DOI: 10.1002/ejoc.200801277

New Mixed Li/Mg and Li/Mg/Zn Amides for the Chemoselective Metallation of Arenes and Heteroarenes

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Dedicated to Professor Alain Krief

Keywords: Magnesium / Zinc / Amides / Metalation / Copper / Homogeneous catalysis

New mixed Li/Mg and Li/Mg/Zn amides have been synthesized starting from readily prepared secondary amines. They allow a highly chemoselective directed magnesiation or zincation of various polyfunctional aromatics and heteroaromatics. The kinetic basicity, solubility and stability of these new bases have been compared with those of the corresponding 2,2,6,6-tetramethylpiperamide-derived bases.

Introduction

Aromatic and heterocyclic organometallics can be prepared by various methods including halogen/metal exchange, metal insertion or directed metallation. Directed lithiation, although widely used, suffers from several drawbacks (low functional-group compatibility, low metallation temperature, unselective reactions of the resulting aryllithium reagent).[1] These disadvantages can be overcome by the alternative preparation of the corresponding arylmagnesium or organozinc compounds. Such organometallics combine a satisfactory reactivity with good functional-group compatibility. Their preparation is possible by direct insertion or halogen/metal exchange reactions. General methods for the preparation of organozinc reagents by exchange[2] or insertion[3] reactions as well as by iodine or bromine/magnesium exchange[4] have recently also been developed.[5] Directed magnesiations using magnesium amides of the type R^1R^2NMgX have been used in pioneering studies by Meunier,[6] Hauser,[7] Eaton[8] and Mulzer.[9] The reactivity of these bases can be greatly improved by the addition of 1 equiv. of LiCl. This additive dramatically increases the solubility and kinetic basicity of these bases by lowering their aggregation state.[10] Thus, the mixed lithium and magnesium base TMPMgCl·LiCl (**1**; TMP: 2,2,6,6-tetramethylpiperamide) allows a fast and selective magnesiation of aromatic and heterocyclic compounds.[11] The recent determination of metallated amide crystal structures by Mulvey and co-workers gives a new insight into this chemistry and provides an explanation for the synergic effect observed between the two metals (Li and Mg) to account for their excellent kinetic basicity.[12] These important structural studies are also supported by the theoretical calculations of Uchiyama and co-workers.[13] Whereas TMPMgCl·LiCl (**1**) has a high metallation power, we report herein alternative magnesium bases that are in some cases more active and can be more readily prepared.

Results and Discussion

Despite the constantly decreasing price of 2,2,6,6-tetramethylpiperidine (TMPH; **2**), a more economical amine would be desirable for the metallation reactions. Its precursor, 2,2,6,6-tetramethyl-4-piperidone (**3**) is comparatively cheap.[14] Thus, we decided to convert the amino ketone **3** into the corresponding *exo*-methylene derivative **4** by a Wittig reaction. The treatment of $MePPh_3I$ or $MePPh_3Br$ with *n*BuLi at –78 °C and subsequent addition of **3** leads to the unsaturated amine **4** in 76% yield.[15] Catalytic reduction with H_2 in the presence of Pd/C[16] provides 2,2,4,6,6-pentamethylpiperidine (PMPH; **5**) in 90% yield (Scheme 1).

Treatment of the new piperidine **5** with *i*PrMgCl·LiCl (0.95 equiv., 25 °C, 24 h)[11a] leads to the corresponding PMPMgCl·LiCl (**6**) as a 1.45 M solution in THF. The additional methyl group in **5** does not increase the base solubility in THF compared with TMPH (**2**). This concentration is comparable to that of TMPMgCl·LiCl (**1**). The magnesiation reactions of various aromatics with the magne-

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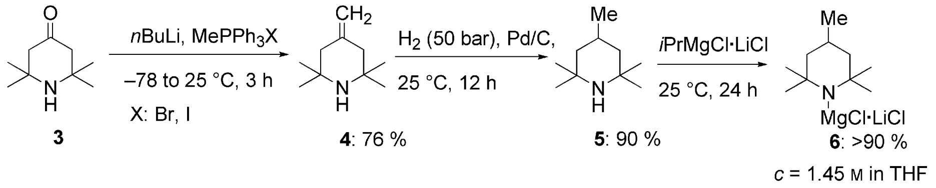
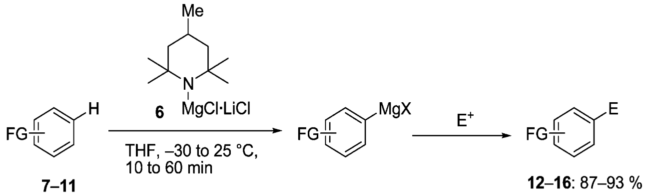
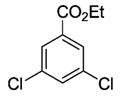
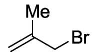
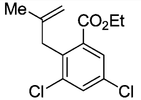
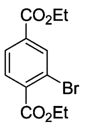
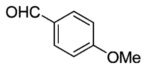
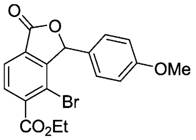
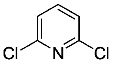
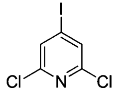
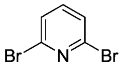
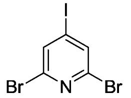
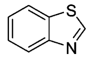
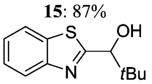


Scheme 1. Preparation of the mixed Li/Mg amide **6**.

sium base **6** are summarized in Table 1. As expected, sensitive functional groups such as esters or the Boc group are well tolerated. The metallation of heterocycles is also possible. The quenching of these magnesium reagents with various electrophiles leads to products of the type **12**–**16** in 87–93% yields (Table 1). Thus, the metallation of the dichlorobenzoate **7** proceeds smoothly at 0 °C within 1 h. A copper(I)-mediated allylation reaction gives the allylated product **12** in 93% yield (Table 1, Entry 1). Also, the intermediate organomagnesium reagent derived from the diester **8** generated at –30 °C within 30 min with an aldehyde can readily be trapped. After the addition of anisaldehyde, the newly formed lactone **13** was obtained in 90% yield (Entry 2). 2,6-Dichloropyridine (**9**) reacts with **6** (1.5 equiv.) at 25 °C within 10 min, whereas the dibromo derivative **10** requires lower temperatures (–30 °C, 0.5 h) to suppress possible halogen dance reactions.[17] After iodolysis, the iodopyridines **14** and **15** were isolated in 91 and 87% yields (Entries 3 and 4), respectively. Benzothiazole (**11**) reacts at 25 °C with the base **6** providing the corresponding Grignard reagent within 10 min. The addition of pivaldehyde leads to the secondary alcohol **16** in 91% yield (Entry 5).

Table 1. Products **12**–**16** obtained by magnesiation with the the base **6** and subsequent trapping with an electrophile.

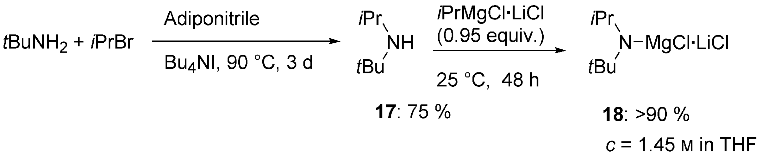


Entry	Substrate	T [°C], t [h]	Electrophile	Product: yield[a]
1	 **7**	0, 1		 **12**: 93%[b]
2	 **8**	–30, 0.5		 **13**: 90% (88%)
3	 **9**	25, 0.2	I_2	 **14**: 91% (93%)
4	 **10**	–30, 0.5	I_2	 **15**: 87%
5	 **11**	25, 0.2	tBuCHO	 **16**: 91% (98%)

[a] Isolated yield of analytically pure product; the yields in parentheses were obtained by using TMPMgCl·LiCl. [b] Obtained after transmetallation with CuCN·2LiCl (10 mol-%).

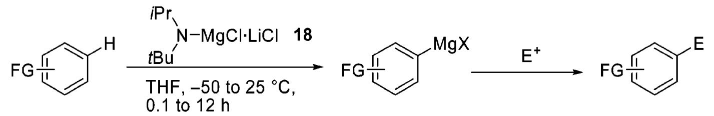
Sterically hindered acyclic magnesium amides may also be an alternative to the use of TMP derivatives. This has already been shown in preliminary experiments.[18] Thus, *tert*-butyl(isopropyl)amine (**17**) can be readily prepared starting form cheap bulk chemicals such as isopropyl bromide, *tert*-butylamine and adiponitrile according to the literature procedure of Brown et al.[19] This synthesis can be performed on a 3 mol scale. Thus, heating of the three components (1:1.5:1 ratio) at reflux in the presence of a catalytic amount of Bu_4NI (10 mol-%) at 90 °C for 3 d produced after a basic workup the amine **17** in 75% yield (Scheme 2). After treatment of the amine **17** with *i*PrMgCl·LiCl,[11] the corresponding base **18** was obtained as a 1.45 M solution in THF. This concentration is comparable to those of TMPMgCl·LiCl (**1**) and PMPMgCl·LiCl (**6**), which leads us to suspect a similar aggregation of all these bases (monomeric or dimeric in solution). Interestingly, the hindered base **18** is twice as soluble in THF as $i\mathrm{Pr_2NMgCl{\cdot}LiCl}$ (max. 0.6 M in THF), which forms more aggregates and does not react in a stoichiometric way with aromatic or heteroaromatic substrates.[11,12,20]

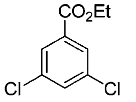
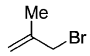
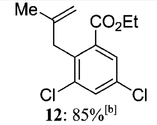
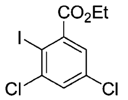
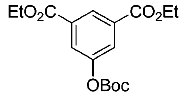
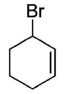
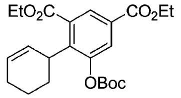
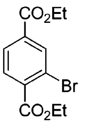
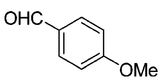
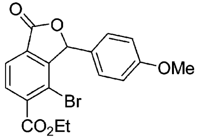
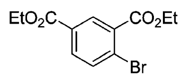
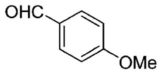
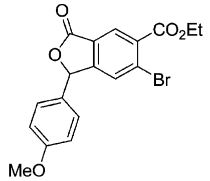
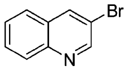
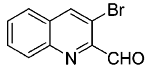
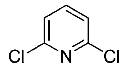
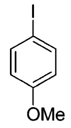
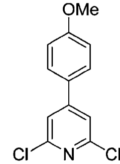
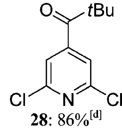
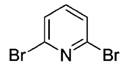
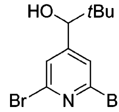
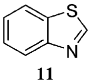
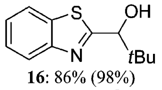
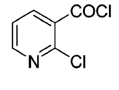
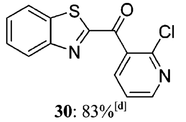
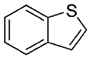
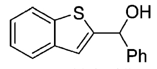
Magnesiation of the substituted ethyl benzoate derivative **7** with the hindered base **18** gives within 1 h the corresponding magnesium reagent, which, after transmetallation with CuCN·2LiCl (10 mol-%), was allylated with 3-bromo-2-methylpropene to afford the tetrasubstituted benzoate **12** in 85% yield (Table 2, Entry 1). Iodolysis of this magnesium



Scheme 2. Synthesis of the amine **17** and its conversion into [*t*Bu(*i*Pr)N]MgCl·LiCl (**18**).

Table 2. Products obtained by magnesiation with the base **18** and subsequent trapping with an electrophile.



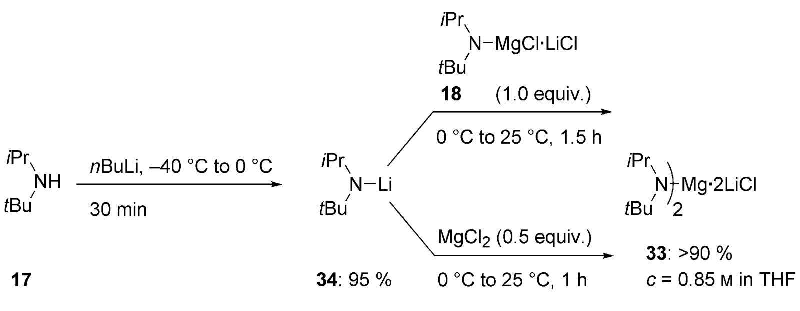
Entry	Substrate	T [°C], t [h]	Electrophile	Product: yield[a]
1	 **7**	0, 1		 **12**: 85%[b]
2	**7**	0, 1	I_2	 **23**: 81%
3	 **19**	0, 1		 **24**: 93%[b] (92%)
4	 **8**	–30, 0.5		 **13**: 96%
5	 **20**	–30, 0.5		 **25**: 86% (88 %)
6	 **21**	–25, 0.3	DMF	 **26**: 81% (91%)
7	 **9**	25, 0.2		 **27**: 85%[c] (93%)
8	**9**	25, 0.2	tBuCOCl	 **28**: 86%[d]
9	 **10**	–50, 0.5	tBuCHO	 **29**: 84%
10	 **11**	25, 0.2	tBuCHO	 **16**: 86% (98%)
11	**11**	25, 0.2		 **30**: 83%[d]
12	 **22**	0, 12	PhCHO	 **31**: 71% (93%)

[a] Isolated yield of the analytically pure product; the yields in parentheses were obtained by using TMPMgCl·LiCl (**1**). [b] Obtained after transmetallation with CuCN·2LiCl (10 mol-%). [c] Obtained after transmetallation with $ZnCl_2$ (1.2–1.6 equiv.), [Pd(dba)$_2$] (5 mol-%) and P(o-furyl)$_3$ (10 mol-%). [d] Obtained after transmetallation with $ZnCl_2$ (1.2–1.6 equiv.) and [Pd(PPh$_3$)$_4$] (2 mol-%).

reagent leads to the iodo ester **23** in 81% yield (Entry 2). Magnesiation of the Boc-protected isophthalate **19** at 0 °C is complete within 1 h. Copper(I)-mediated allylation[21] with 3-bromocyclohexene yields the allylated product **24** in 93% yield (Entry 3). Magnesiation of diethyl 2-bromoterephthalate (**8**) and diethyl 4-bromoisophthalate (**20**) occurs at –30 °C within 30 min. After the addition of anisaldehyde, the newly formed lactones **13** and **25** were isolated in 96 and 86% yields, respectively (Entries 4 and 5). The metallation of the heterocycles can be performed under conditions similar to those used with the bases **1** or **6**. Thus, 3-bromoquinoline (**21**) reacts with the magnesium base **18** at –25 °C within 20 min. Quenching with *N*,*N*-dimethylformamide introduces a formyl function at the 2-position and leads to the aldehyde **26** in 81% yield (Entry 6). 2,6-Dichloropyridine (**9**) reacts with the magnesium amide **18** at 25 °C within 10 min. Transmetallation with $ZnCl_2$ in THF at –40 °C gives the corresponding organozinc reagent, which undergoes a Pd-catalysed Negishi cross-coupling reaction[22] with 4-iodoanisole to afford the 4-substituted pyridine **27** in 85% yield (Entry 7). Pd-catalysed acylation[23] of this zinc reagent by using $[Pd(PPh_3)_4]$ as catalyst (2 mol-%) and pivaloyl chloride (3.0 equiv., –40 to 25 °C, 2 h) leads to the ketone **28** in 86% yield (Entry 8). The dibromopyridine **10** again requires lower temperatures to prevent halogen dance reactions.[17] Deprotonation at the 4-position at –50 °C is complete within 30 min. After the addition of pivaldehyde, the alcohol **29** is produced in 84% yield (Entry 9). The reaction of benzothiazole (**11**) with the magnesium base **18** proceeds at 25 °C within 15 min. After the addition of pivaldehyde, the secondary alcohol **16** was isolated in 86% yield (Entry 10). Pd-catalysed acylation[23] with $[Pd(PPh_3)_4]$ (2 mol-%) and 2-chloronicotinyl chloride leads to the ketone **30** in 83% yield (Entry 11). Benzothiophene (**22**) reacts at 0 °C with the base **18** within 12 h. Quenching with benzaldehyde leads to the benzylic alcohol **31** in 71% yield (Entry 12). These results show that both magnesium bases **6** and **18** display similar behaviour in relation to solubility, metallation rates and yields of the resulting products. However, PMPH (**5**) is gained from a two-step synthesis that includes a Wittig reaction. The straightforward synthesis of the amine **17** makes it superior towards PMPH (**5**) for the preparation of the corresponding Mg bases.

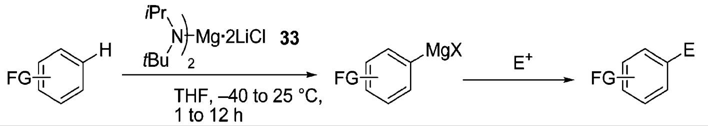
The synthesis and use of highly active Mg bis(amides) of the type $(R_2N)_2Mg\cdot2LiCl$ is necessary for the deprotonation of poorly activated substrates such as benzoates, benzonitriles or pyrimidines. Recently, we showed that $TMP_2Mg\cdot2LiCl$ (**32**) is a highly active and chemoselective base for such metallation reactions.[24] As [*t*Bu(*i*Pr)N] $_2Mg\cdot2LiCl$ (**33**) also allows such deprotonation reactions,[18] the scope of this magnesiation base was examined. Magnesium bis(amide) can be prepared through two pathways. One involves the transmetallation of the monolithium amide [*t*Bu(*i*Pr)N]Li (**34**) with 0.5 equiv. of freshly prepared $MgCl_2$ solution in THF (prepared by allowing 1,2-dichloroethane to react with Mg turnings in dry THF). After removal of the solvents under reduced pressure, the solid is redissolved in THF to give a 0.85 M solution of **33** in THF (Scheme 3), which can be used in the deprotonation reactions described below.

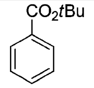
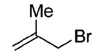
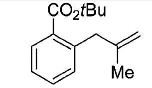
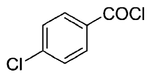
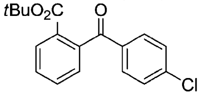
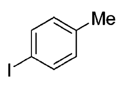
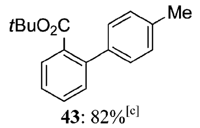
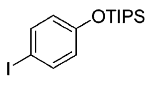
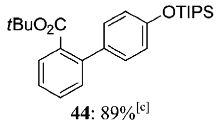
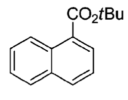
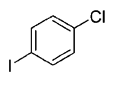
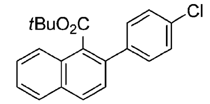
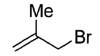
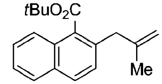
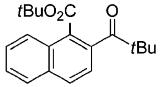
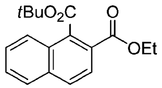
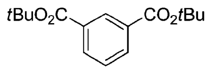
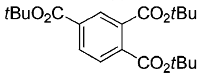
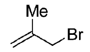
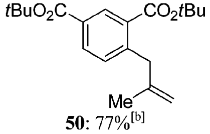
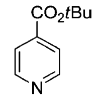
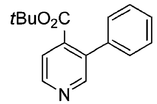
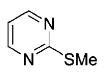
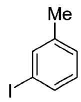
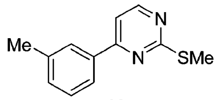
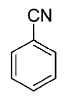
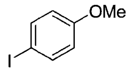
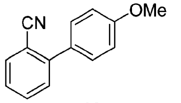
However, the most convenient preparation of **33** is to treat [*t*Bu(*i*Pr)N]MgCl·LiCl (**18**) with [*t*Bu(*i*Pr)N]Li (**34**) in a 1:1 ratio. This provides the base **33** in concentrations of up to 0.85 M in THF (Scheme 3). This high concentration allows fast and selective metallation of various aromatic and heteroaromatic substrates (Table 1). Importantly, these solutions can be stored at 4 °C for at least 21 d without losing activity. This contrasts with $TMP_2Mg\cdot2LiCl$, which is only stable for 24 h without loss of activity. Thus, *tert*-butyl benzoate (**35**) is magnesiated with $[tBu(iPr)N]_2Mg\cdot2LiCl$ (**33**; 1.1 equiv.) at 25 °C within 1 h. After transmetallation to the corresponding arylzinc species, a copper(I)-mediated allylation[21] was performed to give the allylated benzoate **41** in 91% yield (Table 3, Entry 1). This arylzinc species was also used in a Pd-catalysed acylation reaction[23] with $[Pd(PPh_3)_4]$ (2 mol-%) to give the benzophenone **42** in 77% yield (Entry 2). Pd-catalysed Negishi cross-coupling[22] reactions were also performed by using $[Pd(dba)_2]$ (5 mol-%) and $P(o\text{-furyl})_3$ (10 mol-%) with 4-iodotoluene or (4-iodophenoxy)(triisopropyl)silane as electrophiles to provide the desired products **43** and **44** in 82 and 89% yields, respectively (Entries 3 and 4). The reaction of *tert*-butyl 1-naphthoate (**36**) with the magnesium bis(amide) **33** proceeds smoothly at 25 °C within 3 h. The resulting organomagnesium reagent was transmetallated with $ZnCl_2$ (1.1 equiv., 1 M in THF) and used in a Negishi cross-coupling[22] reaction with 1-chloro-4-iodobenzene to give the naphthyl derivative **45** in 97% yield (Entry 5). This organozinc species also undergoes copper(I)-mediated allylation to yield the allylated product **46** in 88% yield. After transmetallation with $ZnCl_2$, the addition of catalytic amounts of $[Pd(PPh_3)_4]$ (2 mol-%)[23] and pivaloyl chloride



Scheme 3. Preparation of $[tBu(iPr)N]_2Mg\cdot2LiCl$ (**33**).

Table 3. Products obtained by magnesiation with the magnesium bis(amide) $[t\mathrm{Bu}(i\mathrm{Pr})\mathrm{N}]_2\mathrm{Mg{\cdot}2LiCl}$ (**33**) and quenching with an electrophile.



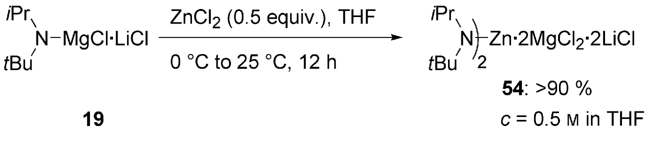
Entry	Substrate	T [°C], t [h]	Electrophile	Product: yield[a]
1	 **35**	25, 1		 **41**: 91%[b] (93%)
2	**35**	25, 1		 **42**: 77%[d]
3	**35**	25, 1		 **43**: 82%[c]
4	**35**	25, 1		 **44**: 89%[c]
5	 **36**	25, 3		 **45**: 97%[c] (83%)
6	**36**	25, 3		 **46**: 88%[b]
7	**36**	25, 3	tBuCOCl	 **47**: 83%[d]
8	**36**	25, 3	EtOCOCl	 **48**: 83%[d]
9	 **37**	25, 6	$\mathrm{Boc_2O}$	 **49**: 90% (94%)
10	**37**	25, 6		 **50**: 77%[b]
11	 **38**	–40, 12	PhI	 **51**: 68%[c]
12	 **39**	–30, 1		 **52**: 76%[c] (93%)
13	 **40**	–30, 3		 **53**: 66%[c] (70%)

[a] Isolated yield of the analytically pure product; the yields in parentheses were obtained by using $\mathrm{TMP_2MgCl{\cdot}2LiCl}$. [b] Obtained after transmetallation with CuCN·2LiCl (10 mol-%). [c] Obtained after transmetallation with $\mathrm{ZnCl_2}$ (1.2–1.6 equiv.), $[\mathrm{Pd(dba)_2}]$ (5 mol-%) and $\mathrm{P}(o\text{-furyl})_3$ (10 mol-%). [d] Obtained after transmetallation with $\mathrm{ZnCl_2}$ (1.2–1.6 equiv.) and $[\mathrm{Pd(PPh_3)_4}]$ (2 mol-%).

leads to the ketone **47** in 83% yield (Entry 6). Palladium-catalysed acylation was also used for the introduction of a new ethyl ester. After the addition of the Pd catalyst [Pd(PPh$_3$)$_4$] (2 mol-%) and ethyl chloroformate, the diester **48** was isolated in 83% yield (Entry 7). The formation of tri-*tert*-butyl benzene-1,2,4-tricarboxylate (**49**) was accomplished by the reaction of di-*tert*-butyl benzene-1,3-dicarboxylate (**37**) with [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl at 25 °C within 6 h. The resulting magnesium reagent was quenched with Boc anhydride to provide the desired tri-*tert*-butyl ester **49** in 90% yield (Entry 9). This compound is usually prepared by a ruthenium-catalysed [2+2+2] alkyne trimerization reaction that produces mixtures of isomers.[25] Further treatment of **37** with [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl at 25 °C for 6 h followed by the addition of ZnCl$_2$, methallyl bromide and catalytic amounts of CuCN·2LiCl (1 M in THF, 10 mol-%) gave the allylated benzoate **50** in 77% yield (Entry 10). Heteroarenes such as *tert*-butyl isonicotinate (**38**) are fully magnesiated at –40 °C within 12 h. After transmetallation with ZnCl$_2$, a Pd-catalysed Negishi reaction with iodobenzene was performed to give the arylated pyridine **51** in 68% yield (Entry 11). 2-(Methylthio)pyrimidine (**39**) is smoothly metallated at –30 °C within 1 h. After transmetallation with ZnCl$_2$, a Negishi cross-coupling[22] reaction with 3-iodotoluene was performed to yield the pyrimidine **52** in 76% yield (Entry 12). Benzonitrile (**40**) is metallated at –30 °C within 3 h. After transmetallation with ZnCl$_2$, Negishi cross-coupling {[Pd(dba)$_2$], 5 mol-%; P(*o*-furyl)$_3$, 10 mol-%} was carried out, which leads to the biphenyl derivative **53** in 66% yield (Entry 13).

These results show that [*t*Bu(*i*Pr)N]$_2$Mg·2LiCl (**33**) is a viable alternative to TMP$_2$Mg·2LiCl (**32**) although some difficulties were observed. For example, ethyl esters are not tolerated, and the extensive formation of the corresponding amide is observed. Only *tert*-butyl esters[26] can be used as substrates for metallation reactions with the bis(amide) base **33**. Surprisingly, in the case of di-*tert*-butyl pyridine-3,5-dicarboxylate, amide formation is still observed. TMP$_2$Mg·2LiCl has to be used for metallating this heterocycle.[18]

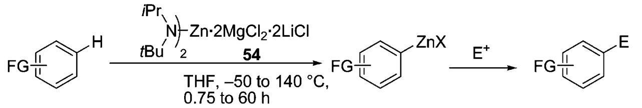
The transmetallation of [*t*Bu(*i*Pr)N]MgCl·LiCl (**19**) with ZnCl$_2$ (0.5 equiv.) furnishes the corresponding zinc base [*t*Bu(*i*Pr)N]$_2$Zn·2MgCl$_2$·2LiCl (**54**). A concentration of 0.5 M in THF is obtained (Scheme 4). The related base (TMP$_2$Zn·2MgCl$_2$·2LiCl[25]) has been found to be a mild zincation reagent for highly functionalized substrates (aldehydes, nitro groups).[27] For poorly activated substrates, the zincation can be accelerated by microwave irradiation.[28]

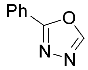
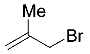
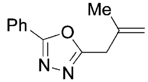
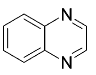
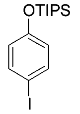
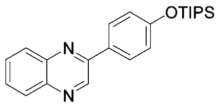
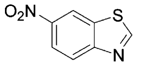
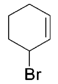
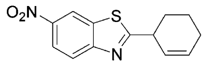
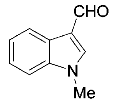
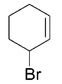
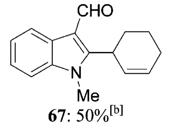
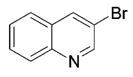
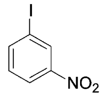
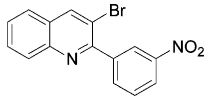
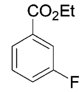
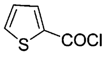
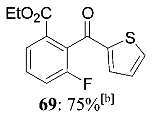
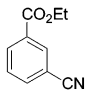
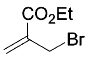
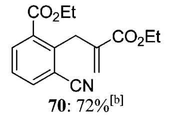
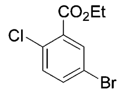
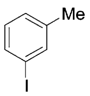
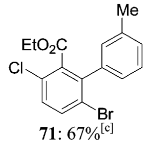
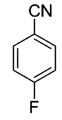
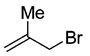
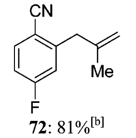
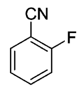
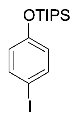
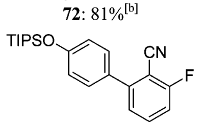
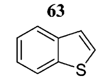
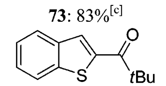


Scheme 4. Formation of the zinc bis-amide **54**.

Thus, 2-phenyl-1,3,4-oxadiazole (**55**) is metallated at 25 °C within 45 min in the presence of the zinc base **54** (0.55 equiv.). The resulting diorganozinc reagent undergoes a copper-catalysed allylation reaction to give the allylated product **64** in 88% yield (Table 4, Entry 1). Magnesiation or lithiation of this substrate is complicated by a competitive ring-opening reaction that leads to benzonitrile.[27] This can be completely avoided by using the zinc bis(amide) **54** as base. Quinoxaline (**56**) is readily zincated at 25 °C within 9 h. After a Pd-catalysed cross-coupling reaction, the quinoxaline derivative **65** was isolated in 81% yield (Entry 2). During this reaction, no dimerization of quinoxaline (**56**) was observed. Such dimerization reactions are typically observed during magnesiation or lithiation reactions of this substrate.[29] Nitro groups are also tolerated, as shown by the zincation of 6-nitrobenzothiazole (**57**). This metallation reaction occurs selectively at the 2-position at –50 °C within 1 h. After a copper(I)-mediated allylation reaction with 3-bromocyclohexene, the 2-allylated benzothiazole **66** was obtained in 79% yield (Entry 3). The presence of an aldehyde, as in the indole derivative **58**, does not affect the metallation procedure, and the 3-formylated indole **58** is smoothly converted after allylation into the expected allylated product **67** in 50% yield (Entry 4). 3-Bromoquinoline (**21**) is zincated at 25 °C within 4 h. After a Pd-catalysed cross-coupling reaction with 3-iodonitrobenzene, the quinoline **68** was isolated in 86% yield (Entry 5). Aromatic esters bearing halogen or cyano substituents are also readily zincated. Thus, ethyl 3-fluorobenzoate (**59**) is converted at 25 °C within 20 h into the corresponding zinc reagent. No halogen dance reactions were observed during the metallation.[17] After copper-catalysed acylation with thiophenoyl chloride, the polyfunctional ketone **69** was obtained in 75% yield (Entry 6). Ethyl 3-cyanobenzoate (**60**) is zincated between both substituents, and subsequent allylation with ethyl 2-(bromomethyl)acrylate[30] gives the 1,2,3-trisubstituted benzene **70** in 72% yield (Entry 7). Ethyl 5-bromo-2-chlorobenzoate (**61**) is metallated between the bromo substituent and the ester group in 60 h. The resulting biphenyl **71** was obtained in 67% yield after Pd-catalysed cross-coupling with 3-iodotoluene (Entry 8). Long reaction times can be considerably reduced by microwave irradiation. Thus, 4-fluorobenzonitrile (**62**) was mixed with 0.55 equiv. of the zinc bis(amide) **54**. This mixture was subjected to microwave irradiation. After 2 h at 100 °C, full conversion was observed. The resulting zinc reagent undergoes copper(I)-catalysed allylation to yield the allylated benzonitrile **72** in 81% yield (Entry 9). The 2-fluoro isomer **63** requires higher temperatures (140 °C) and a 2 h reaction time for complete formation of the zinc reagent. A Pd-catalysed cross-coupling reaction with (4-iodophenoxy)(triisopropyl)silane provides the biphenyl **73** in 83% yield (Entry 10). Benzothiophene (**22**) is zincated at 140 °C within 1 h and undergoes Pd-catalysed acylation with pivaloyl chloride to afford the ketone **74** in 83% yield (Entry 11). The new zinc bis(amide) base **54** displays a reactivity similar to that of TMP$_2$Zn·2MgCl$_2$·2LiCl.[27] However, this last base seems to have a broader scope than **54** as ethyl esters are converted into the corresponding amides under these harsh metallation conditions.

Table 4. Products obtained by zincation with zinc bis(amide) **54** and quenching with an electrophile.



Entry	Substrate	T [°C], t [h]	E$^+$	Product: yield[a]
1	 **55**	25, 0.75		 **64**: 88%[b]
2	 **56**	25, 9		 **65**: 81%[c]
3	 **57**	–50, 1		 **66**: 79%[b]
4	 **58**	25, 1.25		 **67**: 50%[b]
5	 **21**	25, 4		 **68**: 86%[c]
6	 **59**	25, 20		 **69**: 75%[b]
7	 **60**	25, 36		 **70**: 72%[b]
8	 **61**	25, 60		 **71**: 67%[c]
9	 **62**	100, 2		 **72**: 81%[b]
10	 **63**	140, 2		 **73**: 83%[c]
11	 **22**	140, 1	tBuCOCl	 **74**: 83%[b]

[a] Isolated yield of the analytically pure product; the yields in parentheses were obtained by using $TMP_2Zn·2MgCl_2·2LiCl$. [b] Obtained after transmetallation with CuCN·2LiCl (10 mol-%). [c] Obtained by Pd-catalysed cross-coupling with $[Pd(dba)_2]$ (5 mol-%) and $P(o\text{-furyl})_3$ (10 mol-%).

Conclusions

We have described new magnesium and zinc amide bases that readily metallate a range of aromatic and heterocyclic substrates. The expedited synthesis of the secondary amine **17** from cheap bulk chemicals makes the corresponding magnesium and zinc amide bases (**18** and **54**) especially attractive. Similar metallation times and yields compared with TMP-derived bases are observed. The preparation of the amine **5** is more elaborate, and the resulting Mg amide does not provide significant advantages over the bases **1** and **18**, which makes the amine **17** more interesting for the preparation of Mg or Zn bases. Interestingly, the Mg bis(amide) **33**, in contrast to $TMP_2Mg·2LiCl$ (**32**), can be stored at 4 °C for several weeks without loss of activity and may therefore be an alternative to the magnesium bis(amide) **32**. However, a drawback of this amide is its increased nucleophilicity towards sterically non-demanding ester groups (for example, RCO_2Et). The corresponding zinc base [*t*Bu(*i*Pr)-N]$_2$Zn·2MgCl$_2$·2LiCl (**54**) also shows similar behaviour to $TMP_2Zn·2MgCl_2·2LiCl$. It allows an efficient preparation of a range of polyfunctional aryl- and heteroarylzinc compounds. Sensitive functional groups such as esters, aldehydes or nitro groups are readily tolerated during these metallation reactions. Nevertheless, metallation reactions using microwave irradiation of substrates bearing sensitive ester groups may result in the formation of the corresponding amide due to the increased nucleophilicity of the amine **17**. However, the cheap and straightforward synthesis of **17**, as well as the long-term storage of **33**, make these new bases potential alternatives to TMP-derived metallating agents.

Experimental Section

General: All reactions were carried out under argon in flame-dried glassware. Syringes used to transfer anhydrous solvents or reagents were purged with argon prior to use. Long-term cooling was performed by using a Thermo Haake EK90 cooling unit and a stirred ethanol bath. THF was continuously heated at reflux and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure, as determined by ^1H NMR spectroscopy (25 °C) and capillary GC. Purification by column chromatography was performed by using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck unless noted otherwise.

Preparation of the Reagent PMPMgCl·LiCl (6): A dry and argon-flushed Schlenk flask was charged with *i*PrMgCl·LiCl (1.2 M in THF, 208 mL, 250 mmol). 2,2,4,6,6-Pentamethylpiperidine (**5**, 40.8 g, 263 mmol) was added dropwise within 5 min. The mixture was stirred at 25 °C, until the evolution of gas had ceased (24–48 h). Complete formation of the base was checked by GC/MS analysis of aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol ([M$^+$] = 150) indicated a full conversion. The freshly prepared PMPMgCl·LiCl solution was titrated[31] prior to use at 0 °C with benzoic acid using (phenyl)[4-(phenylazo)-phenyl]amine as indicator. A concentration of 1.45 M in THF was obtained.

Preparation of the Reagent (*t*Bu)(*i*Pr)NMgCl·LiCl (18): A dry and argon-flushed Schlenk flask was charged with *i*PrMgCl·LiCl (1.2 M in THF, 208 mL, 250 mmol). *tert*-Butyl(isopropyl)amine (**17**, 30.3 g, 263 mmol) was added dropwise within 5 min. The mixture was stirred at 25 °C, until evolution of the gas had ceased (48 h). Complete formation of the base was checked by GC/MS analysis of aliquots quenched with benzaldehyde. The absence of 2-methyl-1-phenylpropan-1-ol ($[M^+] = 150$) indicated a full conversion. The freshly prepared [*t*Bu(*i*Pr)]NMgCl·LiCl solution was titrated[31] prior to use at 0 °C with benzoic acid using (phenyl)[4-(phenylazo)-phenyl]amine as indicator. A concentration of 1.45 M in THF was obtained.

Preparation of the Reagent $[(tBu)(iPr)N]_2Mg\cdot 2LiCl$ (33): In a dry and argon-flushed Schlenk tube, *tert*-butyl(isopropyl)amine (**17**, 3.46 g, 30 mmol) was dissolved in dry THF (30 mL). This solution was cooled to –40 °C, and *n*BuLi (2.4 M in hexane, 12.5 mL, 30 mmol) was added dropwise within 2 min. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated [*t*Bu(*i*Pr)]NMgCl·LiCl (1.45 M in THF, 20.7 mL, 30 mmol) was then added dropwise (within 5 min) to the [*t*Bu(*i*Pr)]NLi solution, and the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The solvents were removed in vacuo to afford a yellowish solid. Freshly distilled THF was slowly added under vigorous stirring, until complete dissolution of the salts. The freshly prepared $[(tBu)(iPr)N]_2Mg\cdot 2LiCl$ solution was titrated[31] prior to use at 0 °C with benzoic acid using (phenyl)[4-(phenylazo)phenyl]amine as indicator. A concentration of 0.85 M in THF was obtained.

Preparation of the Reagent $[(tBu)N(iPr)]_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (54): A dried, argon-flushed 250 mL Schlenk flask equipped with a magnetic stirring bar and rubber septum was charged with $ZnCl_2$ (4.09 g, 30 mmol). The flask was heated to 150 °C under high vacuum (1×10^{-3} mbar) and vigorous stirring for at least 6 h. After cooling to 25 °C, dry THF (10 mL) was added, and the resulting slurry was cooled to 0 °C with an ice bath. Then **18** (41.4 mL, 1.45 M in THF, 60 mmol) was added through a syringe. The mixture was stirred for 12 h, until complete dissolution of the salts. Precipitates of the base **54** can easily be redissolved by adding a few mL of dry THF. The freshly prepared $[(tBu)(iPr)N]_2Zn\cdot 2MgCl_2\cdot 2LiCl$ solution was titrated prior to use at 0 °C with benzoic acid using (phenyl)[4-(phenylazo)phenyl]amine as indicator. A concentration[31] of 0.5 M in THF was obtained.

Preparation of the Starting Materials: The following starting materials were prepared according to literature procedures: 2,2,4,6,6-Pentamethylpiperidine (**5**),[15] *tert*-butyl(isopropyl)amine (**17**),[16] *tert*-butyl benzoate (**35**),[26] *tert*-butyl 1-naphthoate (**36**),[26] *tert*-butyl isonicotinate (**38**),[26] di-*tert*-butyl isophthalate (**37**),[26] diethyl 5-[(*tert*-butoxycarbonyl)oxy]isophthalate (**19**),[26] ethyl 3,5-dichlorobenzoate (**7**),[27] diethyl 4-bromoisophthalate (**20**)[27] and diethyl 2-bromoterephthalate (**8**).[27]

Typical Procedure 1 (TP1). Metallation of Aromatics and Heterocycles: In a flame-dried and argon-flushed Schlenk tube equipped with a rubber septum and a magnetic stirring bar the aromatic or heteroaromatic substrate (1 equiv.) was dissolved in dry THF (1 M solution). The mixture was cooled to the indicated temperature. Then the Mg or Zn base (0.6–1.5 equiv.) was added dropwise through a syringe. The mixture was stirred at the given temperature. Complete metallation was detected by GC analysis of reaction aliquots quenched with I_2 in dry THF. The reaction mixture was then quenched with an electrophile (aldehydes or iodine or according to TP3–5). The reaction mixture was quenched by the addition of 15–30 mL of a satd. aq. NH_4Cl solution and then added to a separating funnel with Et_2O (10–20 mL) and EtOAc (10–20 mL). The organic layer was extracted with a satd. aq. NH_4Cl solution (3 × 15 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography on silica.

Typical Procedure 2 (TP2). Microwave-Assisted Zincation Reaction: In a flame-dried and argon-flushed 10 mL microwave-sealed tube equipped a magnetic stirring bar the corresponding substrate (1 equiv.) was dissolved in the indicated amount of **54** (0.6 equiv.). The mixture was heated to the indicated temperature in an Initiator Sixty EXP Microwave System (Biotage) and stirred at this temperature for the time given. Complete metallation was detected by GC analysis of reaction aliquots quenched with I_2 in dry THF. Then the reaction mixture was quenched with an electrophile and worked up as described below (according to TP3–5).

Typical Procedure 3 (TP3). Quenching by the Negishi Cross-Coupling Reaction: After complete metallation according to TP1 or TP2, $ZnCl_2$ (1 M in THF, 1.2 equiv.) was added at –40 °C or below. The mixture was then stirred for 15 min. Then $[Pd(dba)_2]$ (5 mol-%) and $P(o\text{-furyl})_3$ (10 mol-%) were added as a solution in THF. After that, the corresponding aryl iodide was added, and the mixture was warmed to room temperature. Complete consumption of the organozinc reagent was monitored by GC analysis (approx. 1–3 h). The reaction mixture was quenched by the addition of a satd. aq. NH_4Cl solution (15–30 mL) and added to a separating funnel with Et_2O (10–20 mL) and EtOAc (10–20 mL). The organic layer was extracted with a satd. aq. NH_4Cl solution (3 × 15 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography on silica.

Typical Procedure 4 (TP4). Quenching by Acylation: After complete metallation according to TP1 or TP2, $ZnCl_2$ (1 M in THF, 1.2 equiv.) was added at –40 °C or below. The mixture was then stirred for 15 min. Then $[Pd(PPh_3)_4]$ (2 mol-%) or CuCN·2LiCl (1 M in THF, 0.1–0.2 equiv.) as indicated was added as a solution in THF. After the addition of the corresponding acyl chloride, the mixture was briefly warmed to 25 °C. Complete consumption of the organozinc reagent was monitored by GC analysis (approx. 1–3 h). The reaction mixture was quenched by the addition of a satd. aq. NH_4Cl solution (15–30 mL of) and added to a separating funnel with Et_2O (10–20 mL) and EtOAc (10–20 mL). The organic layer was extracted with a satd. aq. NH_4Cl solution (3 × 15 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to flash column chromatography on silica.

Typical Procedure 5 (TP5). Quenching by Allylation: After complete metallation according to TP1 or TP2, $ZnCl_2$ (1 M in THF, 1.2 equiv.) (if indicated) was added at –40 °C or below. The mixture was stirred for 15 min. CuCN·2LiCl (1 M in THF, 0.1–0.2 equiv.) was added followed by the corresponding allyl bromide, and the mixture was warmed to room temperature. Complete consumption of the organozinc reagent was monitored by GC analysis (approx. 1–3 h). The reaction mixture was quenched by the addition of a satd. aq. NH_4Cl solution (15–30 mL) and added to a separating funnel with Et_2O (10–20 mL) and EtOAc (10–20 mL). The organic layer was extracted with a satd. aq. NH_4Cl solution (3 × 15 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL), dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo.

The residue was subjected to flash column chromatography on silica.

Synthesis of Ethyl 3,5-Dichloro-2-(2-methylallyl)benzoate (12): The title compound was prepared according to TP4 from ethyl 3,5-dichlorobenzoate (**7**, 436 mg, 2.00 mmol), Mg base **6** or **18** (1.51 mL, 1.45 M in THF, 2.20 mmol), 3-bromo-2-methylpropene (327 mg, 0.35 mL, 2.40 mmol) and CuCN·2LiCl (0.2 mL, 1 M in THF, 0.1 mmol). Metallation conditions: 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **12** as a light-yellow oil (465 mg, 93% with base **6**; 506 mg, 85% with base **18**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.7 (s, 1 H), 7.6 (s, 1 H), 4.8 (s, 1 H) 4.3 (q, *J* = 7.0 Hz, 2 H), 4.2 (s, 1 H), 3.8 (s, 2 H), 1.8 (s, 3 H), 1.4 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 143.1, 137.1, 136.9, 134.3, 132.3, 132.2, 128.8, 110.5, 61.6, 37.1, 23.3, 14.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 272 (88) [M]$^+$, 257 (48), 231 (49), 229 (100), 228 (49), 227 (66), 226 (64), 191 (60), 163 (40), 128 (34). IR (ATR): $\tilde{\nu}$ = 2979, 1726, 1581, 1556, 1444, 1387, 1374, 1365, 1291, 1249, 1219, 1198, 1162, 1139, 1082, 1038, 1021, 935, 885, 873, 843, 792, 782, 769, 750, 727 cm^{-1}. HRMS (EI): calcd. 272.0371; found 272.0375.

Synthesis of Ethyl 4-Bromo-3-(4-methoxyphenyl)-1-oxo-1,3-dihydro-2-benzofuran-5-carboxylate (13): The title compound was prepared according to TP1 from diethyl 2-bromoterephthalate (603 mg, 2.00 mmol), Mg base **6** or **18** (2.07 mL, 1.45 M in THF, 3.00 mmol) and anisaldehyde (409 mg, 0.37 mL, 3.00 mmol). Metallation conditions: –30 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 1:1) gave **13** as a yellow oil (703 mg, 90% with base **6**; 750 mg, 96% with base **18**). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 7.9 Hz, 1 H), 7.9 (d, *J* = 7.8 Hz, 1 H), 7.1 (d, *J* = 8.7 Hz, 2 H), 6.9 (d, *J* = 9.0 Hz, 2 H), 4.4 (q, *J* = 7.2 Hz, 2 H), 6.3 (s, 1 H), 3.8 (s, 3 H), 1.4 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.3, 165.4, 160.6, 149.7, 138.6, 132.2, 130.1, 129.9, 125.7, 124.2, 117.3, 114.3, 84.0, 62.4, 55.3, 14.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 436 (1) [M]$^+$, 393 (48), 392 (41), 391 (51), 347 (39), 345 (39), 275 (93), 273 (95), 267 (100), 239 (88), 135 (64). IR (ATR): $\tilde{\nu}$ = 2981, 2937, 1767, 1725, 1609, 1586, 1514, 1457, 1444, 1407, 1392, 1368, 1320, 1297, 1273, 1248, 1200, 1176, 1139, 1113, 1064, 1026, 966, 861, 852, 833, 820, 774, 746, 726, 648, 644, 632, 606, 575 cm^{-1}. HRMS (EI): calcd. 436.0522; found 436.0536.

Synthesis of 2,6-Dichloro-4-iodopyridine (14): The title compound was prepared according to TP1 from 2,6-dichloropyridine (**9**, 296 mg, 2.00 mmol), **6** (2.07 mL, 1.45 M in THF, 3.00 mmol) and iodine (558 mg, 2.20 mmol). Metallation conditions: 25 °C, 10 min. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **14** as a colourless solid (465 mg, 91%). M.p. 157–158.8 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.7 (br., 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.6, 131.5, 107.6 ppm. MS (70 eV, EI): *m*/*z* (%) = 274 (63), 272 (100) [M]$^+$, 147 (27), 109 (18), 75 (15), 50 (12). IR (ATR): $\tilde{\nu}$ = 2970, 1738, 1536, 1521, 1360, 1217, 1159, 1146, 848, 807, 740 cm^{-1}. HRMS (EI): calcd. 272.8609; found 272.8599.

Synthesis of 2,6-Dibromo-4-iodopyridine (15): The title compound was prepared according to TP1 from 2,6-dibromopyridine (**10**, 474 mg, 2.00 mmol), **6** (2.07 mL, 1.45 M in THF, 3.00 mmol) and iodine (558 mg, 2.20 mmol). Metallation conditions: –30 °C, 30 min. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **15** as a colourless solid (631 mg, 87%). M.p. 180.7–181.6 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.9 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 135.4, 107.4 ppm. MS (70 eV, EI): *m*/*z* (%) = 362 (100) [M]$^+$, 360 (51), 283 (559), 281 (58), 156 (11), 154 (11), 126 (12), 76 (28). 50 (19). IR (ATR): $\tilde{\nu}$ = 3090, 2970, 1739, 1531, 1510, 1365, 1342, 1228, 1221, 1156, 1086, 850, 758, 719, 701 cm^{-1}. HRMS (EI): calcd. 360.7599; found 360.7574.

Synthesis of 1-(Benzothiazol-2-yl)-2,2-dimethylpropan-1-ol (16): The title compound was prepared according to TP1 from benzothiazole (**11**, 270 mg, 0.22 mL, 2.00 mmol), Mg base **6** or **18** (2.07 mL, 1.45 M in THF, 3.00 mmol) and pivaldehyde (233 mg, 0.30 mL, 2.20 mmol). Metallation conditions: 25 °C, 0.2 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 3:1) gave **16** as a yellow solid (402 mg, 91% with base **6**; 380 mg, 86% with base **18**). M.p. 107.0–109.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 8.1 Hz, 2 H), 7.9 (d, *J* = 7.9 Hz, 2 H), 7.5 (t, *J* = 7.7 Hz, 2 H), 7.4 (t, *J* = 7.6 Hz, 2 H), 4.7 (s, 1 H), 3.4 (s, 1 H), 1.1 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.6, 152.1, 134.8, 125.9, 125.0, 122.9, 121.5, 80.0, 36.1, 25.8 ppm. MS (70 eV, EI): *m*/*z* (%) = 221 (6) [M]$^+$, 167 (10), 165 (100), 136 (10), 57 (10). IR (ATR): $\tilde{\nu}$ = 3422, 3060, 2972, 2961, 2951, 2929, 2867, 1510, 1500, 1475, 1464, 1453, 1436, 1390, 1368, 1360, 1329, 1313, 1284, 1236, 1218, 1187, 1168, 1153, 1125, 1086, 1075, 1060, 1015, 900, 862, 764, 757, 731, 709, 687 cm^{-1}. HRMS (EI): calcd. 221.0874; found 221.0860.

Synthesis of Ethyl 3,5-Dichloro-2-iodobenzoate (23): The title compound was prepared according to TP1 from 3,5-dichloroethylbenzoate (**7**, 436 mg, 2.00 mmol), Mg base **18** (1.51 mL, 1.45 M in THF, 2.20 mmol) and iodine (611 mg, 2.40 mmol). Metallation conditions: 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 60:1) gave **23** as a pale-brown oil (556 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (d, *J* = 2.4 Hz, 1 H), 7.5 (d, *J* = 2.4 Hz, 1 H), 4.4 (q, *J* = 7.2 Hz, 2 H), 1.4 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 141.6, 141.3, 135.0, 130.8, 127.7, 95.7, 62.5, 14.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 344 (81) [M]$^+$, 318 (25), 315 (38), 301 (62), 271 (20), 254 (16), 144 (22), 109 (17), 44 (24). IR (ATR): $\tilde{\nu}$ = 2979, 1728, 1564, 1546, 1464, 1443, 1404, 1390, 1379, 1363, 1266, 1236, 1184, 1140, 1112, 1093, 1012, 907, 897, 868, 858, 816, 797, 770, 734, 725, 701 cm^{-1}. HRMS (EI): calcd. 272.0371; found 272.0375.

Synthesis of Diethyl 5-(*tert*-Butoxycarbonyloxy)-4-(cyclohex-2-enyl)isophthalate (24): The title compound was prepared according to TP1 and TP5 from diethyl 5-[(*tert*-butoxycarbonyl)oxy]isophthalate (**19**, 678 mg, 2.00 mmol), Mg base **18** (1.51 mL, 1.45 M in THF, 2.20 mmol), 3-bromocyclohexene (355 mg, 0.28 mL, 2.40 mmol) and CuCN·2LiCl (0.2 mL, 1 M in THF, 0.1 mmol). Metallation conditions: 0 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 1:1) gave **24** as a yellow solid (778 mg, 93%). M.p. 70,3–73.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.1 (d, *J* = 1.9 Hz, 1 H), 7.8 (d, *J* = 1.7 Hz, 1 H), 5.8 (m, 1 H), 5.5 (d, *J* = 9.8 Hz, 1 H), 4.3–4.5 (m, 4 H), 4.0 (m, 1 H), 2.1–2.2 (m, 1 H), 2.0–2.1 (m, 1 H), 1.9–2.0 (m, 2 H), 1.6 (m, 2 H), 1.5 (s, 9 H), 1.2–1.5 (m, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.6, 164.9, 151.4, 150.3, 142.8, 134.3, 129.4, 128.2, 127.9, 127.4, 127.1, 83.6, 61.6, 61.4, 37.5, 28.5, 27.7, 27.4, 24.4, 22.7, 14.3, 14.2 ppm. MS (70 eV, EI): *m*/*z* (%) = 418 (2) [M]$^+$, 362 (43), 318 (26), 317 (11), 273 (31), 272 (100), 271 (15), 244 (13), 243 (11), 238 (13), 199 (14), 193 (12), 57 (66), 44 (26), 41 (18). IR (ATR): $\tilde{\nu}$ = 2980, 2935, 1758, 1719, 1457, 1448, 1394, 1368, 1319, 1277, 1266, 1238, 1218, 1174, 1144, 1100, 1060, 1024, 984, 951, 927, 907, 898, 866, 843, 821, 787, 764, 719, 639 cm^{-1}. HRMS (EI): calcd. 418.1992; found 418.1995.

Synthesis of Ethyl 6-Bromo-1-(4-methoxyphenyl)-3-oxo-1,3-dihydro-2-benzofuran-5-carboxylate (25): The title compound was prepared according to TP1 from diethyl 4-bromoisophthalate (**20**, 603 mg, 2.00 mmol), Mg base **18** (2.07 mL, 1.45 M in THF, 3.00 mmol) and anisaldehyde (409 mg, 0.37 mL, 3.00 mmol). Metallation conditions: –30 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 1:1) gave **25** as a colourless solid (671 mg, 86%). M.p.

130.2–132.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.3 (s, 1 H), 7.6 (s, 1 H), 7.1 (d, J = 8.8 Hz, 2 H), 6.9 (d, J = 8.8 Hz, 2 H), 6.3 (s, 1 H), 4.4 (q, J = 7.2 Hz, 2 H), 3.8 (s, 3 H), 1.4 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.6, 164.9, 160.8, 152.7, 134.2, 129.1, 128.8, 128.4, 128.1, 126.8, 125.2, 114.6, 82.1, 62.3, 55.4, 14.1 ppm. MS (70 eV, EI): m/z (%) = 392 (95), 391 (23) $[M]^+$, 390 (100), 275 (20), 273 (21), 267 (20), 256 (27), 254 (24), 135 (61). IR (ATR): $\tilde{\nu}$ = 2990, 2967, 2955, 1757, 1727, 1616, 1579, 1514, 1468, 1460, 1449, 1443, 1428, 1392, 1365, 1325, 1307, 1290, 1283, 1248, 1200, 1178, 1159, 1114, 1105, 1078, 1028, 1020, 969, 932, 924, 893, 878, 867, 843, 834, 821, 802, 781, 754, 734, 726, 681, 658 cm^{-1}. HRMS (EI): calcd. 391.0181; found 391.0087.

Synthesis of 3-Bromoquinoline-2-carbaldehyde (26): The title compound was prepared according to TP1 from 3-bromoquinoline (**21**, 415 mg, 2.00 mmol), Mg base **18** (2.0 mL, 1.45 M in THF, 3.00 mmol) and dry DMF (257 mg, 0.27 mL, 3.50 mmol). Metallation conditions: –25 °C, 0.3 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 3:1) gave **26** as a yellow solid (304 mg, 81%). M.p. 104.8–106.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.4 (s, 1 H) 8.5 (s, 1 H) 8.3 (d, J = 8.3 Hz, 1 H) 7.8–7.9 (m, 2 H) 7.7–7.8 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.2, 147.8, 146.4, 141.5, 130.9, 130.5, 130.3, 130.1, 126.7, 114.7 ppm. MS (70 eV, EI): m/z (%) = 235 (57) $[M]^+$, 209 (75), 208 (22), 207 (77), 206 (14), 128 (100), 127 (46), 101 (29), 75 (14), 44 (19). IR (ATR): $\tilde{\nu}$ = 2857, 1713, 1677, 1661, 1632, 1611, 1582, 1566, 1544, 1485, 1444, 1403, 1392, 1361, 1315, 1298, 1254, 1227, 1192, 1145, 1133, 995, 985, 964, 912, 893, 874, 783, 757, 637, 611 cm^{-1}. HRMS (EI): calcd. 234.9633; found 234.9626.

Synthesis of 2,6-Dichloro-4-(4-methoxyphenyl)pyridine (27): The title compound was prepared according to TP1 and TP3 from 2,6-dichloropyridine (**9**, 296 mg, 2.00 mmol), Mg base **18** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol), 4-iodoanisole (515 mg, 2.20 mmol), $[Pd(dba)_2]$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: 25 °C, 10 min. Flash chromatography on silica (*n*-pentane/diethyl ether, 19:1) gave **27** as a colourless solid (437 mg, 85%). M.p. 68.7–70.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6 (d, J = 9.0 Hz, 2 H), 7.4 (s, 2 H), 7.0 (d, J = 9.0 Hz, 2 H), 3.9 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 153.4, 151.0, 130.5, 128.4, 127.8, 120.0, 114.8, 113.9, 55.5 ppm. MS (70 eV, EI): m/z (%) = 253 (100) $[M]^+$, 239 (10), 237 (16), 209 (22), 1140 (11). IR (ATR): $\tilde{\nu}$ = 2970, 2937, 2839, 1739, 1607, 1580, 1515, 1417, 1371, 1289, 1255, 1232, 1184, 1173, 1113, 1065, 1036, 985, 866, 821, 808, 767 cm^{-1}. HRMS (EI): calcd. 253.0061; found 253.0070.

Synthesis of 1-(2,6-Dichloropyridin-4-yl)-2,2-dimethylpropan-1-one (28): The title compound was prepared according to TP1 and TP4 from 2,6-dichloropyridine (**9**, 296 mg, 2.00 mmol), Mg base **18** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol), pivaloyl chloride (724 mg, 6.00 mmol) and $[Pd(PPh_3)_4]$ (46 mg, 2 mol-%). Metallation conditions: 25 °C, 10 min. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **28** as a colourless solid (399 mg, 86%). M.p. 58.6–60.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.3 (s, 2 H), 1.3 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 151.4, 150.9, 120.4, 44.6, 27.0 ppm. MS (70 eV, EI): m/z (%) = 233 (2) $[M]^+$, 231 (3), 177 (17), 175 (26), 149 (18), 147 (25), 57 (100), 41 (23). IR (ATR): $\tilde{\nu}$ = 3072, 2979, 2938, 1738, 1688, 1577, 1521, 1481, 1460, 1395, 1364, 1284, 1211, 1168, 1048, 1002, 879, 831, 818, 764, 753, 721, 632 cm^{-1}. HRMS (EI): calcd. 231.0218; found 231.0221.

Synthesis of 1-(2,6-Dibromopyridin-4-yl)-2,2-dimethylpropan-1-ol (29): The title compound was prepared according to TP1 from 2,6-dibromopyridine (**10**, 475 mg, 2.00 mmol), Mg base **18** (2.0 mL, 1.45 M in THF, 3.00 mmol) and pivaldehyde (277 mg, 2.20 mmol). Metallation conditions: –50 °C, 0.5 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 40:1) gave **29** as a colourless solid (544 mg, 84%). M.p. 167.8–169.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.4 (s, 2 H), 4.3 (s, 1 H), 2.1 (s, 1 H), 1.0 (s, 9 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.6, 140.4, 126.3, 80.3, 36.1, 25.9 ppm. MS (70 eV, EI): m/z (%) = 321 (1) $[M]^+$, 269 (97), 268 (18), 267 (88), 265 (100), 186 (9), 158 (10), 156 (9), 57 (50), 41 (9). IR (ATR): $\tilde{\nu}$ = 3432, 2968, 2962, 2931, 2866, 1575, 1528, 1480, 1402, 1373, 1364, 1325, 1295, 1236, 1217, 1201, 1175, 1158, 1087, 1072, 1015, 985, 938, 927, 897, 884, 860, 774, 752, 681, 615 cm^{-1}. HRMS (EI): calcd. 320.9364 found 320.9370.

Synthesis of Benzothiazol-2-yl(2-chloropyridin-3-yl)methanone (30): The title compound was prepared according to TP1 and TP4 from benzothiazole (**11**, 270 mg, 2.00 mmol), Mg base **18** (2.07 mL, 1.45 M in THF, 3.00 mmol), $ZnCl_2$ (3.1 mL, 1 M in THF, 3.1 mmol), 2-chloronicotinyl chloride (1.06 g, 6.00 mmol) and $[Pd(PPh_3)_4]$ (46 mg, 2 mol-%). Metallation conditions: 25 °C, 10 min. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **30** as a colourless solid (456 mg, 83%). M.p. 142.2–143.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.6 (m, 1 H), 8.2 (m, 1 H), 8.1 (dd, J = 7.6, 1.9 Hz, 1 H), 8.0 (m, 1 H), 7.6 (m, 2 H), 7.4 (dd, J = 7.4, 5.0 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 186.2, 165.1, 153.6, 151.5, 148.8, 139.4, 137.5, 132.6, 128.3, 127.3, 126.0, 122.4, 121.9 ppm. MS (70 eV, EI): m/z (%) = 274 (5) $[M]^+$, 246 (11), 240 (50), 239 (62), 238 (55), 141 (28), 139 (100), 113 (16), 111 (54), 76 (16). IR (ATR): $\tilde{\nu}$ = 3094, 2989, 2970, 1739, 1674, 1575, 1554, 1486, 1456, 1424, 1397, 1324, 1291, 1278, 1230, 1137, 1126, 1080, 1052, 954, 890, 843, 809, 755, 726, 702, 652, 602 cm^{-1}. HRMS (EI): calcd. 273.9968; found 27.9962.

Synthesis of 1-Benzothien-2-yl(phenyl)methanol (31): The title compound was prepared according to TP1 from benzothiophene (**22**, 266 mg, 0.23 mL, 2.00 mmol), Mg base **18** (2.07 mL, 1.45 M in THF, 3.00 mmol) and benzaldehyde (233 mg, 0.22 mL, 2.20 mmol). Metallation conditions: 0 °C, 12 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 4:1) gave **31** as a colourless solid (338 mg, 71%). M.p. 87.4–88.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.8 (d, J = 7.2 Hz, 1 H), 7.7 (d, J = 8.3 Hz, 1 H), 7.5 (d, J = 7.6 Hz, 2 H), 7.4 (t, J = 7.5 Hz, 2 H), 7.3 (s, 2 H), 7.3 (s, 1 H), 7.1 (s, 1 H), 6.1 (d, J = 3.1 Hz, 1 H), 2.5 (d, J = 4.1 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.6, 142.5, 139.9, 139.4, 128.6, 128.3, 126.4, 124.3, 124.2, 123.6, 122.4, 121.2, 73.0 ppm. MS (70 eV, EI): m/z (%) = 240 (79) $[M]^+$, 223 (15), 221 (16), 161 (16), 136 (12), 135 (100), 105 (50), 91 (12), 77 (17), 44 (11). IR (ATR): $\tilde{\nu}$ = 3143, 3058, 3028, 1492, 1455, 1434, 1327, 1306, 1295, 1247, 1197, 1177, 1154, 1103, 1031, 1021, 1010, 1001, 818, 786, 769, 749, 728, 722, 699, 666, 627 cm^{-1}. HRMS (EI): calcd. 240.0609; found 240.0595.

Synthesis of *tert*-Butyl 2-(2-Methylprop-2-en-1-yl)benzoate (41): The title compound was prepared according to TP1 and TP5 from *tert*-butyl benzoate (**35**, 356 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 mL, 1.0 M in THF, 10 mol-%) and 3-bromo-2-methylpropene (297 mg, 2.20 mmol). Metallation conditions: 25 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **41** as a colourless oil (422 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (m, 1 H), 7.4 (m, 1 H), 7.3 (m, 2 H), 4.8 (s, 1 H), 4.5 (s, 1 H), 3.7 (s, 2 H), 1.8 (s, 3 H), 1.6 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 145.2, 139.9, 132.8, 131.0, 131.0, 130.0, 126.0, 111.7, 81.1, 41.6, 28.2, 22.8 ppm. MS (70 eV, EI): m/z (%) = 232 (0.04) $[M]^+$, 177 (29), 176 (100), 162 (35), 161 (74), 159 (94), 158 (91), 143 (15), 134 (24). IR (ATR): $\tilde{\nu}$ = 2970, 2938, 1738, 1716, 1447, 1366, 1293, 1275, 1252, 1229, 1217, 1172, 1129, 1077, 1049, 890, 849, 738, 711 cm^{-1}. HRMS (EI): calcd. 232.1463; found 232.1444.

Synthesis of *tert*-Butyl 2-(4-Chlorobenzoyl)benzoate (42): The title compound was prepared according to TP1 and TP4 from *tert*-butyl benzoate (**35**, 356 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), 4-chlorobenzoyl chloride (385 mg, 2.20 mmol) and $[Pd(PPh_3)_4]$ (46 mg, 2 mol-%). Metallation conditions: 25 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 5:1) gave **42** as a colourless solid (486 mg, 77%). M.p. 65.8–67.3 °C ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.0 (m, 1 H), 7.7 (d, *J* = 8.7 Hz, 2 H), 7.6 (m, 2 H), 7.4 (d, *J* = 8.7 Hz, 2 H), 7.3 (m, 1 H), 1.3 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 165.0, 140.6, 139.5, 135.7, 132.0, 131.1, 130.9, 130.1, 129.7, 128.8, 127.4, 82.7, 27.6 ppm. MS (70 eV, EI): *m/z* (%) = 316 (5) [M]$^+$, 261 (34), 260 (23), 245 (27), 243 (83), 181 (81), 152 (28), 149 (17), 139 (32), 111 (11), 57 (21). IR (ATR): $\tilde{\nu}$ = 2972, 2933, 1737, 1706, 1666, 1583, 1571, 1485, 1455, 1441, 1396, 1366, 1301, 1286, 1267, 1173, 1138, 1082, 1011, 969, 930, 896, 866, 849, 775, 762, 748, 737, 712, 676, 645 cm^{-1}. HRMS (EI): calcd. 316.0866; found 318.0869.

Synthesis of *tert*-Butyl 4′-Methylbiphenyl-2-carboxylate (43): The title compound was prepared according to TP1 and TP3 from *tert*-butyl benzoate (**35**, 356 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), 4-iodotoluene (480 mg, 2.20 mmol), $[Pd(dba)_2]$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: 25 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **43** as a colourless oil (440 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (m, 1 H), 7.5 (m, 1 H), 7.4 (m, 1 H), 7.3 (m, 1 H), 7.2 (s, 4 H), 2.4 (s, 3 H), 1.3 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 142.0, 138.9, 136.7, 133.0, 130.6, 130.5, 129.5, 128.6, 128.5, 126.9, 81.2, 27.6, 21.2 ppm. MS (70 eV, EI): *m/z* (%) = 268 (6) [M]$^+$, 213 (13), 212 (100), 195 (37), 165 (16), 152 (11). IR (ATR): $\tilde{\nu}$ = 2970, 2928, 1706, 1599, 1477, 1444, 1366, 1298, 1247, 1217, 1172, 1126, 1087, 1047, 848, 819, 755, 705 cm^{-1}. HRMS (EI): calcd. 268.1463; found 268.1458.

Synthesis of *tert*-Butyl 4′-[(Triisopropylsilyl)oxy]biphenyl-2-carboxylate (44): The title compound was prepared according to TP1 and TP3 from *tert*-butyl benzoate (**35**, 356 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), (4-iodophenoxy)(triisopropyl)silane (850 mg, 2.20 mmol), $[Pd(dba)_2]$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: 25 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **44** as a colourless oil (758 mg, 89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.7 (m, 2 H), 7.5 (m, 2 H), 7.4 (m, 2 H), 7.2 (d, *J* = 8.7 Hz, 2 H), 6.9 (d, *J* = 8.7 Hz, 2 H), 1.3 (s, 9 H), 1.1 (m, 21 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 155.4, 141.4, 134.4, 133.3, 130.5, 130.4, 129.6, 129.3, 126.7, 119.3, 81.2, 27.7, 18.0, 12.7 ppm. MS (70 eV, EI): *m/z* (%) = 427 (12), 426 (36) [M]$^+$, 328 (25), 327 (100), 309 (22), 299 (28), 281 (22), 255 (10), 254 (11), 253 (53), 239 (279), 127 (14), 75 (11), 57 (14). IR (ATR): $\tilde{\nu}$ = 2970, 2944, 2867, 1737, 1712, 1607, 1515, 1477, 1444, 1366, 1301, 1260, 1232, 1217, 1172, 1126, 1047, 911, 882, 837, 762, 686, 652 cm^{-1}. HRMS (EI): calcd. 426.2590; found 426.2586.

Synthesis of *tert*-Butyl 2-(4-Chlorophenyl)-1-naphthoate (45): The title compound was prepared according to TP1 and TP3 from *tert*-butyl 1-naphthoate (**36**, 456 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol) 4-iodo-1-chlorobenzene (525 mg, 2.20 mmol), $[Pd(dba)_2]$ (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: 25 °C, 3 h. Trituration with pentane gave **45** as a brown solid (657 mg, 97%). M.p. 95.6–97.1 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.0 (m, *J* = 8.3 Hz, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.4 (m, 5 H), 1.4 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 139.5, 136.0, 133.6, 132.5, 131.7, 130.4, 129.8, 129.4, 129.0, 128.4, 128.2, 128.1, 127.5, 127.1, 126.4, 125.0, 82.4, 27.9 ppm. MS (70 eV, EI): *m/z* (%) = 338 (10) [M]$^+$, 284 (27), 282 (100), 265 (28), 202 (26). IR (ATR): $\tilde{\nu}$ = 2971, 2930, 1737, 1711, 1597, 1491, 1364, 1286, 1274, 1243, 1175, 1162, 1135, 1109, 1091, 1014, 1009, 959, 890, 859, 849, 814, 795, 748, 723, 676, 664 cm^{-1}. HRMS (EI): calcd. 338.1074; found 338.1075.

Synthesis of *tert*-Butyl 2-(2-Methylprop-2-en-1-yl)-1-naphthoate (46): The title compound was prepared according to TP1 and TP5 from *tert*-butyl 1-naphthoate (**36**, 456 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 mL, 1.0 M in THF, 10 mol-%) and 3-bromo-2-methylpropene (297 mg, 2.20 mmol). Metallation conditions: 25 °C, 3 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 50:1) gave **46** as a colourless oil (496 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.8 (m, 3 H), 7.5 (m, 2 H), 7.4 (d, *J* = 8.5 Hz, 1 H), 4.9 (s, 1 H), 4.7 (s, 1 H), 3.6 (s, 2 H), 1.7 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 144.1, 133.8, 132.3, 132.0, 129.9, 129.0, 128.0, 127.4, 126.8, 125.6, 124.7, 112.8, 82.4, 41.7, 28.3, 22.4 ppm. MS (70 eV, EI): *m/z* (%) = 282 (1) [M]$^+$, 226 (45), 211 (100), 209 (15), 181 (23), 165 (19). IR (ATR): $\tilde{\nu}$ = 2970, 2942, 1738, 1718, 1508, 1455, 1366, 1283, 1248, 1227, 1222, 1171, 1152, 1132, 1044, 1023, 891, 847, 807, 755, 735 cm^{-1}. HRMS (EI): calcd. 282.1620; found 282.1606.

Synthesis of *tert*-Butyl 2-(2,2-Dimethylpropanoyl)-1-naphthoate (47): The title compound was prepared according to TP1 and TP4 from *tert*-butyl 1-naphthoate (**36**, 456 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), pivaloyl chloride (385 mg, 2.20 mmol) and $[Pd(PPh_3)_4]$ (46 mg, 2 mol-%). Metallation conditions: 25 °C, 3 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **47** as a colourless solid (518 mg, 83%). M.p. 76.1–78.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.2 (m, 1 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 7.5 (d, *J* = 8.7 Hz, 1 H), 1.7 (s, 9 H), 1.4 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 221.3, 167.6, 138.7, 133.4, 130.9, 130.0, 129.4, 128.2, 127.6, 127.0, 125.9, 122.0, 83.0, 44.4, 28.2, 27.9 ppm. MS (70 eV, EI): *m/z* (%) = 312 8 (0.1) [M]$^+$, 254 (5), 199 (12), 198 (100), 126 (4), 57 (11). IR (ATR): $\tilde{\nu}$ = 2970, 2932, 2871, 1737, 1711, 1683, 1622, 1567, 1475, 1458, 1395, 1380, 1366, 1266, 1248, 1159, 1133, 1069, 1026, 997, 882, 864, 852, 842, 822, 802, 790, 762, 741, 727, 682, 624 cm^{-1}. HRMS (EI): calcd. 312.1725; found 312.1710.

Synthesis of 1-*tert*-Butyl 2-Ethyl Naphthalene-1,2-dicarboxylate (48): The title compound was prepared according to TP1 and TP4 from *tert*-butyl 1-naphthoate (**36**, 456 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), $ZnCl_2$ (2.4 mL, 1 M in THF, 2.4 mmol), ethyl chloroformate (1.08 g, 10.0 mmol) and $[Pd(PPh_3)_4]$ (46 mg, 2 mol-%). Metallation conditions: 25 °C, 3 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **48** as a colourless solid (498 mg, 83%). M.p. 103.8–105.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.0 (m, 2 H), 7.9 (m, 2 H), 7.6 (m, 2 H), 4.5 (q, *J* = 7.2 Hz, 2 H), 1.7 (s, 9 H), 1.4 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9, 165.8, 136.0, 135.1, 129.5, 128.9, 128.1, 128.1, 127.5, 126.0, 125.1, 124.7, 82.8, 61.4, 28.2, 14.4 ppm. MS (70 eV, EI): *m/z* (%) = 300 (32) [M]$^+$, 245 (16), 244 (100), 227 (25), 200 (30), 199 (90), 172 (27), 155 (73), 127 (29), 115 (19), 57 (17). IR (ATR): $\tilde{\nu}$ = 2980, 2970, 1738, 1722, 1712, 1467, 1438, 1364, 1289, 1265, 1241, 1217, 1173, 1158, 1133, 1116, 1042, 1018, 867, 850, 828, 796, 766, 752, 730, 669 cm^{-1}. HRMS (EI): calcd. 300.1262; found 300.1354.

Synthesis of Tri-*tert*-butyl Benzene-1,2,4-tricarboxylate (49): The title compound was prepared according to TP1 from di-*tert*-butyl isophthalate (**37**, 556 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol) and Boc$_2$O (1.08 g, 5.00 mmol). Metallation conditions: 25 °C, 6 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **49** as a pale-green oil (680 mg, 90%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.2 (d, J = 1.2 Hz, 1 H), 8.1 (dd, J = 8.0, 1.7 Hz, 1 H), 7.6 (d, J = 8.0 Hz, 1 H), 1.6 (m, 23 H), 1.5 (m, 4 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.4, 166.0, 164.3, 137.4, 133.6, 133.6, 131.2, 129.8, 128.6, 85.2, 83.9, 82.4, 81.9, 58.5, 47.7, 29.3, 28.1, 28.0, 27.6, 27.4, 22.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 378 (0.02) [M]$^+$, 305 (47), 267 (36), 249 (24), 211 (51), 194 (37), 193 (23), 175 (19), 167 (80), 148 (847), 57 (838), 56 (100). IR (ATR): ṽ = 2970, 2941, 1736, 1718, 1455, 1393, 1367, 1293, 1273, 1245, 1217, 1157, 1113, 1066, 935, 869, 841, 763, 741 cm^{-1}. HRMS (EI): calcd. 378.2842; found 378.2047.

Synthesis of Di-*tert*-butyl 4-(2-Methylprop-2-en-1-yl)isophthalate (50): The title compound was prepared according to TP1 and TP5 from di-*tert*-butyl isophthalate (**37**, 556 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), ZnCl$_2$ (2.4 mL, 1 M in THF, 2.4 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%) and 3-bromo-2-methylpropene (297 mg, 2.20 mmol). Metallation conditions: 25 °C, 6 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 20:1) gave **50** as a colourless oil (511 mg, 77%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.4 (d, J = 1.7 Hz, 1 H), 8.2 (dd, J = 7.7, 1.7 Hz, 1 H), 7.9 (dd, J = 8.0, 1.9 Hz, 1 H), 4.8 (s, 1 H), 4.5 (s, 1 H), 3.8 (s, 2 H), 1.6 (m, 21 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.8, 165.1, 144.6, 144.6, 133.2, 132.9, 132.2, 131.6, 131.1, 130.4, 130.0, 128.2, 112.1, 81.6, 81.5, 81.2, 41.5, 28.2, 28.1, 22.8 ppm. MS (70 eV, EI): *m*/*z* (%) = 332 (0.02) [M]$^+$, 276 (52), 259 (16), 220 (59), 205 (100), 203 (28), 202 (16), 149 (7), 57 (25). IR (ATR): ṽ = 2970, 2938, 1738, 1715, 1608, 1452, 1393, 1366, 1315, 1290, 1247, 1217, 1156, 1140, 1117, 1075, 939, 891, 849, 768, 756, 732 cm^{-1}. HRMS (EI): calcd. 332.1988; found 332.1976.

Synthesis of *tert*-Butyl 3-Phenylisonicotinate (51): The title compound was prepared according to TP1 and TP3 from *tert*-butyl isonicotinate (**38**, 358 mg, 2.00 mmol), Mg base **33** (3.53 mL, 0.85 M in THF, 3.00 mmol), ZnCl$_2$ (3.2 mL, 1 M in THF, 3.2 mmol), iodobenzene (449 mg, 2.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: –40 °C, 12 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 1:1) gave **51** as a red oil (347 mg, 68%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.7 (d, J = 5.1 Hz, 1 H), 8.6 (s, 1 H), 7.6 (d, J = 5.6 Hz, 1 H), 7.4 (m, 3 H), 7.3 (m, 2 H), 1.3 (s, 9 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.2, 151.0, 148.7, 140.0, 137.7, 135.9, 128.8, 128.3, 127.9, 122.5, 99.4, 82.8, 27.5 ppm. MS (70 eV, EI): *m*/*z* (%) = 255 (3) [M]$^+$, 200 (16), 199 (100), 198 (19), 182 (30), 154 (9), 127 (10), 57 (11). IR (ATR): ṽ = 2970, 1736, 1715, 1477, 1445, 1397, 1368, 1316, 1296, 1217, 1159, 1119, 1075, 1006, 856, 837, 761, 717, 699, 672 cm^{-1}. HRMS (EI): calcd. 255.1259; found 255.1264.

Synthesis of 4-(3-Methylphenyl)-2-(methylthio)pyrimidine (52): The title compound was prepared according to TP1 and TP3 from 2(methylthio)pyrimidine (**39**, 252 mg, 2.00 mmol), Mg base **33** (3.53 mL, 0.85 M in THF, 3.00 mmol), ZnCl$_2$ (3.2 mL, 1 M in THF, 3.2 mmol), 3-iodotoluene (480 mg, 2.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: –40 °C, 12 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 18:88) gave **52** as a colourless solid (328 mg, 76%). M.p. 55.2–56.3 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.5 (d, J = 5.3 Hz, 1 H), 7.9 (s, 1 H), 7.8 (d, J = 8.0 Hz, 1 H), 7.4 (m, 3 H), 2.7 (s, 3 H) 2.5 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 172.7, 164.1, 157.4, 138.6, 136.3, 131.9, 128.8, 127.8, 124.4, 112.0, 21.5, 14.2 ppm. MS (70 eV, EI): *m*/*z* (%) = 217 (14), 216 (100) [M]$^+$, 215 (30), 170 (37), 169 (22), 155 (14), 115 (12). IR (ATR): ṽ = 3058, 2970, 2925, 1739, 1561, 1542, 1492, 1415, 1348, 1315, 1301, 1208, 1194, 1185, 1126, 1080, 969, 918, 890, 850, 796, 768, 693, 654, 628 cm^{-1}. HRMS (EI): calcd. 216.0721; found 216.0708.

Synthesis of 4′-Methoxybiphenyl-2-carbonitrile (53): The title compound was prepared according to TP1 and TP3 from benzonitrile (**40**, 206 mg, 2.00 mmol), Mg base **33** (2.59 mL, 0.85 M in THF, 2.20 mmol), ZnCl$_2$ (2.4 mL, 1 M in THF, 2.40 mmol), 3-iodotoluene (480 mg, 2.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: –30 °C, 3 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **53** as a colourless solid (276 mg, 66%). M.p. 77.1–79.1 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.8 (m, 1 H), 7.6 (m, 1 H), 7.5 (d, J = 9.0 Hz, 2 H), 7.4 (m, 2 H), 7.0 (d, J = 9.0 Hz, 2 H) 3.9 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.1, 133.7, 132.7, 130.5, 130.0, 129.9, 129.0, 128.4, 127.0, 114.2, 77.4, 76.6, 55.4 ppm. MS (70 eV, EI): *m*/*z* (%) = 209 (100) [M]$^+$, 194 (17), 166 (30), 140 (12). IR (ATR): ṽ = 2994, 2970, 2224, 1739, 1611, 1598, 1516, 1480, 1443, 1435, 1370, 1300, 1270, 1248, 1184, 1035, 833, 820, 750, 696 cm^{-1}. HRMS (EI): calcd. 209.0841; found 209.841.

Synthesis of 2-(2-Methylallyl)-5-phenyl-1,3,4-oxadiazole (64): The title compound was prepared according to TP1 and TP5 from 2-phenyl-1,3,4-oxadiazole (**55**, 290 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%) and 3-bromo-2-methylpropene (324 mg, 2.20 mmol). Metallation conditions: 25 °C, 0.75 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 4:1) gave **64** as a colourless solid (352 mg, 88%). M.p. 56.3–57.5 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.1 (dt, J = 5.5, 2.1 Hz, 3 H), 7.5–7.6 (m, 2 H), 5.0 (d, J = 15.5 Hz, 2 H), 3.7 (s, 2 H), 1.9 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.1, 164.7, 138.4, 131.6, 129.1, 126.8, 123.9, 115.0, 34.1, 22.2 ppm. MS (70 eV, EI): *m*/*z* (%) = 201 (11), 200 (100) [M]$^+$, 199 (26), 185 (17), 160 (72), 77 (12). IR (ATR): ṽ = 2979, 2935, 2919, 1739, 1653, 1607, 1568, 1550, 1484, 1450, 1428, 1394, 1374, 1335, 1292, 1266, 1227, 1217, 1184, 1178, 1092, 1071, 1048, 1019, 1007, 990, 981, 976, 964, 960, 923, 917, 898, 858, 799, 773, 710, 694, 686, 665, 642, 633, 628, 622, 615, 610, 606, 601 cm^{-1}. HRMS (EI): calcd. 200.0950; found 200.0948.

Synthesis of 2-[4-(Triisopropylsilyloxy)phenyl]quinoxaline (65): The title compound was prepared according to TP1 and TP3 from quinoxaline (**56**, 272 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%), P(*o*-furyl)$_3$ (46 mg, 10 mol-%) and (4-iodophenoxy)(triisopropyl)silane (750 mg, 2.00 mmol). Metallation conditions: 25 °C, 9 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **65** as a yellow oil (613 mg, 81%). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.3 (s, 1 H), 8.1 (t, J = 7.2 Hz, 4 H), 7.7 (td, J = 14.3, 6.8 Hz, 2 H), 7.1 (d, J = 8.4 Hz, 2 H), 1.2–1.3 (m, 3 H), 1.1 (d, J = 7.2 Hz, 18 H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 158.4, 151.6, 143.1, 142.3, 141.1, 130.2, 129.5, 129.4, 129.1, 129.0, 128.9, 120.6, 17.9, 12.7 ppm. MS (70 eV, EI): *m*/*z* (%) = 379 (13), 378, (45) [M]$^+$, 336 (30), 335 (30), 308 (12), 307 (55), 293 (14), 280 (18), 279 (100), 265 (52), 205 (11), 139 (31). IR (ATR): ṽ = 2943, 2891, 2866, 1602, 1576, 1544, 1514, 1488, 1462, 1422, 1389, 1336, 1313, 1269, 1229, 1169, 1134, 1125, 1107, 1071, 1047, 1011, 996, 957, 906, 882, 840, 760, 738, 729, 683, 661, 654, 643, 630, 626, 621, 606 cm^{-1}. HRMS (EI): calcd. 378.2127; found 378.2133.

Synthesis of 2-(Cyclohex-2-enyl)-6-nitrobenzothiazole (66): The title compound was prepared according to TP1 and TP5 from 6-nitrobenzothiazole (**57**, 360 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%)

and 3-bromocyclohexene (355 mg, 2.20 mmol). Metallation conditions: –50 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **66** as yellow solid (410 mg, 79%). M.p. 97.0–98.3 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.8, (s, 1 H), 8.4 (d, *J* = 8.9 Hz, 1 H), 8.1 (d, *J* = 8.9 Hz, 1 H), 6.1–6.1 (m, 1 H), 5.9–6.0 (m, 1 H), 4.0–4.1 (m, 1 H), 2.2–2.3 (m, 3 H), 1.9–2.0 (m, 1 H), 1.7–1.9 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 183.2, 157.2, 144.6, 135.4, 131.6, 125.8, 122.9, 121.5, 118.2, 41.1, 30.2, 24.8, 20.4 ppm. MS (70 eV, EI): *m/z* (%) = 261 (16), 260 (100) [M]$^+$, 259 (32), 245 (22), 232 (13), 231 (49), 214 (18), 213 (19), 194 (46), 79 (16), 67 (13), 63 (21), 44 (19). IR (ATR): ṽ = 3109, 2952, 2927, 2905, 1569, 1559, 1512, 1444, 1429, 1340, 1333, 1291, 1281, 1245, 1223, 1172, 1129, 1120, 1072, 1041, 972, 908, 891, 867, 838, 814, 750, 728, 723, 675, 653, 638, 622 cm^{-1}. HRMS (EI): calcd. 260.0619; found 260.0608.

Synthesis of 2-(Cyclohex-2-enyl)-1-methyl-1*H*-indole-3-carbaldehyde (67): The title compound was prepared according to TP1 and TP5 from 1-methyl-1*H*-indole-3-carbaldehyde (**58**, 318 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%) and 3-bromocyclohexene (355 mg, 2.20 mmol). Metallation conditions: 25 °C, 1.25 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 3:1) gave **67** as a yellow oil (240 mg, 50%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.3 (s, 1 H), 8.3–8.4 (m, 1 H), 7.3–7.4 (m, 3 H), 6–00–6.1 (m, 1 H), 5.8–5.9 (m, 1 H), 3.8 (s, 3 H), 3.8–3.9 (m, 1 H), 2.1–2.2 (m, 3 H), 1.9–2.1 (m, 1 H), 1.8–1.9 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 185.3, 153.6, 137.2, 129.4, 127.5, 125.7, 123.3, 123.0, 121.7, 114.3, 109.3, 34.1, 30.8, 30.5, 24.6, 22.2 ppm. MS (70 eV, EI): *m/z* (%) = 240 (14), 239 (100) [M]$^+$, 238 (13), 222 (19), 210 (11), 210 (14), 184 (38), 182 (14), 167 (17), 157 (12). IR (ATR): ṽ = 2930, 2859, 1739, 1683, 1641, 1611, 1580, 1517, 1468, 1447, 1413, 1386, 1323, 1294, 1246, 1223, 1218, 1186, 1156, 1126, 1104, 1073, 1048, 1038, 1015, 982, 932, 917, 890, 860, 818, 801, 747, 729, 702, 674, 656, 642, 635, 631, 626, 622, 616, 611, 605 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{17}NO$ 239.1310; found 239.1302.

Synthesis of 3-Bromo-2-(3-nitrophenyl)quinoline (68): The title compound was prepared according to TP1 and TP3 from 3-bromoquinoline (**21**, 416 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%), P(*o*-furyl)$_3$ (46 mg, 10 mol-%) and 3-iodonitrobenzene (500 mg, 2.00 mmol). Metallation conditions: 25 °C, 4 h. Recrystallization from CH_2Cl_2 and Et_2O gave **68** as a colourless solid (564 mg, 86%). M.p. 209.8–211.3 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.7 (t, *J* = 1.7 Hz, 1 H), 8.6 (s, 1 H), 8.4 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1 H), 8.1–8.2 (m, 2 H), 7.8–7.9 (m, 2 H), 7.7–7.8 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 155.4, 151.7, 148.0, 146.6, 140.5, 135.7, 130.6, 129.6, 129.1, 128.5, 128.2, 126.6, 124.9, 123.7 ppm. MS (70 eV, EI): *m/z* (%) = 331 (10), 330 (60), 329 (13), 328 (60) [M]$^+$, 285 (18), 284 (100), 283 (18), 282 (95), 249 (49), 219 (11), 204 (12), 203 (71), 202 (33), 201 (13), 176 (12), 142 (13), 141 (11), 127 (10), 101 (22), 88 (17), 75 (14). IR (ATR): ṽ = 2989, 2970, 1739, 1530, 1488, 1482, 1435, 1400, 1394, 1372, 1366, 1348, 1300, 1276, 1270, 1262, 1241, 1229, 1217, 1195, 1147, 1130, 1103, 1087, 1072, 1058, 968, 955, 907, 902, 892, 857, 818, 790, 781, 749, 743, 740, 709, 682, 669, 661, 622, 606, 603 cm^{-1}. HRMS (EI): calcd. 327.9847; found 327.9841.

Synthesis of Ethyl 3-Fluoro-2-(2-thienylcarbonyl)benzoate (69): The title compound was prepared according to TP1 from ethyl 3-fluorobenzoate (**59**, 416 mg, 2.00 mmol) and Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol). After cooling to –40 °C, CuCN·2LiCl (2.2 mL, 1 M in THF, 2.2 mmol) was added, followed by 2-thiophenoyl chloride (322 mg, 2.20 mmol). The mixture was briefly warmed to 25 °C and stirred for 12 h. The metallation was quenched by the addition of a satd. aq. NH$_4$Cl solution (15–30 mL) and added to a separating funnel with Et$_2$O (10–20 mL) and EtOAc (10–20 mL). The organic layer was extracted with a satd. aq. NH$_4$Cl solution (3 × 15 mL). The combined aqueous layers were extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine (20 mL), dried with anhydrous MgSO$_4$, filtered and concentrated in vacuo. Flash chromatography on silica (*n*-pentane/diethyl ether, 5:1) gave **69** as a colourless solid (417 mg, 75%). M.p. 89.8–91.3 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.9–8.0 (m, 1 H), 7.7 (dd, *J* = 5.0, 1.2 Hz, 1 H), 7.6 (td, *J* = 8.1, 5.4 Hz, 1 H), 7.4–7.4 (m, 2 H), 7.1 (dd, *J* = 5.0, 3.7 Hz, 1 H), 4.2 (q, *J* = 7.2 Hz, 2 H), 1.2 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 184.5, 164.6 (d, $J_{C\text{-}F}$ = 3 Hz), 159.1 (d, $J_{C\text{-}F}$ = 248 Hz), 144.6 134.7, 134.1, 130.9, 130.8, 130.8, 128.5 (d, $J_{C\text{-}F}$ = 20 Hz), 126.3 (d, $J_{C\text{-}F}$ = 3 Hz), 120.30 (d, $J_{C\text{-}F}$ = 22 Hz), 61.91, 13.63 ppm. MS (70 eV, EI): *m/z* (%) = 278 (46) [M]$^+$, 234 (27), 233 (36), 167 (31), 111 (100). IR (ATR): ṽ = 3094, 2986, 1716, 1650, 1606, 1577, 1560, 1522, 1517, 1476, 1448, 1419, 1413, 1391, 1363, 1353, 1278, 1237, 1194, 1158, 1148, 1112, 1085, 1067, 1051, 1024, 994, 957, 928, 914, 884, 863, 849, 824, 813, 803, 763, 752, 725, 684, 667, 648, 633, 621, 615, 607 cm^{-1}. HRMS: calcd. 278.0413; found 278.0405.

Synthesis of Ethyl 3-Cyano-2-[2-(ethoxycarbonyl)allyl]benzoate (70): The title compound was prepared according to TP1 and TP5 from ethyl 3-cyanobenzoate (**60**, 350 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%) and ethyl 2-(bromomethyl)acrylate (420 mg, 2.20 mmol). Metallation conditions: 25 °C, 30 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 2:1) gave **70** as a yellow oil (413 mg, 72%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.1 (dd, *J* = 7.9, 1.5 Hz, 1 H), 7.8 (dd, *J* = 7.7, 1.5 Hz, 1 H), 6.2–6.3 (m, 1 H), 5.0–5.1 (m, 1 H), 7.5 (t, *J* = 7.9 Hz, 1 H), 4.3 (q, *J* = 7.2 Hz, 2 H), 4.3 (s, 2 H), 4.3 (q, *J* = 7.2 Hz, 2 H), 1.4 (t, *J* = 7.1 Hz, 3 H), 1.3 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 166.2, 166.0, 143.1, 138.5, 136.1, 134.8, 132.7, 127.4, 125.5, 117.3, 116.0, 61.8, 61.0, 34.0, 14.2, 14.1 ppm. MS (70 eV, EI): *m/z* (%) = 287 (4) [M]$^+$, 242 (24), 241 (60), 214 (14), 213 (74), 186 (30), 185 (100), 170 (73), 169 (57), 168 (35), 167 (17), 158 (10), 156 (12), 141 (16), 140 (36). IR (ATR): ṽ = 2984, 2940, 2901, 2230, 1714, 1635, 1583, 1448, 1393, 1367, 1268, 1207, 1190, 1173, 1130, 1095, 1084, 1066, 1057, 1022, 947, 863, 818, 766, 754, 682, 669, 646, 641, 635, 623, 601 cm^{-1}. HRMS: calcd. 287.1158; found 287.1156.

Synthesis of Ethyl 6-Bromo-3-chloro-3′-methylbiphenyl-2-carboxylate (71): The title compound was prepared according to TP1 and TP3 from ethyl 5-bromo-2-chlorobenzoate (**61**, 525 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%), P(*o*-furyl)$_3$ (46 mg, 10 mol-%) and 3-iodotoluene (436 mg, 2.00 mmol). Metallation conditions: 25 °C, 60 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 19:1) gave **71** as a red oil (470 mg, 67%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.6 (d, *J* = 8.4 Hz, 1 H), 7.2–7.3 (m, 2 H), 7.2 (d, *J* = 7.7 Hz, 1 H), 7.1 (d, *J* = 7.7 Hz, 2 H), 4.0 (q, *J* = 7.1 Hz, 2 H), 2.4 (s, 3 H), 1.0 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.6, 141.7, 137.7, 137.6, 135.8, 135.3, 134.2, 134.0, 129.9, 129.5, 129.1, 127.9, 126.4, 122.2, 61.7, 21.4, 13.6 ppm. MS (70 eV, EI): *m/z* (%) = 356 (22), 355 (14), 354 (82), 353 (10), 352 (62) [M]$^+$, 326 (17), 324 (12), 311 (27), 310 (29), 309 (100), 308 (32), 307 (77), 295 (35), 294 (27), 230 (22), 229 (19), 228 (60), 200 (12), 199 (19), 166 (18), 165 (55), 164 (25), 163 (22), 44 (14). IR (ATR): ṽ = 2980, 1732, 1606, 1586, 1574, 1461, 1436, 1403, 1386, 1364, 1281, 1257, 1241, 1162, 1135, 1098, 1057, 1010, 912, 876, 859, 811, 793, 777, 762, 752, 702, 654, 645, 620, 612, 606 cm^{-1}. HRMS: calcd. 351.9866; found 351.9859.

Synthesis of 4-Fluoro-2-(2-methylprop-2-en-1-yl)benzonitrile (72): The title compound was prepared according to TP2 and TP5 from 4-fluorobenzonitrile (**62**, 242 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.2 mmol), CuCN·2LiCl (0.2 mL, 1 M in THF 10 mol-%) and 3-bromo-2-methylpropene (297 mg, 2.20 mmol). Metallation conditions: 100 °C, 2 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 19:1) gave **72** as a colourless oil (283 mg, 81 %). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.6 (dd, J = 4.7, 2.1 Hz, 1 H), 7.5 (m, 1 H), 7.1 (t, J = 9.1 Hz, 1 H), 4.9 (s, 1 H), 4.7 (s, 1 H), 3.4 (s, 2 H), 1.7 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.2, 161.9, 142.1, 135.4, 135.3, 132.5, 132.3, 128.9, 128.7, 118.2, 116.8, 116.5, 113.3, 108.4, 108.4, 36.5, 36.5, 22.1 ppm (complexity due to C–F splitting observed, definitive assignments not made). MS (70 eV, EI): *m/z* (%) = 175 (66) [M]$^+$, 161 (10), 160 (100), 158 (10), 147 (13), 135 (12), 134 (30), 133 (11), 107 (11), 57 (13), 43 (59). IR (ATR): $\tilde{\nu}$ = 2970, 2942, 2920, 2231, 1739, 1653, 1590, 1493, 1443, 1376, 1247, 1230, 1217, 1103, 1066, 895, 829, 780, 728, 682 cm^{-1}. HRMS (EI): calcd. 175.0797; found 175.790.

Synthesis of 3-Fluoro-4′-[(triisopropylsilyl)oxy]biphenyl-2-carbonitrile (73): The title compound was prepared according to TP2 and TP3 from 2-fluorobenzonitrile (**63**, 242 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.2 mmol), (4-iodophenoxy)(triisopropyl)silane (850 mg, 2.20 mmol), [Pd(dba)$_2$] (56 mg, 5 mol-%) and P(*o*-furyl)$_3$ (46 mg, 10 mol-%). Metallation conditions: 140 °C, 2 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 9:1) gave **73** as a colourless solid (610 mg, 83 %). M.p. 81.7–82.9 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.7 (td, J = 7.7, 1.7 Hz, 1 H), 7.6 (m, 1 H), 7.4 (dd, J = 6.7, 1.8 Hz, 2 H), 7.0 (m, 2 H), 1.3 (m, 3 H), 1.1 (d, J = 7.0 Hz, 18 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 161.9, 158.4, 156.7, 135.3, 135.3, 131.6, 130.4, 130.2, 130.0, 130.0, 126.1, 126.1, 124.9, 124.8, 120.2, 114.2, 114.2, 102.4, 102.1, 17.9, 12.7 ppm (complexity due to C–F splitting observed, definitive assignments not made). MS (70 eV, EI): *m/z* (%) = 369 (57) [M]$^+$, 326 (28), 298 (41), 271 (64), 257 (29), 196 (24), 135 (100), 128 (22), 77 (20). IR (ATR): $\tilde{\nu}$ = 2946, 2867, 2231, 1739, 1604, 1513, 1457, 1403, 1384, 1366, 1304, 1264, 1235, 1171, 1110, 1074, 1014, 993, 909, 883, 847, 822, 791, 740, 721, 688, 650, 625 cm^{-1}. HRMS (EI): calcd. 369.1924; found. 369.1916.

Synthesis of 1-(1-Benzothien-2-yl)-2,2-dimethylpropan-1-one (74): The title compound was prepared according to TP2 and TP4 from benzothiophene (**22**, 268 mg, 2.00 mmol), Zn base **54** (2.4 mL, 0.5 M in THF, 1.2 mmol), pivaloyl chloride (385 mg, 2.20 mmol) and CuCN·2LiCl (0.2 mL, 1 M in THF, 10 mol-%). Metallation conditions: 140 °C, 1 h. Flash chromatography on silica (*n*-pentane/diethyl ether, 40:1) gave **74** as a colourless oil (363 mg, 83 %). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.0 (s, 1 H), 7.9 (m, 2 H), 7.4 (m, 2 H), 1.5 (s, 9 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 200.3, 142.1, 141.6, 139.2, 128.8, 127.1, 125.8, 124.8, 122.5, 44.2, 28.2 ppm. MS (70 eV, EI): *m/z* (%) = 218 (15) [M]$^+$, 161 (81), 89 (11), 43 (14). IR (ATR): $\tilde{\nu}$ = 2970, 2930, 2901, 1739, 1647, 1593, 1558, 1510, 1474, 1457, 1430, 1394, 1366, 1274, 1217, 1144, 1126, 1072, 937, 898, 864, 842, 789, 758, 742, 723 cm^{-1}. HRMS (EI): calcd. 218.0765; found 218.0759.

Acknowledgments

We thank the Fonds der Chemischen Industrie (FCI), the Deutsche Forschungsgemeinschaft (DFG) and the ERC (European Research Council) for financial support. We thank V. Hartdegen for preliminary experiments. G. C. thanks the Humboldt Foundation for a fellowship. We also thank Chemetall GmbH (Frankfurt), Evonik Industries AG (Essen), Heraeus GmbH (Hanau) and BASF AG (Ludwigshafen) for their generous gifts of chemicals.

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Received: December 22, 2008