solid; m.p. 66–68 °C; yield: 0.25 g (25%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.57 (d, J = 4.5 Hz, 1H), 7.65 (td, J = 7.6, 1.5 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.23 (dd, J = 7.0, 5.3 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 5.81 ppm (s, 1H); OH not seen; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 160.2, 148.1, 147.2, 137.1, 130.0 (d, J = 32.2 Hz), 127.3, 126.5 (d, J = 29.9 Hz), 125.5 (q, J = 3.8 Hz), 122.8, 121.3, 74.5 ppm.

2-Iodo-4-methylpyridine (9a):[20] The standard protocol was applied to 2-bromo-4-methylpyridine (0.34 mL, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Orange oil; yield: 0.58 g (88%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.19 (d, J = 5.0 Hz, 1H), 7.56 (s, 1H), 7.07 (d, J = 5.0 Hz, 1H), 2.28 ppm (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 150.0, 149.1, 135.4, 124.0, 118.2, 20.3 ppm.

2-Iodo-3-methylpyridine (10a):[21] The standard protocol was applied to 2-bromo-3-methylpyridine (0.34 mL, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Yellow oil; yield: 0.58 g (88%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.15 (d, J = 2.0 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.15 (dd, J = 7.1, 4.7 Hz, 1H), 2.38 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 147.7, 139.1, 136.7, 125.4, 122.8, 26.2 ppm.

2-Allyl-3-methylpyridine (10b): The standard protocol was applied to 2-bromo-3-methylpyridine (0.34 mL, 3.0 mmol) for 1 h, and allyl bromide (0.44 mL, 5.0 mmol) was used as electrophile. Highly volatile yellow oil; yield: 0.10 g (25%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.39 (dd, J = 4.7, 0.9 Hz, 1H), 7.41 (dd, J = 7.6, 0.7 Hz, 1H), 7.04 (dd, J = 7.6, 4.9 Hz, 1H), 6.05 (ddt, J = 17, 10, 6.4 Hz, 1H), 5.01–5.13 (m, 2H), 3.57–3.60 (m, 2H), 2.30 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 158.1, 146.9, 137.7, 135.1, 131.4, 121.5, 116.1, 40.4, 18.6 ppm; HRMS: $C_9H_{12}N$ $[M+H]^+$: calcd: 134.0964; found: 134.0968.

(4-Methoxyphenyl)(3-methylpyridin-2-yl)methanol (10c):[22] The standard protocol was applied to 2-bromo-3-methylpyridine (0.34 mL, 3.0 mmol) for 1 h, and 4-methoxybenzaldehyde (0.50 mL, 4.0 mmol) was used as electrophile. Yellow solid; m.p. 50–52 °C (lit.[22] 57–58 °C); yield: 0.14 g (20%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.46 (d, J = 4.5 Hz, 1H), 7.42 (d, J = 7.5 Hz, 1H), 7.12–7.19 (m, 3H), 6.79–6.84 (m, 2H), 5.95 (br s, 1H), 5.69 (s, 1H), 3.76 (s, 3H), 2.07 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 159.1, 158.2, 144.9, 138.5, 134.7, 130.4, 129.0, 122.6, 113.9, 72.0, 55.2, 17.9 ppm.

2-Iodo-3-methoxypyridine (11a):[23] The standard protocol was applied to 2-bromo-3-methoxypyridine (0.58 g, 3.0 mmol) for 4 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Beige solid; m.p. 54–56 °C (lit.[23] 56–57 °C); yield: 0.42 g (60%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.99 (dd, J = 4.6, 1.4 Hz, 1H), 7.20 (dd, J = 8.1, 4.6 Hz, 1H), 7.01 (dd, J = 8.1, 1.4 Hz, 1H), 3.91 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 155.2, 142.5, 123.5, 116.8, 111.7, 56.3 ppm.

2-Iodo-6-methoxypyridine (12a):[24] The standard protocol was applied to 2-bromo-6-methoxypyridine (0.38 mL, 3.0 mmol) for 4 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Yellowish solid; m.p. 43–45 °C (lit.[24] 44–45 °C); yield: 0.54 g (80%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.29 (dd, J = 7.3, 0.7 Hz, 1H), 7.17 (dd, J = 8.1, 7.4 Hz, 1H), 6.68 (dd, J = 8.1, 0.7 Hz, 1H), 3.91 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 163.4, 139.6, 127.5, 113.7, 109.8, 54.1 ppm.

2-Methoxy-6-(methylthio)pyridine (12b):[18] The standard protocol was applied to 2-bromo-6-methoxypyridine (0.38 mL, 3.0 mmol) for 4 h, and dimethyl disulfide (0.72 mL, 8.0 mmol) was used as electrophile. Yellow oil; yield: 0.18 g (39%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.38 (dd, J = 8.0, 7.6 Hz, 1H), 6.76 (dd, J = 7.6, 0.6 Hz, 1H), 6.40 (dd, J = 8.0, 0.6 Hz, 1H), 3.94 (s, 3H), 2.55 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 163.7, 157.2, 138.5, 113.6, 105.3, 53.3, 13.2 ppm.

2-Chloro-5-iodopyridine (13a):[24] The standard protocol was applied to 5-bromo-2-chloropyridine (0.59 g, 3.0 mmol) for 4 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Yellow solid; m.p. 97–99 °C (lit.[25] 97 °C) yield: 0.57 g (80%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.60 (d, J = 2.3 Hz, 1H), 7.92 (dd, J = 8.3, 2.3 Hz, 1H), 7.14 ppm (dd, J = 8.3, 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.7, 151.0, 146.8, 126.1, 90.7 ppm.

2-Chloro-5-(phenylthio)pyridine (13b):[25] The standard protocol was applied to 5-bromo-2-chloropyridine (0.59 mL, 3.0 mmol) for 4 h, and a solution of diphenyl disulfide (1.10 g, 5.0 mmol) in dry toluene (5 mL) was used as electrophile. Yellow oil; yield: 0.13 g (20%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.30 (d, J = 2.5 Hz, 1H), 7.51 (dd, J = 8.3, 2.5 Hz, 1H), 7.31–7.40 (m, 5H), 7.22 ppm (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 150.5, 149.8, 140.3, 133.3, 132.9, 132.0, 129.7, 128.2, 124.6 ppm.

3-Iodoquinoline (14a):[26] The standard protocol was applied to 3-bromoquinoline (0.42 mL, 3.0 mmol) for 4 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Beige solid; m.p. 42–44 °C (lit.[27] 45 °C); yield: 0.35 g (46%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 9.03 (d, J = 2.1 Hz, 1H), 8.54 (d, J = 1.9 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.69–7.77 (m, 2H), 7.53–7.59 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 155.6, 146.3, 143.7, 130.0, 129.9, 129.5, 127.4, 126.8, 89.8 ppm.

2-Bromo-6-iodopyridine (3a):[2a] The standard protocol using Bu_4ZnLi_2 as reagent was applied to 2,6-dibromopyridine (0.72 g, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. White solid; m.p. 147–148 °C (lit.[2a] 134 °C); yield: 0.72 g (84%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.18 ppm (dd, J = 7.8, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 140.8, 139.2, 133.9, 127.3, 115.7 ppm.

2-Bromo-6-(methylthio)pyridine (3b):[2a] The standard protocol was applied to 2,6-dibromopyridine (0.72 g, 3 mmol) for 1 h, and dimethyl disulfide (0.72 mL, 8.0 mmol) was used as electrophile. Yellow oil; yield: 0.16 g (26%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.31 (t, J = 7.7 Hz, 1H), 7.08–7.15 (m, 2H), 2.54 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 161.3, 141.6, 137.8, 122.9, 120.1, 13.5 ppm.

2-Bromo(6-[D])pyridine (3c):[2a] The standard protocol was applied to 2,6-dibromopyridine (0.72 g, 3.0 mmol) for 1 h, and [D_1]methanol (0.32 mL, 8.0 mmol) was used as electrophile. Yellow oil; yield: 0.15 g (31%) (>98% [D]); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.46–7.60 (m, 2H), 7.26 ppm (d, J = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 149.9 (t, J = 27.9 Hz), 142.3 (t, J = 1.9 Hz), 138.5, 128.3, 122.5 ppm.

5-Bromo-2-iodopyridine (5b): The standard protocol using Bu_4ZnLi_2 as reagent was applied to 2,5-dibromopyridine (0.73 g, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. 5-Bromo-2-iodopyridine (**5b**; 80%) was obtained in the non-separable mixture with 2-bromo-5-iodopyridine (**5a**; 8%). Data for **5b**:[27] ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.44 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.44 ppm (d, J = 8.4 Hz, 1H); data for **5a**:[28] ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.59 (s, 1H), 7.82 (dd, J = 8.3, 2.2 Hz, 1H), 7.29 ppm (d, J = 8.3 Hz, 1H);

3-Bromo-5-iodopyridine (4a):[29] The standard protocol was applied to 3,5-dibromopyridine (0.73 g, 3.0 mmol) for 1 h, and a solution of I_2 (1.27 g, 5.0 mmol) in dry THF (5 mL) was used as electrophile. Yellow solid; m.p. 114–116 °C (lit.[29] 117–118 °C); yield: 0.55 g (65%); ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.74 (d, J = 1.8 Hz, 1H), 8.62 (d, J = 1.6 Hz, 1H), 8.18 ppm (dd, J = 1.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 153.9, 149.4, 146.2, 121.1, 93.2 ppm.

3-Bromo(5-[D])pyridine (4b):[2a] The standard protocol was applied to 3,5-dibromopyridine (0.73 g, 3.0 mmol) for 1 h, and [D_1]methanol (0.32 mL, 8.0 mmol) was used as electrophile. Orange oil; yield: 0.24 g (50%) (>98% [D]); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.70 (d, J = 2.3 Hz, 1H), 8.54 (s, 1H), 7.82 ppm (d, J = 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 151.1, 147.8, 138.6, 124.9, 121.0 ppm.

3-Bromo-5-(phenylthio)pyridine (4c):[29] The standard protocol was applied to 3,5-dibromopyridine (0.73 g, 3.0 mmol) for 1 h, and diphenyl disulfide (1.10 g, 5.0 mmol) in dry toluene (5 mL) was used as electrophile. Orange liquid; yield: 0.23 g (29%); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.56 (br s, 1H), 8.46 (br s, 1H), 7.57–7.61 (m, 1H), 7.29–7.40 ppm (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 151.0, 147.8, 137.9, 134.0, 131.9, 129.5, 127.9, 123.9 ppm.

Typical procedure for dizincation of dibromopyridines: A solution of dibromopyridine substrate (1.0–2.0 mmol) in toluene (5 mL) was added to a stirred suspension of Bu_4ZnLi_2·TMEDA (2.0 mmol) in toluene (6 mL) at 20 °C. After 1–1.5 h at room temperature, the reaction was quenched with the electrophile (I_2, 4-MeOPhCHO or PhSSPh) (8 mmol). The mixture was stirred for 18 h before addition of an aqueous solution of ammonia (5 mL), aqueous saturated solution of $Na_2S_2O_3$ (5 mL) (if electrophile was I_2) and extraction with EtOAc (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by chromatography on silica gel.

2,6-Diiodopyridine (6a):[30] The standard protocol was applied to 2,6-dibromopyridine (0.48 g, 2.0 mmol) for 1.5 h, and a solution of I_2 (2.54 g, 10 mmol) in dry THF (10 mL) was used as electrophile. Yellow solid; m.p. 192–194 °C (lit.[30] 196–197 °C); yield: 0.55 g (84%); ^{1}H NMR

($CDCl_3$, 400 MHz): $\delta = 7.70$ (d, $J = 7.70$ Hz, 2H), 6.96 ppm (t, $J = 7.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 138.4$, 134.2, 116.2 ppm.

Pyridine-2,6-diylbis((4-methoxyphenyl)methanol) (6b): The standard protocol was applied to 2,6-dibromopyridine (0.48 g, 2.0 mmol) for 1.5 h, and 4-methoxybenzaldehyde (0.99 mL, 8.0 mmol) was used as electrophile. Yellow oil; yield: 0.14 g (20%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta =$ 7.56 (t, $J = 7.7$ Hz, 1H), 7.28 (d, $J = 8.7$ Hz, 4H), 7.09 (d, $J = 7.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 4H), 5.74 (s, 2H), 3.78 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 160.3$, 159.3, 137.7, 135.1, 128.3, 119.7, 114.0, 75.0, 55.3 ppm. HRMS: $C_{21}H_{21}NO_4Na$ $[M+Na]^+$: calcd: 374.1363; found: 374.1359.

2,5-Diiodopyridine (8a):[31] The standard protocol was applied to 2,5-dibromopyridine (0.32 g, 1.3 mmol) for 2 h, and a solution of I_2 (2.54 g, 10 mmol) in dry THF (10 mL) was used as electrophile. Yellow brown solid; m.p. 150–152 °C (lit.[31] 148–149.7 °C); yield: 0.38 g (88%); ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 8.58$ (d, $J = 2.2$ Hz, 1H), 7.60 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.50 ppm (d, $J = 8.2$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta =$ 156.7, 145.7, 136.5, 116.4, 93.1 ppm.

3,5-Diiodopyridine (7a):[32] The standard protocol was applied to 3,5-dibromopyridine (0.24 g, 1.0 mmol) for 1 h, and a solution of I_2 (2.54 g, 10.0 mmol) in dry THF (10 mL) was used as electrophile. Pink orange solid; m.p. 170–172 °C (lit.[32] 170–172 °C); yield: 0.28 g (85%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.75$ (d, $J = 1.8$ Hz, 2H), 8.35 ppm (t, $J = 1.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 154.2$, 151.4, 93.9 ppm.

3,5-Di(phenylthio)pyridine (7b):[33] The standard protocol was applied to 3,5-dibromopyridine (0.24 g, 1.0 mmol) for 1 h, and a solution of diphenyl disulfide (1.76 g, 8.0 mmol) in dry toluene (10 mL) was used as electrophile. Yellowish solid; m.p. 50–52 °C (lit.[33] 55 °C); yield: 0.12 g (40%); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.30$ (d, $J = 2.0$ Hz, 2H), 7.28–7.36 ppm (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 147.8$, 137.4, 134.6, 132.7, 132.4, 129.6, 128.2 ppm.

Typical procedure for the cross-coupling of pyridyl zincates: The bromopyridine (3.0 mmol) at 20 °C under argon was added to a stirred suspension of nBu$_4$ZnLi$_2$·TMEDA (1.0 mmol) in toluene (3 mL). After 1 h at room temperature, $[PdCl_2(PPh_3)_2]$ (0.15 mmol, 105 mg), PPh_3 (0.30 mmol, 76 mg), and the aromatic halide (3 mmol) were added. The mixture was refluxed for 12 h. After cooling, the mixture was treated with NH_4OH (5 mL) and filtered over a Celite pad. After extraction with EtOAc (20 mL), the organic phase was dried ($MgSO_4$) and evaporated. The residue was then purified by column chromatography.

2-(3-Methoxyphenyl)pyridine (2e):[34] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h and 3-iodoanisole (0.37 mL, 3.0 mmol) was used as aromatic halide. Pale yellow oil; yield: 0.36 g (65%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.66$ (dt, $J = 4.8$, 1.3 Hz, 1H), 7.67 (dd, $J = 4.9$, 1.5 Hz, 2H), 7.60–7.59 (m, 1H), 7.53 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.21–7.12 (m, 1H), 6.94 (dd, , $J =$ 8.2, 2.6, 0.9 Hz, 1H), 3.84 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta =$ 160.1, 157.1, 149.5, 140.8, 136.7, 129.7, 122.2, 120.6, 119.3, 115.0, 112.0, 55.3 ppm.

6-Methoxy-2,2′-bipyridine (2f):[35] The standard protocol was applied to 2-bromopyridine (0.29 mL, 3.0 mmol) for 1 h and 2-bromo-6-methoxypyridine (0.38 mL, 3.0 mmol) was used as aromatic halide. Yield : 0.33 g (58%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.66$ (d, $J = 5.6$ Hz, 1H), 8.40 (d, $J = 8.0$ Hz, 1H), 8.02 (d, $J = 7.4$ Hz, 1H), 7.79 (td, $J = 7.6$, 1.8 Hz, 1H), 7.70 (t, $J = 8.1$ Hz, 1H), 7.30–7.25 (m, 1H), 6.77 (d, $J = 8.7$ Hz, 1H), 4.04 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 168.5$, 156.1, 153.4, 149.0, 139.3, 136.7, 123.4, 120.9, 113.7, 111.0, 53.2 ppm.

2-(4-Methoxyphenyl)-3-methylpyridine (10d): The standard protocol was applied to 2-bromo-3-methylpyridine (0.34 mL, 3.0 mmol) for 1 h, and 4-iodoanisole (0.72 g, 3.0 mmol) was used as aromatic halide.Pale yellow oil; yield: 0.23 g (46%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.50$ (dd, $J =$ 3.6, 1.2 Hz, 1H), 7.55–7.45 (m, 3H), 7.12 (dd, $J = 7.6$, 4.7 Hz, 1H), 7.0–6.9 (m, 2H), 3.84 (s, 3H), 2.35 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 159.3$, 158.2, 146.8, 138.3, 133.1, 130.5, 130.2, 121.6 , 113.4, 55.2, 20.1 ppm. HRMS: $C_{13}H_{14}NO$ $[M+H]^+$: calcd: 200.1070; found: 200.1073.

2-Methoxy-6-(4-methoxyphenyl)pyridine (12c):[36] The standard protocol was applied to 2-bromo-6-methoxypyridine (0.38 mL, 3.0 mmol) for 1 h, and 4-iodoanisole (0.72 g, 3.0 mmol) was used as aromatic halide. White solid; yield: 0.42 g (63%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.02$–7.96 (m, 2H), 7.56 (t, $J = 7.9$ Hz, 1H), 7.25 (d, $J = 7.4$ Hz, 1H), 6.99–6.94 (m, 2H), 6.62 (d, $J = 8.2$ Hz, 1H), 4.02 (s, 3H), 3.84 ppm (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 163.6$, 160.3, 154.4, 139.0, 131.7, 127.9, 113.9, 113.6, 111.8, 110.8, 108.3, 55.3, 53.1 ppm.

2-Chloro-6-(4-chlorophenyl)pyridine (13c):[37] The standard protocol was applied to 5-bromo-2-chloropyridine (0.61 g, 3.0 mmol) for 4.5 h, and 1-chloro-4-iodobenzene (0.78 g, 3.3 mmol) was used as aromatic halide. Pale yellow solid, m.p. 112 °C; yield: 0.42 g (62%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.57$ (d, $J = 2.5$ Hz, 1H), 7.80 (dd, $J = 5.7$, 2.6 Hz, 1H), 7.48–7.45 (m, 4H), 7.4 ppm (d, $J = 7.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 150.7$, 147.8, 136.9, 134.9, 134.8, 134.5, 129.4, 128.3, 124.3 ppm.

5-(6-Chloropyridin-3-yl)pyrimidine (13d):[38] The standard protocol was applied to 5-bromo-2-chloropyridine (0.61 g, 3.0 mmol) for 4.5 h, and 5-bromopyrimidine (0.541 g, 3.3 mmol) was used as aromatic halide. Pale yellow solid, m.p. 170 °C; yield: 0.29 g (50%); ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 9.29$ (s, 1H), 8.96 (s, 2H), 8.63 (d, $J = 2.2$ Hz, 1H), 7.87 (dd, $J = 5.7$, 2.6 Hz, 1H), 7.51 ppm (d, $J = 8.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 158.5$, 154.8, 152.4, 147.7, 136.9, 130.4, 129.1, 124.9 ppm.

2,6-Di(4-methoxyphenyl)pyridine (6c):[39] 2,6-Dibromopyridine (0.48 g, 2.0 mmol) was added to a stirred suspension of nBu$_4$ZnLi$_2$·TMEDA (2.0 mmol) in toluene (6 mL) at 20 °C under argon. After 1.5 h at room temperature, $[PdCl_2(PPh_3)_2]$ (0.14 g, 0.2 mmol), PPh_3 (0.11 g, 0.4 mmol), and 4-iodoanisole (0.53 g, 2.2 mmol) were added. The mixture was refluxed for 12 h before addition of an aqueous solution of ammonia (5 mL) at room temperature. The mixture was filtered on Celite and washed with EtOAc. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure before purification by chromatography on silica gel to give 0.24 g (41%) of 2,6-di(4-methoxyphenyl)-pyridine. Yellowish solid; m.p. 184–186 °C (lit.[40] 185–188 °C). ^1H NMR ($CDCl_3$, 250 MHz): $\delta = 8.10$ (d, $J = 8.9$ Hz, 4H), 7.69–7.75 (m, 1H), 7.56 (d, $J = 8.6$ Hz, 2H), 7.01 (d, $J = 8.9$ Hz, 4H), 3.87 ppm (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): $\delta = 160.4$, 156.3, 137.2, 132.3, 128.2, 117.1, 114.0, 55.3 ppm.

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