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Deprotonation of pyridine carboxamides using lithium magnesiates bases

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Abstract

Regioselective deprotonation of *N*-methyl- and *tert*-butylpyridine carboxamides using lithium magnesiates bases was achieved at room temperature avoiding nucleophilic addition on the pyridine molecule and auto-condensation of the arylmetal intermediates on the amide group was described. The hydrogen–magnesium exchange was evidenced using ^{1}H NMR spectroscopy at room temperature and the reactivity of the lithium 2-, 3- and 4-carboxamidopyridinylmagnesiates complexes towards electrophiles and in cross-coupling reactions was studied.

Keywords: Pyridine carboxamides; Magnesiation; Magnesiate base

1. Introduction

Directed *ortho*-metallation (DoM) is one of the most important reaction for functionalization of heterocycles.[1] Lithiation using alkyllithium and lithium amides has been extensively and mainly developed since lithiated species display a high reactivity towards many electrophilic functions. Nevertheless, lithiation often requires low-temperature conditions and the lithiated species can be hardly involved in cross-coupling reactions. Direct magnesiation at higher temperature using Grignard and Hauser bases has been first explored but due to the weak reactivity of these bases the scope of this method is rather narrow until now. Since the past decade, the zinc, magnesium and aluminium ate complexes appeared as new emerging deprotonating agents for chemo and regioselective generation of aryl and heteroarylmetal complexes.[2] Kondo and co-workers reported in 1999 the first use of lithium di(*tert*-butyl)(tetramethylpiperidino)zincate (^{t}Bu$_2$ZnTMPLi) for regio and chemoselective zincatation at room temperature of aromatics flanked with high electrophilic functions such as esters of benzene and thiophene.[3] More recently, lithium triisobutyl(tetramethylpiperidino)aluminate (^{t}Bu$_3$AlTMPLi) has been designed for the generation of aryl and heteroarylaluminate complexes mainly at room temperature.[3] Mulvey and co-workers reported in 1999 the preparation of a mixed-metal sodium–magnesium macrocyclic amide, which has been used for the site selective dideprotonation of benzene and toluene.[4] Richey and co-workers observed in 2004 that treatment of benzene halides with magnesiates partially resulted in benzyne formation.[5] Since 2001, our group has been interested in deprotonation of heteroaromatics using lithium magnesiates as deprotonative agent. We recently disclosed the deprotonation of chloro and fluoropyridines, thiophene, oxazole and benzoxazole derivatives.[6] In this paper, we wish to report on the deprotonation of *N*-methyl- and *N*-*tert*-butylpyridine carboxamides with lithium magnesiates as deprotonative agents. The hydrogen–magnesium exchange was evidenced using ^{1}H NMR spectroscopy and the reaction of the resulting lithium 2-, 3- and 4-carboxamidopyridinylmagnesiate complexes with electrophiles and in cross-coupling reactions was later checked.

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2. Results and discussions

2.1. Deprotonation of N-alkylpicolinamides with lithium magnesiate bases

Deprotonation of *N*-methyl and *N*-*tert*-butylpicolinamides (**1** and **2**) was first attempted with lithium tributyl magnesiate (Bu_3MgLi) as deprotonative agent at room temperature (Table 1). The reaction was carried out using 1 equiv of Bu_3MgLi in THF for 2 h. The lithium magnesiate intermediate was reacted with D_2O affording the *C*3 deuterated compounds **1a** and **2a** in 40 and 95% yields, respectively (Table 1, entries 1 and 2).

The use of 2/3 equiv of Bu_3MgLi corresponding to a stoichiometric amount of base only led to poor or medium deuterium incorporation, 10 and 65% of **1a** and **2a**, respectively, from **1** and **2**. Furthermore, the use of 1 equiv of Bu_3MgLi and a longer 4 h metallation time did not improve the deuterium incorporation since **1a** was obtained in only 39% yield after D_2O quenching. *N*-*tert*-Butylamide appeared to be a better DoM group than *N*-methylamide as already described for lithiation. Thus, Epsztajn and co-workers demonstrated that *N*-methyl picolinamide (**1**)[7] reacted in THF at −78 °C with *n*-BuLi (2 equiv) to give a low 32% conversion of *N*- and *C*3-dilithiated picoline amide. In contrast, *N*-*tert*-butylpicolinamide (**2**) was lithiated by Mulzer and co-workers[8] with *n*-BuLi (2 equiv) at −78 °C and allowed to react at −18 °C with *N*-formylpiperidine (NFMP) to give the corresponding *C*3 formylpicolinamide in modest 48 and 60% yields operating in THF or Et_2O, respectively.

The lithium magnesiate intermediate obtained by treating **2** with Bu_3MgLi was reacted with I_2 and 3,4,5-trimethoxybenzaldehyde to afford the corresponding *C*3 substituted compounds **2b** and **2c** in 55 and 82% yields (Table 1, entries 3 and 4). Unfortunately the efficiency of the hydrogen−magnesium exchange could not be directly checked by recording the ^1H NMR spectra of lithium *N*-*tert*-butyl-2-carboxamidopyridinylmagnesiate complex, which appears to be insoluble in THF. Mulzer and co-workers reported the first magnesiation of *N*-*tert*-butylpicolinamide (**2**) using Hauser's base TMPMgCl but a higher temperature (65 °C) and a large excess of base (6 equiv) was needed to ensure an efficient deprotonation.[8] Thus, we describe here an improved method of picolinamide magnesiation at room temperature. We further investigated the magnesiation of 4-chloro-*N*-*tert*-butylpicolinamide (**3**). A quantitative regioselective incorporation of deuterium between the two *ortho*-directing groups was observed by treating **3** with 1 equiv of Bu_3MgLi followed by quenching the lithium magnesiate intermediate with D_2O (Table 1, entry 5). Furthermore, I_2 and 3,4,5-trimethoxybenzaldehyde were successfully reacted to give the *C*3 substituted products **3b** and **3c** in 64 and 50% yields (Table 1, entries 6 and 7).

Table 1
C3 substitution of *N*-methyl and *N*-*tert*-butylpicolinamides (**1**–**3**)

R^1= Me, R^2=H **1**
R^1=^{t}Bu, R^2=H **2**
R^1=^{t}Bu, R^2=Cl **3**

Entry	R^1	R^2	Electrophile, E	Product	Yield[a]
1	CH_3	H	D_2O, D	**1a**	40
2	^{t}Bu	H	D_2O, D	**2a**	95
3		H	I_2, I	**2b**	55
4		H	ArCHO, CH(OH)Ar	**2c**	82
5		Cl	D_2O, D	**3a**	100
6		Cl	I_2, I	**3b**	64
7		Cl	ArCHO,[b] CH(OH)Ar	**3c**	50

[a] Yield of isolated products.
[b] ArCHO=3,4,5-trimethoxybenzaldehyde.

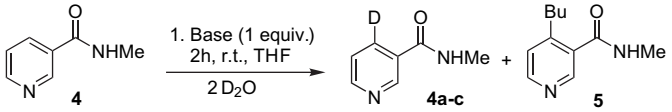
2.2. Deprotonation of N-alkylnicotinamides with lithium magnesiates bases

It is well known that alkyllithiums could not be used for deprotonation of nicotinamides due to competitive 1,4-addition and lithiation could only be achieved using lithium amides.[9]

Similarly, we previously reported that treatment of *N*-*tert*-butylnicotinamide (**6**) with $MgBu_2$ or the more steric hindered ^{i}PrMgCl exclusively led to 1,4-nucleophilic addition on the pyridine nucleus.[10] Mulzer and co-workers have employed this latter process to prepare 4-arylnicotinamides by nucleophilic addition of arylmagnesium bromide to *N*-methyl and *N*-*tert*-butylnicotinamides (**4** and **6**).[9e] Mulzer also reported the unique example of deprotonation of *N*,*N*-diethylnicotinamide using Hauser's base TMPMgCl.[8]

Deprotonation of *N*-methylnicotinamide (**4**) with 1 equiv of Bu_3MgLi in THF at room temperature for 2 h (Table 2, entry 1) followed by trapping the lithium magnesiate intermediate with I_2 afforded exclusively 4-butyl *N*-methylnicotinamide (**5**) in quantitative amounts. We then turned to the use of mixed lithium magnesiate bases such as lithium alkylamidomagnesiates $Bu_2TMPMgLi$, $BuTMP_2MgLi$ and $BuTMP_3MgLi_2$ and lithium tri(amido)magnesiate TMP_3MgLi.

Table 2
Assays of deprotonation of *N*-methylnicotinamide (**4**) using lithium magnesiate bases



Entry	Base	Electrophile, E	4-Substituted nicotinamide[a] (%)		**5**[a] (%)
1	Bu_3MgLi	D_2O, D	—		100
2	$Bu_2TMPMgLi$		—		48
3	$BuTMP_2MgLi$		82	**4a**	—
4	$BuTMP_3MgLi_2$		80	**4a**	—
5	TMP_3MgLi		61	**4a**	—
6	$BuTMP_2MgLi$	I_2, I	78	**4b**	—
7	$BuTMP_2MgLi$	ArCHO,[b] Ar(CH)OH	62	**4c**	—

[a] Yield of isolated product.
[b] ArCHO=3,4,5-trimethoxybenzaldehyde.

Comparative results depicted in Table 2 (entries 2–5) showed that the best deuterium incorporation was obtained using the $BuTMP_2MgLi$ as base. Quenching with D_2O gave the *C*4 deuterio compound **4a** in 82% yield (Table 2, entry 3). The lithium *N*-methyl-3-carboxamidopyridinylmagnesiate complex was then trapped by I_2 and 3,4,5-trimethoxybenzaldehyde to provide the corresponding 4-substituted compounds **4b** and **4c** in good yields (Table 2, entries 6 and 7). Treatment of *N*-*tert*-butylnicotinamide (**6**) with $BuTMP_2MgLi$ was further investigated and we recorded the ^1H NMR spectrum of the resulting lithium magnesiate complex where the complete disappearance of the H4 signal of the starting material was clearly observed. Surprisingly, an important shielding of H6 at the *meta* position of magnesium atom was noticed in ^1H NMR spectra (8.02 ppm instead of 8.72 ppm for the starting material) (Scheme 1).

It appeared then that the structure of the lithium *N*-*tert*-butyl-3-carboxamidomagnesiate complex is different from the one proposed in Scheme 1 using the dual basicity of $BuTMP_2MgLi$,[11] i.e., first the deprotonation of the secondary amide function with the butyl group of $BuTMP_2MgLi$ followed by a second deprotonation of the pyridine molecule with a TMP group (Scheme 1). Actually, we suspected the existence of aggregates in which the pyridine nitrogen atom would interfere as metal ligand. High field NMR studies are currently undertaken to bring more precise structural informations.

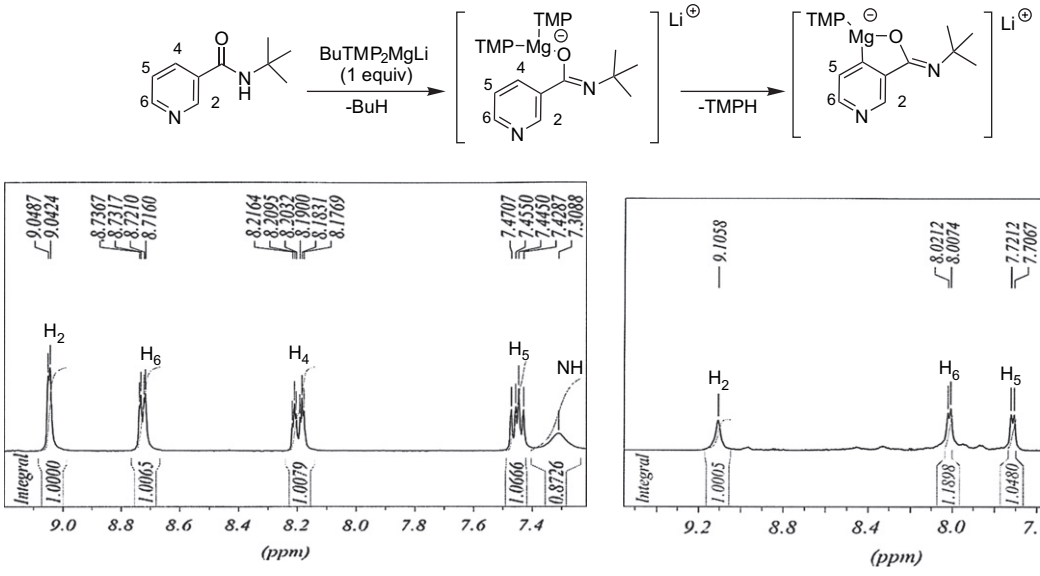
The lithium *N*-*tert*-butyl-3-carboxamidopyridinylmagnesiate complex was then reacted with various electrophiles to give the corresponding 4-substituted nicotinamides **6a–e** in 54–64% yields (Table 3, entries 1–5). 6-Chloro-*N*-*tert*-butylnicotinamide (**7**) was further treated with 1 equiv of $BuTMP_2MgLi$ before quenching the lithium magnesiate intermediate with D_2O, I_2, C_2Cl_6 and 4-chlorobenzaldehyde to afford the corresponding 4-substituted-6-chloro-*N*-*tert*-butylnicotinamides **7a–d** in moderate yields (Table 3, entries 6–9).

Moreover, the use of I_2 as electrophile led to the dimeric side-product **12** in 33% yield (entry 7). This could be avoided by replacing $BuTMP_2MgLi$ by $BuTMP_3MgLi_2$. The employment of $BuTMP_3MgLi_2$ gave similar results than the use of $BuTMP_2MgLi$ for deuterium and halogen incorporation at C4 position of **7** (Table 3, entries 7 and 8) but surprisingly the novel lithium 6-chloro-*N*-*tert*-butylnicotinylmagnesiate complex formed by treatment of **7** with $BuTMP_3MgLi_2$ revealed to be unreactive towards 4-chlorobenzaldehyde even using an excess (Table 3, entry 9).

2.3. Deprotonation of N-alkylisonicotinamides with lithium magnesiates bases

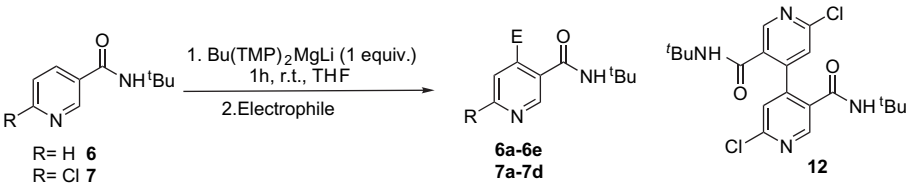
Epsztajn and co-workers first demonstrated that *N*-methylisonicotinamide (**8**) reacted in THF with 2 equiv of *n*-BuLi to give the corresponding lithiated amide with poor 30% yield.[7] We recently reported that *N*-*tert*-butylisonicotinamide (**10**) reacts with Bu_2Mg in THF under reflux to give after quenching with D_2O a low deuterium incorporation at C3 position. The 1,2-butyl addition product was mainly formed.[10]

Deprotonation of *N*-methylisonicotinamide (**8**) was successfully achieved using 1 equiv of Bu_3MgLi base at room temperature for 2 h (Table 4). Quenching the lithium magnesiate intermediate with D_2O, I_2 and C_2Cl_6 afforded the *C*3 monosubstituted *N*-methylisonicotinamides **8a–c** and the 3,4-disubstituted *N*-methylisonicotinamides **9a–c** were also formed in moderate yields (Table 4, entries 1–3). Increase of the steric hindrance on the amide function allowed to avoid the second metallation. Treatment of **10** with 1 equiv of Bu_3MgLi at room temperature in THF for 2 h led to clean hydrogen–magnesium exchange as showed in the ^1H NMR spectra of the lithium *N*-*tert*-butyl-4-carboxamidopyridinylmagnesiate complex (Scheme 2). As previously observed an



Scheme 1. ^1H NMR spectra of lithium *N*-*tert*-butyl-3-carboxamidopyridinylmagnesiate.

Table 3
C4 substitution of *N*-methylnicotinamide (**6**) and 6-chloro-*N*-methylnicotinamide (**7**)



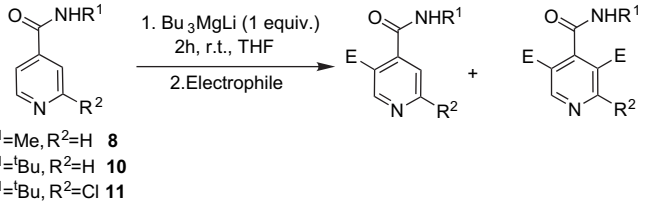
Entry	R	Electrophile, E	Product	Yield[a]
1	H	D_2O	**6a**	64
2	H	I_2, I	**6b**	55
3	H	C_2Cl_6, Cl	**6c**	54
4	H	TMSCl, TMS	**6d**	60
5	H	ArCHO, CH(OH)Ar	**6e**	60
6	Cl	D_2O, D	**7a**	58 (68)[c]
7	Cl	I_2, I	**7b**	45[b] (55)[c,d]
8	Cl	C_2Cl_6, Cl	**7c**	54 (50)[c]
9	Cl	ArCHO,[e] CH(OH)Ar	**7d**	50 (0)[c]

[a] Isolated yields.
[b] Dimmer compound **12** was formed in 33% isolated yield.
[c] Isolated yield using $BuTMP_3MgLi_2$.
[d] Compound **12** was not formed.
[e] ArCHO=4-chlorobenzaldehyde.

important shielding of the H-6 proton was observed (8.28 ppm instead of 8.73 ppm for the starting isonicotinamide). Actually, we suspected the existence of aggregates in which the pyridine nitrogen atom would interfere as metal ligand, thus changing the magnetic environment of the H-6 proton. High field NMR studies and quantum computations are currently undertaken to bring more precise structural informations.

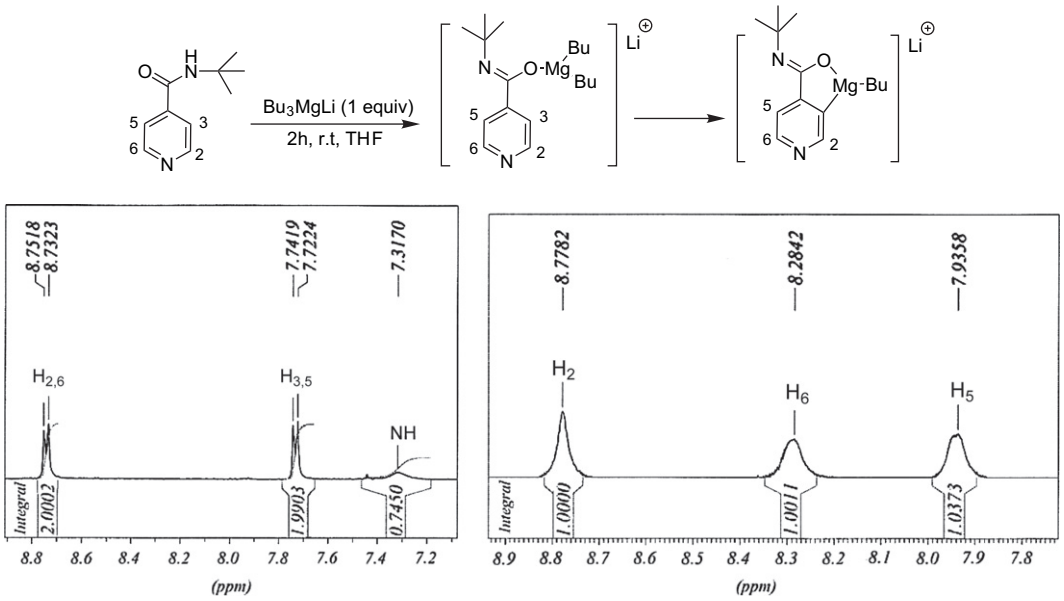
The *N-tert*-butyl-4-carboxamidopyridinylmagnesiate complex was then quenched with electrophiles affording the *C*3-monsubstituted products **10a–f** in goods yields (Table 4, entries 4–9). We further investigated the magnesiation of 2-chloro-*N-tert*-butylisonicotinamide (**11**) using 1 equiv of Bu_3MgLi. Trapping the lithium magnesiate intermediate with D_2O and I_2 afforded the expected C3 deuterated and iodo products **11a** and **b** in poor 42 and 39% yields,

Table 4
Assays of magnesiation of *N*-methyl and *N-tert*-butylisonicotinamides (**8–11**) using Bu_3MgLi base



Entry	R^1	R^2	Electrophile, E	Monosubstituted (%)[a]	Product	Disubstituted (%)[a]	Product
1			D_2O, D	62	**8a**	20	**9a**
2	Me	H	I_2, I	57	**8b**	15	**9b**
3			C_2Cl_6, Cl	44	**8c**	16	**9c**
4			D_2O, D	100	**10a**	—	
5			I_2, I	66	**10b**	—	
6		H	Br_2, Br	43	**10c**		
7	tBu		C_2Cl_6, Cl	62	**10d**	—	
8			TMSCl, TMS	94	**10e**	—	
9			ArCHO,[b] CH(OH)Ar	75	**10f**	—	
10		Cl	D_2O, D	42 (80)[c]	**11a**	—	
11			I_2, I	39 (66)[c]	**11b**	—	

[a] Yield of isolated products.
[b] ArCHO=3,4,5-trimethoxybenzaldehyde.
[c] Bu_3MgLi was replaced by Bu_4MgLi_2.



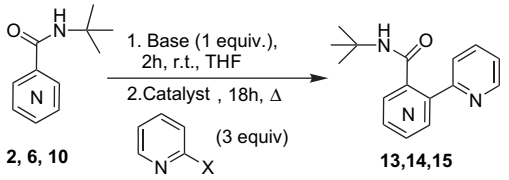
Scheme 2. ^{1}H NMR spectra of lithium *N-tert*-butyl-4-carboxamidopyridinylmagnesiate.

respectively (Table 4, entries 10 and 11). Nevertheless, the use of the higher order dilithium tetrabutylmagnesiate Bu_4MgLi_2 allowed an excellent incorporation of deuterium and iodide at C3 position of **11** (Table 4, entry 10–11).

2.4. First attempts at cross-coupling for lithium carboxamidopyridinylmagnesiate complexes with arylhalides

As last part of this study, the pyridine lithium magnesiate complexes obtained by deprotonation of *N-tert*-butylpicolinamide (**2**) and *N-tert*-butylisonicotinamide (**10**) with Bu_3MgLi base and *N-tert*-butylnicotinamide (**6**) with $BuTMP_2MgLi$ under optimized conditions as described beforehand were engaged in palladium cross-coupling reactions with 2-bromo and 2-chloropyridine. Two catalyst systems previously designed by the laboratory, $PdCl_2$dppf (5 mol %), and Ni(acac)$_2$ and PPh_3, were used.[6] The results are depicted in Table 5. Surprisingly, only *N-tert*-butylisonicotinamide (**10**) could be coupled with 2-chloropyridine in modest 47% yield under nickel catalysis (Table 5, entry 6).

Table 5
Assays of magnesiation of *N-tert*-butylpyridine carboxamides **2**, **6** and **10** followed by in situ catalyzed cross-coupling reactions with 2-halopyridines



Entry	Substrate	Base	X	Catalyst	Product	Yield[a] (%)
1	**2**	Bu_3MgLi	Br	$PdCl_2$(dppf)	**13**	—
2	**6**	$BuTMP_2MgLi$		(5 mol %)	**14**	—
3	**10**	Bu_3MgLi			**15**	—
4	**2**	Bu_3MgLi	Cl	Ni(acac)$_2$, PPh_3	**13**	—
5	**6**	$BuTMP_2MgLi$		(5 mol %)	**14**	—
6	**10**	Bu_3MgLi			**15**	47

[a] Yield of isolated product.

3. Conclusion

This present work described the first systematic study of regioselective deprotonation of *N*-methyl- and *tert*-butylpicoline, nicotine and isonicotinamide using lithium alkyl- and amidomagnesiate bases at room temperature. The use of magnesiates allows the regioselective *ortho*-magnesiation avoiding nucleophilic addition on the pyridine nucleus and auto-condensation of the arylmetal intermediates on the amide group. The lithium tri- and tetrabutylmagnesiates Bu_3MgLi and Bu_4MgLi_2 were specifically designed for magnesiation of *N*-alkylisonicotinamide and picolinamide at C3 whereas the mixed lithium alkylamidomagnesiate $BuTMP_2MgLi$ was selected for magnesiation of the *N*-alkylnicotinamide to avoid 1,4-addition of a butyl group. The optimized magnesiation conditions were successfully extended to chlorocarboxamidopyridines. We also demonstrated that the new lithium carboxamidopyridinylmagnesiate complexes display a good reactivity towards electrophiles. A preliminary study on the reactivity of the latter in cross-coupling reactions with 2-halopyridine was achieved. It revealed that only *N-tert*-butylisonicotinamide (**10**) could be coupled with 2-chloropyridine under nickel catalysis in modest 47% yield. A broad screening of catalytic systems is being currently undertaken. These first results clearly showed that the reactivity of the lithium carboxamidopyridinylmagnesiates seems to be highly dependent on the structure of the complex. Furthermore, an important shielding in ^{1}H NMR spectroscopy of one proton *ortho* to the pyridine nitrogen could be observed in the case of nicotine and isonicotinamides. These

observations may be related to a particular interaction between metal and pyridine nitrogen. More advanced NMR studies are currently done.

4. Experimental section

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Methanol and ethanol were distilled from magnesium turning. Dimethylacetamide was stored over 4 Å molecular sieves before distillation. Flash chromatographic separations were done on Merck silica gel (70–230 mesh). The melting points were measured on a Kofler melting point apparatus and were not corrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer operating at 300 MHz. Infrared spectra were recorded on a Perkin–Elmer FTIR 1650 spectrophotometer. Elemental analyses were carried out on a Carlo Erba 1160. Commercially available starting materials were used without further purification.

4.2. Starting materials

N-Methyl and (*tert*-butyl)pyridine carboxamides **1**, **2**, **4**, **6**, **8** and **10** were prepared from a procedure described in the literature.[6,7,12,13]

4.2.1. Preparation of 6-chloro N-(tert-butyl)nicotinamide (7) and 2-chloro N-(tert-butyl)isonicotinamide (11)

6-Chloronicotinic acid or 2-chloroisonicotinic acid (65 mmol) and thionyl chloride (30 ml) were heated under reflux for 2 h under N_2. After evaporation of thionyl chloride under reduced pressure, the crude acyl chloride was dissolved in CH_2Cl_2 (100 ml) and the resulted solution was cooled at 0 °C before addition of *tert*-butylamine (130 mmol). After stirring 20 h at room temperature, the product was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give crude **7** and **11**.

4.2.1.1. N-(tert-Butyl)-6-chloropyridine-3-carboxamide (7). Column chromatography on silica gel (CH_2Cl_2) afforded **7** (12 g, 57.2 mmol, 88%) as a white solid. Mp 108–109 °C. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.61 (d, J=2.4 Hz, 1H), 7.96 (dd, J=8.3, 2.4 Hz, 1H), 7.33 (d, J=8.3 Hz, 1H), 5.81 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.4, 154.1, 148.2, 138.1, 130.8, 124.6, 52.7, 29.1. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.38; H, 6.08; N, 13.15.

4.2.1.2. N-(tert-Butyl)-2-chloropyridine-4-carboxamide (11)[14]. Column chromatography on silica gel (CH_2Cl_2) afforded **11** (7.7 g, 36.4 mmol, 56%) as a white solid. Mp 97–98 °C. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (d, J=5.1 Hz, 1H), 7.57 (s, 1H), 7.47 (d, J=5.1 Hz, 1H), 6.00 (s, 1H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.9, 152.7, 150.8, 146.4, 122.2, 120.1, 52.8, 29.0. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.34; H, 6.68; N, 13.07.

4.2.2. Preparation of 4-chloro N-(tert-butyl)picolinamide (3)

Thionyl chloride (30 ml) was added to picolinic acid (40 mmol) and sodium bromide (0.4 g, 4 mmol) at room temperature under N_2. The resulting mixture was stirred at reflux for 24 h. After evaporation of thionyl chloride under reduced pressure, the crude product was dissolved in CH_2Cl_2 (30 ml) and the resulting solution was cooled at 0 °C before dropwise addition of *tert*-butylamine (80 mmol). After stirring 20 h at room temperature, aq K_2CO_3 (2 M, 40 ml) was added and the separated aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to give crude **3**.

4.2.2.1. N-(tert-Butyl)-4-chloropyridine-2-carboxamide (3). Column chromatography on silica gel (CH_2Cl_2) afforded **3** (6.0 g, 26.8 mmol, 70%) as a solid. Mp <44 °C. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.32 (d, J=5.1 Hz, 1H), 8.07 (d, J=2.1 Hz, 1H), 7.83 (s, 1H), 7.30 (dd, J=5.1, 2.1 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.4, 152.6, 149.0, 146.1, 126.3, 122.6, 51.4, 29.0. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 55.94; H, 6.32; N, 13.35.

4.3. General procedure of deprotonation using lithium tributyl magnesiate (Bu_3MgLi) and condensation with D_2O as external quench

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 ml) at −10 °C was added BuLi (6 mmol). After stirring for 1 h at room temperature, the required pyridocarbaxamides **1**–**4**, **8**, **10** and **11** were added (2 mmol). After 2 h at room temperature, D_2O (8 mmol) was added and the mixture stirred for 2 h at room temperature before addition of satd aq NH_4Cl (1 ml). The product was extracted with CH_2Cl_2, the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography on silica gel (CH_2Cl_2/Et_2O 1:1) afforded the deuteriopyridine carboxamides **1a**, **2a**, **3a**, **10a** and **11a** in yields indicated in Tables 1–4 except from compound **4** for which the product of 1,4-butyl addition **5** was only obtained and except from compound **8** for which a mixture of *C*3 monodeuterated compound **8a** and *C*-3,5-dideuterated compound **9b** was obtained (see Table 4).

4.3.1. 4-Butyl-N-(tert-butyl)pyridine-3-carboxamide (5)

Column chromatography on silica gel (CH_2Cl_2) afforded **5** from **4** (284 mg, 1.48 mmol, 74%) as a brown solid. Mp 61–62 °C. ^1H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (s, 1H), 8.44 (d, J=5.1 Hz, 1H), 7.11 (d, J=5.1 Hz, 1H), 5.85 (m, 1H), 2.96 (d, J=4.9 Hz, 1H), 2.73 (t, J=7.9 Hz, 2H), 1.52 (m, 2H), 1.30 (m, 2H), 0.86 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.7, 150.9, 150.1, 147.5, 133.0, 124.9, 32.7, 32.4, 26.8, 22.7, 14.1. Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.22; H, 8.46; N, 14.38.

4.4. Deprotonation of N-(tert-butyl)picolinamide and isonicotinamide (2, 3, 10 and 11) using lithium tributyl magnesiate (Bu_3MgLi) and condensation with electrophiles

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 ml) at −10 °C was added BuLi (6 mmol). After stirring for 1 h at room temperature, the required *N-tert*-butylpyridine 2- and 4-carboxamides (**2**, **3**, **10** and **11**) were added (2 mmol). After 2 h at room temperature, the electrophile was added and the mixture was stirred for 2 h at room temperature before addition of satd aq NH_4Cl (1 ml). The product was extracted with CH_2Cl_2, the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure to give crude **2b**–**2c**, **3b**–**3c**, **10b**–**10f** and **11b**.

4.4.1. N-(tert-Butyl)-3-iodopyridine-2-carboxamide (2b)

Compound **2b** was obtained from **2** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **2b** (334 mg, 1.10 mmol, 55%) as a yellow powder. Mp 93–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.37 (dd, J=4.5, 1.3 Hz, 1H), 8.22 (dd, J=7.9, 1.3 Hz, 1H), 7.74 (s, 1H), 6.93 (dd, J=7.9, 4.5 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.4, 150.7, 149.6, 147.3, 126.3, 89.0, 51.5, 29.0. Anal. Calcd for $C_{10}H_{13}IN_2O$: C, 39.49; H, 4.31; N, 9.21. Found: C, 39.38; H, 4.62; N, 9.25.

4.4.2. N-(tert-Butyl)-3-[(hydroxy)(3,4,5-trimethoxyphenyl)-methyl]pyridine-2-carboxamide (2c)

Compound **2c** was obtained from **2** by trapping the magnesiate intermediate with 3,4,5-trimethoxybenzaldehyde (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **2c** (614 mg, 1.64 mmol, 82%) as a yellow solid. Mp <50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.38 (dd, J=4.5, 1.3 Hz, 1H), 8.02 (s, 1H), 7.38 (dd, J=7.9, 1.3 Hz, 1H), 7.27 (dd, J=7.9, 4.5 Hz, 1H), 6.52 (s, 2H), 6.10 (s, 1H), 3.78 (s, 3H), 3.75 (s, 6H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.4, 153.4, 149.2, 147.0, 141.2, 138.8, 138.1, 126.2, 104.2, 73.2, 61.2, 56.4, 51.7, 28.9. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 63.93; H, 7.18; N, 7.26.

4.4.3. N-(tert-Butyl)-4-chloro-3-iodopyridine-2-carboxamide (3b)

Compound **3b** was obtained from **3** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 7:3) afforded **3b** (433 mg, 1.28 mmol, 64%) as a yellow solid. Mp 142–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.19 (d, J=5.1 Hz, 1H), 7.33 (d, J=5.1, 1H), 7.16 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.3, 155.7, 151.8, 148.0, 125.6, 95.2, 52.0, 28.9. Anal. Calcd for $C_{10}H_{12}ClIN_2O$: C, 35.48; H, 3.57; N, 8.27. Found: C, 35.32; H, 3.64; N, 8.24.

4.4.4. N-(tert-Butyl)-4-chloro-3-[(hydroxy)(3,4,5-trimethoxyphenyl)methyl]pyridine-2-carboxamide (3c)

Compound **3c** was obtained from **3** by trapping the magnesiate intermediate with 3,4,5-trimethoxybenzaldehyde (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **3c** (409 mg, 1.0 mmol, 50%) as a yellow solid. Mp 111–112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.31 (d, J=5.1 Hz, 1H), 7.47 (d, J=5.1 Hz, 1H), 7.38 (s, 1H), 7.34 (d, J=11.7 Hz, 1H), 6.42 (d, J=11.7 Hz, 1H), 6.37 (s, 2H), 3.72 (s, 3H), 3.71 (s, 6H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.4, 153.1, 152.9, 147.4, 146.4, 139.0, 138.8, 137.1, 127.2, 103.7, 70.5, 61.1, 56.5, 52.0, 28.5. Anal. Calcd for $C_{20}H_{25}ClN_2O_5$: C, 58.75; H, 6.16; N, 6.85. Found: C, 58.45; H, 6.27; N, 6.77.

4.4.5. N-(tert-Butyl)-3-iodopyridine-4-carboxamide (10b)

Compound **10b** was obtained from **10** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 7:3) afforded **10b** (401 mg, 1.32 mmol, 66%) as a white solid. Mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.89 (s, 1H), 8.50 (d, J=4.9 Hz, 1H), 7.25 (d, J=4.9 Hz, 1H), 5.50 (s, 1H), 1.43 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8, 157.8, 150.0, 149.0, 122.7, 92.3, 52.9, 28.9. Anal. Calcd for $C_{10}H_{13}IN_2O$: C, 39.49; H, 4.31; N, 9.21. Found: C, 39.52; H, 4.03; N, 9.31.

4.4.6. 3-Bromo-N-(tert-butyl)pyridine-4-carboxamide (10c)

Compound **10c** was obtained from **10** by trapping the magnesiate intermediate with 1,2-dibromotetrachloroethane (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 1:1) afforded **10c** (221 mg, 0.86 mmol, 43%) as a yellow solid. Mp 139–140 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.69 (s, 1H), 8.50 (d, J=4.7 Hz, 1H), 7.35 (d, J=4.7 Hz, 1H), 5.72 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.0, 152.6, 148.7, 145.9, 123.3, 117.6, 53.0, 29.0. Anal. Calcd for $C_{10}H_{13}BrN_2O$: C, 46.71; H, 5.10; N, 10.89. Found: C, 47.11; H, 4.95; N, 10.68.

4.4.7. N-(tert-Butyl)-3-chloropyridine-4-carboxamide (10d)

Compound **10d** was obtained from **10** by trapping the magnesiate intermediate with C_2Cl_6 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 1:1) afforded **10d** (269 mg, 1.24 mmol, 62%) as a white solid. Mp 136–137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.57 (s, 1H), 8.49 (d, J=4.8 Hz, 1H), 7.45 (d, J=4.8 Hz, 1H), 5.90 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.0, 150.2, 148.1, 143.5, 128.1, 123.2, 52.9, 28.9. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.67; H, 6.06; N, 13.18.

4.4.8. N-(tert-Butyl)-3-(trimethylsilyl)pyridine-4-carboxamide (10e)

Compound **10e** was obtained from **10** by trapping the magnesiate intermediate with TMSCl (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 7:3) afforded **10e** (470 mg, 1.88 mmol, 94%) as a brown solid. Mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.71 (s, 1H), 8.55 (d, J=4.9 Hz, 1H), 7.16 (d, J=4.9 Hz, 1H), 5.64 (s, 1H),

1.41 (s, 9H), 0.30 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.9, 155.3, 150.8, 150.0, 132.9, 120.9, 52.2, 28.8, 0.0. Anal. Calcd for $C_{13}H_{22}N_2OSi$: C, 62.35; H, 8.86; N, 11.19. Found: C, 61.72; H, 9.17; N, 10.95.

4.4.9. *N-(tert-Butyl)-3-[(hydroxy)(3,4,5-trimethoxyphenyl)-methyl]pyridine-4-carboxamide (**10f**)*

Compound **10f** was obtained from **10** by trapping the magnesiate intermediate with 3,4,5-trimethoxybenzaldehyde (6 mmol). Column chromatography on silica gel (EtOAc/CH_2Cl_2 8:2) afforded **10f** (562 mg, 1.50 mmol, 75%) as an orange solid. Mp 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (m, 2H), 7.23 (d, J=4.9 Hz, 1H), 6.44 (s, 2H), 594 (s, 1H), 5.76 (s, 1H), 5.43 (s, 1H), 3.74 (s, 3H), 3.72 (s, 6H), 1.19 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.5, 153.2, 150.2, 149.3, 144.3, 138.2, 137.1, 136.5, 122.6, 103.9, 72.3, 60.9, 56.3, 52.4, 28.5. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.16; H, 7.00; N, 7.48. Found: C, 62.56; H, 6.82; N, 6.76.

4.4.10. *N-(tert-Butyl)-2-chloro-3-iodopyridine-4-carboxamide (**11b**)*

Compound **11b** was obtained from **11** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **11b** (253 mg, 0.78 mmol, 39%) as a brown solid. Mp 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.42 (d, J=4.9 Hz, 1H), 7.18 (d, J=4.9 Hz, 1H), 5.54 (s, 1H), 1.56 (s, 9H). ^{13}C NMR (75 MHz, CDCl3) δ ppm 166.8, 156.3, 154.9, 149.4, 120.6, 94.2, 53.3, 29.0. Anal. Calcd for $C_{10}H_{12}ClIN_2O$: C, 35.48; H, 3.57; N, 8.27. Found: C, 38.63; H, 3.49; N, 7.92.

4.5. *Deprotonation of N-methylisonicotinamide (**8**) using lithium tributyl magnesiate (Bu_3MgLi) and condensation with I_2 and C_2Cl_6*

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 ml) at −10 °C was added BuLi (6 mmol). After stirring for 1 h at room temperature, the required *N*-methyl pyridine-4-carboxamides (**8**) were added (2 mmol). After 2 h at room temperature, I_2 and C_2Cl_6 (6 mmol) were added and the mixture stirred for 2 h at room temperature before addition of satd aq NH_4Cl (1 ml). The product was extracted with CH_2Cl_2, the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure to give a crude mixture of monosubstituted *N*-methyl pyridine-4-carboxamides **8b–c** and disubstituted *N*-methyl pyridine-4-carboxamides **9b–c**, which was separated by column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1).

4.5.1. *N-Methyl-3-iodopyridine-4-carboxamide (**8b**)*

White solid (302 mg, 1.14 mmol, 57%). Mp 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.92 (s, 1H), 8.53 (d, J=4.7 Hz, 1H), 7.29 (d, J=4.7 Hz, 1H), 5.77 (m, 1H), 2.98 (d, J=5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.2, 158.2, 149.4, 149.1, 122.9, 92.2, 27.1. Anal. Calcd for $C_7H_7IN_2O$: C, 32.08; H, 2.69; N, 10.69. Found: C, 33.36; H, 2.94; N, 10.57.

4.5.2. *N-Methyl-3,5-diiodopyridine-4-carboxamide (**9b**)*

White solid (117 mg, 0.30 mmol, 15%). Mp 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.75 (s, 2H), 5.65 (s, 1H), 3.00 (d, J=4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 167.2, 155.1, 153.0, 90.7, 25.6. Anal. Calcd for $C_7H_6I_2N_2O$: C, 21.67; H, 1.56; N, 7.22. Found: C, 21.53; H, 1.61; N, 7.36.

4.5.3. *N-Methyl-3-chloropyridine-4-carboxamide (**8c**)*

Brown solid (150 mg, 0.86 mmol, 44%). Mp 76–77 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (s, 1H), 8.42 (d, J=5.1 Hz, 1H), 7.44 (d, J=5.1 Hz, 1H), 6.12 (m, 1H), 2.90 (d, J=4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.4, 150.5, 148.4, 142.3, 128.3, 123.6, 27.1. Anal. Calcd for $C_7H_7ClN_2O$: C, 49.28; H, 4.14; N, 16.42. Found: C, 49.71; H, 4.29; N, 15.89.

4.5.4. *N-Methyl-3,5-dichloropyridine-4-carboxamide (**9c**)*

Oil (67 mg, 0.33 mmol, 16%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.46 (s, 2H), 5.74 (s, 1H), 3.00 (d, J=4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.2, 147.9, 142.9, 129.4, 26.4. Anal. Calcd for $C_7H_6Cl_2N_2O$: C, 41.00; H, 2.95; N, 13.66. Found: C, 41.21; H, 2.89; N, 13.52.

4.6. *Deprotonation of N-methyl and (tert-butyl)nicotinamides (**4**, **6** and **7**) using lithium dibutyl(2,2,6,6-tetramethyl-piperidino)magnesiate ($Bu_2TMPMgLi$) and condensation with electrophiles*

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 ml) at −10 °C were added BuLi (6 mmol) and 2,2,6,6-tetramethylpiperidine TMPH (2 mmol). After stirring for 1 h at room temperature, the required *N*-alkylnicotinamides **4**, **6** and **7** was added (2 mmol). After 2 h at room temperature, the electrophile (6 mmol) was added and the mixture stirred for 2 h at room temperature before addition of satd aq NH_4Cl (1 ml). The product was extracted with CH_2Cl_2, the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure to give crude **4a–4c**, **6a–6e** and **7a–7c**.

4.6.1. *4-Deuterio-N-methylpyridine-3-carboxamide (**4a**)*

Compound **4a** was obtained from **4** by trapping the magnesiate intermediate with D_2O (8 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **4a** (0.2 g, 1.6 mmol, 82%) as a white solid. Mp 102–108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.90 (s, 1H), 8.64 (d, J=4.9 Hz, 1H), 7.33 (d, J=4.9 Hz, 1H), 6.45 (s, 1H), 2.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.8, 151.9, 148.6, 135.2, 130.6, 123.6, 27.1. Anal. Calcd for $C_7H_7DN_2O$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.06; H, 5.97; N, 20.10.

4.6.2. *N-Methyl-4-iodopyridine-3-carboxamide (**4b**)*

Compound **4b** was obtained from **4** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **4b** (0.4 g, 1.6 mmol, 78%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.43 (m, 1H), 8.31 (s, 1H), 8.12 (d, J=5.3 Hz, 1H), 7.87 (d, J=5.3 Hz, 1H), 2.68 (d, J=4.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm

167.7, 150.4, 147.4, 139.2, 134.6, 106.9, 26.4. Anal. Calcd for $C_7H_7IN_2O$: C, 32.08; H, 2.69; N, 10.69. Found: C, 31.94; H, 2.85; N, 10.62.

4.6.3. *N-Methyl-4-[(hydroxy)(3,4,5-trimethoxyphenyl)-methyl]pyridine-3-carboxamide (**4c**)*

Compound **4c** was obtained from **4** by trapping the magnesiate intermediate with 3,4,5-trimethoxybenzaldehyde (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **4c** (0.4 g, 1.2 mmol, 62%) as white solid. Mp 165–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.50 (s, 1H), 8.46 (d, J=4.9 Hz, 1H), 7.55 (s, 1H), 7.26 (d, J=4.9 Hz, 1H), 6.50 (s, 2H), 5.95 (s, 1H), 5.85 (s, 1H), 3.74 (s, 3H), 3.73 (s, 6H), 2.83 (d, J=4.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.2, 153.4, 152.7, 151.8, 148.1, 137.4, 131.3, 123.2, 104.0, 72.8, 61.2, 56.4, 27.3. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 58.87; H, 6.48; N, 7.22.

4.6.4. *N-(tert-Butyl)-4-deuteriopyridine-3-carboxamide (**6a**)*

Compound **6a** was obtained from **6** by trapping the magnesiate intermediate with D_2O (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **6a** (0.23 g, 1.3 mmol, 64%) as a white solid. Mp 89–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.84 (s, 1H), 8.63 (d, J=4.9 Hz, 1H), 7.29 (d, J=4.9 Hz, 1H), 5.93 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.6, 151.6, 148.4, 134.9, 131.8, 123.3, 52.2, 29.0. Anal. Calcd for $C_{10}H_{13}DN_2O$: C, 67.01; H, 8.43; N, 15.63. Found: C, 68.96; H, 8.32; N, 15.79.

4.6.5. *N-(tert-Butyl)-4-iodopyridine-3-carboxamide (**6b**)*

Compound **6b** was obtained from **6** by trapping the magnesiate intermediate with I_2 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded **6a** (0.33 g, 1.1 mmol, 55%) as an unstable brown solid. Mp not measured. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.37 (s, 1H), 8.05 (d, J=5.1 Hz, 1H), 7.66 (d, J=5.1 Hz, 1H), 5.93 (s, 1H), 1.46 (s, 9H).

4.6.6. *N-(tert-Butyl)-4-chloropyridine-3-carboxamide (**6c**)*

Compound **6c** was obtained from **6** by trapping the magnesiate intermediate with C_2Cl_6 (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 1:1) afforded **6c** (0.23 g, 1.1 mmol, 54%) as a yellow solid. Mp 117–118 °C. ^{1}H NMR δ ppm 8.72 (s, 1H), 8.45 (d, J=5.3 Hz, 1H), 7.27 (d, J=5.3 Hz, 1H), 5.84 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.9, 151.1, 150.1, 141.0, 132.8, 125.1, 52.8, 29.0. Anal. Calcd for $C_{10}H_{13}ClN_2O$: C, 56.47; H, 6.16; N, 13.17. Found: C, 56.43; H, 6.28; N, 12.61.

4.6.7. *N-(tert-Butyl)-4-trimethylsilylpyridine-3-carboxamide (**6d**)*

Compound **6d** was obtained from **6** by trapping the magnesiate intermediate with TMSCl (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 7:3) afforded **6d** (0.15 g, 0.6 mmol, 60%) as a yellow solid. Mp 87–88 °C. ^{1}H NMR δ ppm 8.54 (s, 1H), 8.52 (d, J=4.9 Hz, 1H), 7.42 (d, J=4.9 Hz, 1H), 5.72 (s, 1H), 1.42 (s, 9H), 0.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 163.0, 150.2, 149.8, 146.9, 139.3, 129.8, 52.3, 29.3. Anal. Calcd for $C_{13}H_{22}N_2OSi$: C, 62.35; H, 8.86; N, 11.19. Found: C, 62.89; H, 8.94; N, 10.79.

4.6.8. *N-(tert-Butyl)-4-[(hydroxy)(3,4,5-trimethoxyphenyl)-methyl]pyridine-3-carboxamide (**6e**)*

Compound **6e** was obtained from **6** by trapping the magnesiate intermediate with 3,4,5-trimethoxybenzaldehyde (6 mmol). Column chromatography on silica gel (EtOAc/CH_2Cl_2 8:2) afforded **6e** (0.22 g, 0.6 mmol, 60%) as a brown solid. Mp 140–141 °C. ^{1}H NMR δ ppm 8.56 (m, 1H), 7.21 (d, J=5.3 Hz, 1H), 6.45 (s, 2H), 5.46 (d, J=5.3 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 6H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 168.1, 153.5, 151.9, 151.8, 148.4, 137.6, 132.5, 123.8, 104.3, 73.7, 61.2, 56.5, 52.8, 28.8. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found: C, 61.73; H, 7.18; N, 6.16.

4.6.9. *N-(tert-Butyl)-6-chloro-4-deuteriopyridine-3-carboxamide (**7a**)*

Compound **7a** was obtained from **7** by trapping the magnesiate intermediate with D_2O (6 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 7:3) afforded **7a** (0.25 g, 1.16 mmol, 58%) as a white solid. Mp 108–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.55 (s, 1H), 7.27 (s, 1H), 5.74 (s, 1H), 1.35 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 164.5, 153.5, 148.6, 137.8, 130.6, 124.1, 52.4, 28.9. Anal. Calcd for $C_{10}H_{12}ClDN_2O$: C, 56.21; H, 6.60; N, 13.11. Found: C, 56.34; H, 6.61; N, 13.32.

4.6.10. *N-(tert-Butyl)-6-chloro-4-iodopyridine-3-carboxamide (**7b**) and 4,4′-bis N-(tert-butyl)-6-chloro-4-deuteriopyridine-3-carboxamide (**12**)*

Trapping the magnesiate intermediate with I_2 (6 mmol) gave a mixture of compounds **7b** and **12**. Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded separately isolated **7b** (335 mg, 0.9 mmol, 45%) as a yellow solid. Mp 100–101 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.16 (s, 1H), 7.72 (s, 1H), 5.53 (s, 1H), 1.36 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.8, 151.8, 147.2, 138.2, 134.6, 106.4, 53.0, 28.9. Anal. Calcd for $C_{10}H_{12}ClIN_2O$: C, 35.47; H, 3.57; N, 8.27. Found: C, 35.92; H, 3.66; N, 8.14. Compound **12** (0.28 g, 0.66 mmol, 33%) as a yellow solid. Mp 223–224 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.52 (s, 2H), 7.06 (s, 2H), 6.75 (s, 2H), 1.14 (s, 18H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.3, 152.6, 148.3, 146.7, 131.4, 123.2, 52.8, 28.6. Anal. Calcd for $C_{20}H_{24}Cl_2N_4O_2$: C, 56.74; H, 5.71; N, 13.23. Found: C, 56.79; H, 5.78; N, 12.69.

4.6.11. *N-(tert-Butyl)-6-chloro-4-chloropyridine-3-carboxamide (**7c**)*

Compound **7c** was obtained from **7** by trapping the magnesiate intermediate with C_2Cl_6 (8 mmol). Column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1) afforded separately isolated **7c** (410 mg, 1.08 mmol, 54%) as oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.51 (s, 1H), 7.33 (s, 1H), 5.87 (s, 1H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 162.9, 152.9, 150.1, 142.9, 131.6, 125.2, 53.1, 29.0. Anal. Calcd for $C_{10}H_{12}Cl_2N_2O$: C, 48.60; H, 4.89; N, 11.34. Found: C, 49.03; H, 5.10; N, 10.81.

*4.6.12. N-(tert-Butyl)-4-[(hydroxy)(4-chlorophenyl)methyl]-pyridine-3-carboxamide (**7d**)*

Compound **7d** was obtained from **7** by trapping the magnesiate intermediate with 4-chlorobenzaldehyde (6 mmol). Column chromatography on silica gel (EtOAc/CH_2Cl_2 9:1) afforded **7d** (0.35 g, 1.0 mmol, 50%) as a yellow solid. Mp 92–93 °C. ^{1}H NMR δ ppm 8.33 (s, 1H), 7.21 (m, 5H), 5.78 (d, J=7.7 Hz, 1H), 5.63 (s, 1H), 5.28 (s, 1H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 165.9, 153.6, 147.2, 138.4, 132.6, 129.8, 127.6, 127.5, 127.2, 126.9, 123.3, 72.0, 51.7, 27.3. Anal. Calcd for $C_{17}H_{18}Cl_2N_2O_2$: C, 57.80; H, 5.14; N, 7.93. Found: C, 57.69; H, 5.23; N, 7.97.

*4.7. Deprotonation of N-(tert-butyl)-6-chloronicotinamide (**7**) using dilithium butyltri(2,2,6,6-tetramethylpiperidino)-magnesiate (BuTMP$_3$MgLi$_2$) and condensation with electrophiles*

To a solution of $MgBr_2$ (2.0 mmol) in THF (3 ml) at −10 °C were added ^{n}BuLi (8 mmol) and 2,2,6,6-tetramethylpiperidine TMPH (6 mmol). After stirring for 1 h at room temperature, *N*-(*tert*-butyl)-6-chloronicotinamide (**7**) was added (2 mmol). After 2 h at room temperature, D_2O, I_2 and C_2Cl_6 (6 mmol) were added and the mixture stirred for 2 h at room temperature before addition of satd aq NH_4Cl (1 ml). The product was extracted with CH_2Cl_2, the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure to give crude **7a**–**7c**, which was purified by column chromatography following the above procedure to give pure **7a** (293 mg, 1.36 mmol, 68%), **7b** (410 mg, 1.10 mmol, 55%) and **7c** (424 mg, 1 mmol, 50%) with the same characteristic data as described before.

*4.8. General procedure for deprotonation of pyridine-carboxamides **1**, **6** and **10** and subsequent cross-coupling with 2-halogenopyridine*

To a solution of carboxyamidopyridinyl magnesiate intermediates resulting from deprotonation of **1**, **6** and **10** by following the general procedures in Sections 4.3 and 4.6 were added 2-bromopyridine (6 mmol) and $PdCl_2$(dppf) (0.3 mmol) or 2-chloropyridine (6 mmol), Ni(acac)$_2$ (0.3 mmol) and triphenylphosphine (0.3 mmol). The resulting solution was refluxed 18 h before addition of satd aq NH_4Cl. After filtration through a short pad of Celite, the product was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to give crude products, which was purified by column chromatography. The starting material was recovered from the reactions between **1**, **6**, **10** and 2-bromopyridine under palladium-catalyzed and reactions between **1**, **6** and 2-chloropyridine under nickel-catalyzed. A coupling product was isolated from the reaction of **10** with 2-chloropyridine as a solid: (**15**, 240 mg, 47%). Mp 65–66 °C. ^{1}H NMR δ ppm 8.77 (s, 1H), 8.70 (m, 2H), 7.82 (t, J=7.7 Hz, 1H), 7.55 (m, 2H), 7.36 (dd, J=7.5, 1.7 Hz, 1H), 6.26 (s, 1H, NH), 1.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 166.5, 154.9, 150.2, 149.4, 149.0, 143.9, 136.7, 132.5, 123.9, 122.8, 122.0, 51.7, 28.1. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.77; H, 6.63; N, 16.35.

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