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Direct Zincation of Functionalized Aromatics and Heterocycles by Using a Magnesium Base in the Presence of $ZnCl_2$

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Dedicated to Professor Wolfgang Steglich on the occasion of his 75th birthday

Abstract: A wide range of polyfunctional aryl and heteroaryl zinc reagents were efficiently prepared in THF by using $(TMP)_2Mg{\cdot}2LiCl$ (TMP = 2,2,6,6-tetramethylpiperamidyl) in the presence of $ZnCl_2$. The possible pathways of this metalation procedure as well as possible reactive intermediates are discussed. This experimental protocol expands the tolerance of functional groups and allows an efficient zincation of sensitive heterocycles such as quinoxaline or pyrazine. The zincated arenes and heteroarenes react with various electrophiles providing the expected products in 60–95% yield.

Keywords: cross-coupling · heterocycles · metalation · organometallics · zincation

Introduction

Directed lithiations are important reactions for the functionalization of aromatics and heterocycles.[1] In contrast, directed metalations using magnesium bases have been much less used.[2] Recently, we have shown that the mixed lithium–magnesium bases (TMP)MgCl·LiCl[3] and especially $(TMP)_2Mg{\cdot}2LiCl$ (**1**; TMP = 2,2,6,6-tetramethylpiperamidyl)[4] are highly active and soluble magnesium bases allowing smooth metalations of various aromatics and heterocycles with an excellent functional group compatibility. However, deprotonation of some heterocyclic aromatic rings such as quinoxaline (**2a**) gave unsatisfactory results due to the high reactivity of the intermediate magnesium species (Scheme 1). It is already known that the metalation of diazines is challenging due to very facile competitive nucleophilic addition reactions.[5] However, in the course of our studies, we have found that the addition of $ZnCl_2$ to the substrate, prior to the addition of the base (**1**), leads to excellent results. Eaton and co-workers have already performed direct lithiations with Li(TMP) in the presence of mercury salts.[6] The in situ generated organomercurials can be further converted to corresponding halides or transmetalated with organomagnesium or organolithium reagents in a process called reverse transmetalation.[7,8] Herein, we wish to report a direct method for the deprotonation and functionalization of some sensitive aromatic and heteroaromatic substrates by using $(TMP)_2Mg{\cdot}2LiCl$ in the presence of $ZnCl_2$. The methodology allows many sensitive aromatics and heterocycles to be metalated at 25 °C, which gives the expected

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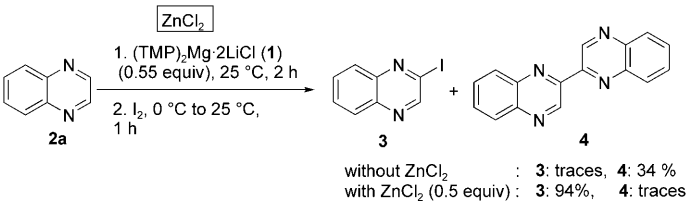


Scheme 1. Functionalization of quinoxaline (**2a**) with $(TMP)_2Mg{\cdot}2LiCl$ (**1**) in THF in the presence and absence of $ZnCl_2$.

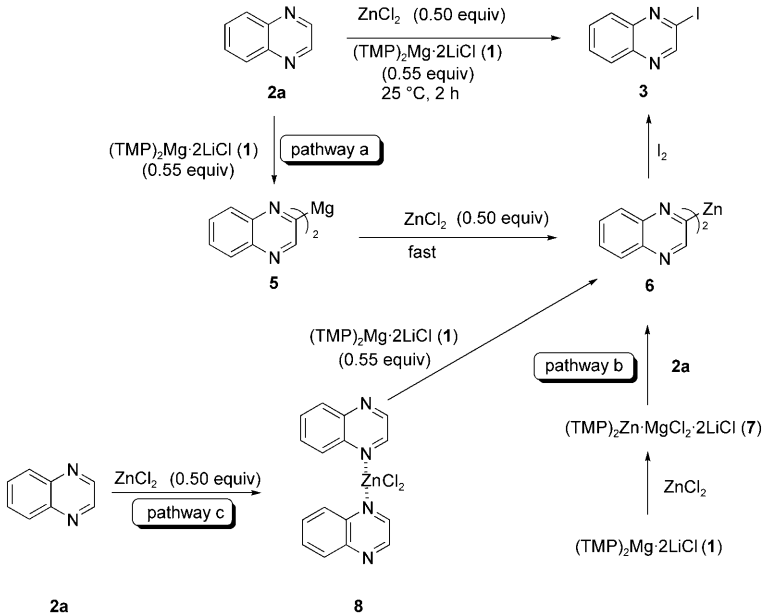
functionalized products in good yields after reaction with electrophiles.

Results and Discussion

We first investigated the metalation of quinoxaline (**2a**). The treatment of **2a** with $(TMP)_2Mg{\cdot}2LiCl$ (**1**; 0.55 equiv) at 25 °C for 2 h in THF gave only traces of the desired quinoxalyl iodide (**3**) after iodolysis, while the major product, the dimeric heterocycle **4**, was isolated in 34% yield (Scheme 1). Attempts to perform the same reaction at lower temperature (0 to −78 °C) also gave unsatisfactory yields due to the formation of dimer **4**. In contrast, treatment of **2a** with $ZnCl_2$ (0.5 equiv) in THF followed by the slow addition of **1** (0.55 equiv) gave a metalated intermediate within 2 h at 25 °C. After iodolysis we observed traces of dimer **4**, and quinoxalyl iodide (**3**) was isolated in 94% yield (Scheme 1).

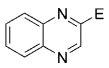
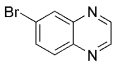
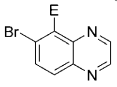
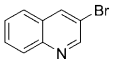
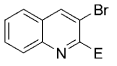
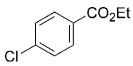
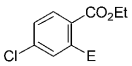
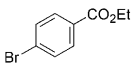
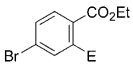
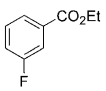
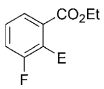
Several reaction pathways leading to this result are conceivable (Scheme 2). In pathway a, base **1** reacts first with quinoxaline (**2a**) affording the magnesiated heterocycle **5**. After a fast transmetalation with $ZnCl_2$ (0.5 equiv) the quinoxalylzinc reagent **6** is formed (Scheme 2, pathway a). Alternatively in pathway b, base **1** reacts rapidly with $ZnCl_2$ to provide $(TMP)_2Zn{\cdot}MgCl_2{\cdot}2LiCl$ (**7**; Scheme 2, pathway b), which subsequently reacts with quinoxaline (**2a**) leading to the zinc reagent **6**. This second pathway can be excluded since the reaction times of the in situ procedure are considerably shorter (25 °C, 2 h) than the metalation using $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**9**) generated separately (25 °C, 5 h; Table 2, entry 1, see below).[9] Also, a freshly prepared solution of **7** in THF obtained by mixing $ZnCl_2$ with **1** displayed an even lower metalation ability. Furthermore, a third pathway has to be considered (Scheme 2, pathway c): the heterocycle **2a** coordinates $ZnCl_2$ affording the tentative Zn complex **8**,[10] which reacts with **1** leading to the zinc derivative **6** after fast transmetalation. This last pathway is the preferred one, since we noticed that **1** reacts very rapidly with $ZnCl_2$ to afford the zinc reagent **7**.[11] Therefore, the order of addition of all the reaction partners (first $ZnCl_2$, then base **1**) is essential for achieving the reported metalation times. To obtain more information about the possible intermediates, additional kinetic studies were performed by changing the ratio between **1** and $ZnCl_2$ (more details are given below).

This metalation procedure, for example, the magnesiation of organic substrates by **1** in THF in the presence of $ZnCl_2$ proves to be quite general. Thus, a number of sensitive aromatics and heterocycles were cleanly deprotonated with **1** in the presence of $ZnCl_2$ at 25 °C (Table 1). The zincated quinoxaline (**6**) underwent a Negishi cross-coupling[12] with *p*-IC_6H_4O(TIPS) (TIPS = triisopropylsilyl) in the presence of $[Pd(dba)_2]$ (2 mol%; dba = dibenzylideneacetone) and P(*o*-furyl)$_3$ (4 mol%) at 25 °C for 1 h, providing the biphenyl derivative **14a** in 71% yield (Table 1, entry 1). Moreover, after transmetalation with CuCN·2 LiCl,[13] the reaction with 3-cyclohexenyl bromide led to **14b** in 65% yield (entry 2). Interestingly, 6-bromoquinoxaline (**2b**) was selectively metalated at position 5 giving the corresponding ketones **14c** and **14d** in 81–86% yields after copper-mediated reactions with pivaloyl and benzoyl chloride (entries 3 and 4). Furthermore, the functionalization of pyrazines and pyrimidines using metalation procedures is also of great importance.[14] By using the $ZnCl_2$–$(TMP)_2Mg{\cdot}2LiCl$ protocol, the metalation of pyrazine (**2c**) was achieved within 30 min. Further reaction with benzaldehyde gave the corresponding alcohol **14e** in 60% yield (entry 5). This protocol was also used to perform metalations on bromo-substituted pyrimidines. Thus, 2-bromopyrimidine (**10a**) and 5-bromopyrimidine (**10b**) were quantitatively zincated within 12 and 0.5 h, respectively. Palladium-catalyzed cross-couplings and copper-mediated allylations gave the corresponding functionalized pyrimidines **15a–f** in 66–91% yield (entries 6–11). Similarly, 3-bromoquinoline (**11**) was exclusively zincated at position 2 providing, after the reactions with electrophiles, the corresponding derivatives **16a** and **16b** in 70–82% yield (entries 12 and 13). The direct zincation of aromatic esters bearing a halogen group using



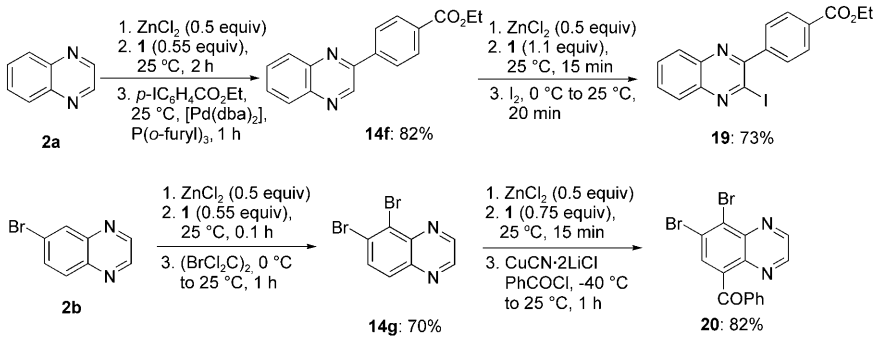
Scheme 2. Postulated intermediates of the metalation of **2a** with $(TMP)_2Mg{\cdot}2LiCl$ (**1**) in the presence of $ZnCl_2$.

Table 1. Products of type **14**–**18** obtained by direct metalation of the substrates **2**–**13** with $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**) at 25 °C in the presence of $ZnCl_2$ (0.5 equiv) followed by the reaction with electrophiles.

Entry	Substrate	*t* [h]	E–X	Product	Yield [%][a]
					
1	**2a**	2	*p*-IC_6H_4O(TIPS)	**14a**: E = *p*-C_6H_4O(TIPS)	71[c]
2	**2a**	2	*c*-C_6H_9Br	**14b**: E = *c*-C_6H_9	65[b]
					
3	**2b**	0.1	*t*BuCOCl	**14c**: E = CO*t*Bu	81[b]
4	**2b**	0.1	PhCOCl	**14d**: E = COPh	86[b]
					
5	**2c**	0.5	PhCHO	**14e**: E = PhC(OH)	60
					
6	**10a**	12	*p*-IC_6H_4CN	**15a**: E = *p*-C_6H_4CN	91[c]
7	**10a**	12	*p*-$IC_6H_4CO_2Et$	**15b**: E = *p*-$C_6H_4CO_2Et$	72[c]
8	**10a**	12	*c*-C_6H_9Br	**15c**: E = *c*-C_6H_9	70[b]
9	**10a**	12	$CH_2{=}C(CH_3)CH_2Br$	**15d**: E = $CH_2{=}C(CH_3)CH_2$	72[b]
					
10	**10b**	0.5	*c*-C_6H_9Br	**15e**: E = *c*-C_6H_9	70[b]
11	**10b**	0.5	$CH_2{=}C(CH_3)CH_2Br$	**15f**: E = $CH_2{=}C(CH_3)CH_2$	66[b]
					
12	**11**	2.5	*p*-$IC_6H_4CO_2Et$	**16a**: *p*-$IC_6H_4CO_2Et$	82[c]
13	**11**	2.5	$CH_2{=}C(CH_3)CH_2Br$	**16b**: E = $CH_2{=}C(CH_3)CH_2$	70[b]
					
14	**12a**	12	*p*-$IC_6H_4CO_2Et$	**17a**: E = *p*-$C_6H_4CO_2Et$	90[c]
15	**12a**	12	$CH_2{=}C(CH_3)CH_2Br$	**17b**: E = $CH_2{=}C(CH_3)CH_2$	76[b]
					
16	**12b**	12	$(BrCl_2C)_2$	**17c**: E = Br	76
17	**12b**	12	PhCOCl	**17d**: E = COPh	76[b]
					
18	**12c**	3	PhCOCl	**17e**: E = COPh	80[b]
19	**12c**	3	$(BrCl_2C)_2$	**17f**: E = Br	74
					
20	**13a**	12	*p*-$IC_6H_4CO_2Et$	**18a**: E = *p*-$C_6H_4CO_2Et$	90[c]
21	**13a**	12	PhCOCl	**18b**: E = COPh	82[b]

[a] Isolated yield of analytically pure product. [b] A transmetalation using CuCN·2 LiCl (1.1 equiv) was performed. [c] Obtained by a palladium-catalyzed cross-coupling.

$(TMP)Zn(tBu)_2Li$ as the metalation reagent usually requires low temperature to avoid the formation of benzynes.[15] Remarkably, the deprotonation of the esters **12a** and **12b** with 0.55 equiv of $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**) in the presence of $ZnCl_2$ was also accomplished at 25 °C leading to the zincated intermediates within 12 h reaction time. After quenching with various electrophiles, the corresponding functionalized ethyl benzoates **17a–d** were isolated in 76–90% yields (entries 14–17). In contrast, full metalation of ethyl 3-fluorobenzoate (**12c**) was completed after 3 h by using only 0.55 equiv of base **1**. Further bromolysis or benzoylation in the presence of CuCN·2 LiCl gave the derivatives **17e** and **17f** in 74–80% yield (entries 18 and 19). Although the lithiation of 1,3-difluorobenzene (**13a**) was achieved with *sec*-butyllithium at −75 °C,[16] the metalation of this substrate can be successfully performed at 25 °C by using the $ZnCl_2$–$(TMP)_2Mg{\cdot}2\,LiCl$ protocol. After a palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate or a copper-mediated benzoylation, the functionalized 1,3-difluorobenzenes **18a** and **18b** were isolated in 82–90% yield (entries 20 and 21). Moreover, this methodology also allows multiple functionalization of heterocyclic substrates. For example, quinoxaline (**2a**) was sequentially functionalized at positions 2 and 3. The zincated quinoxaline **6** was reacted with ethyl 4-iodobenzoate using $[Pd(dba)_2]$ (2 mol%) and P(*o*-furyl)$_3$ (4 mol%) as a catalytic system to provide the functionalized quinoxaline **14f** in 82% yield. A subsequent zincation of **14f** followed by the reaction with iodine afforded iodide **19** in 73% overall yield (Scheme 3). Surprisingly, 6-bromoquinoxaline (**2b**) was first metalated at position 5 to give dibromide **14g** by the reaction with $(BrCl_2C)_2$ in 70% yield. The presence of the extra bromine atom in position 6 changes the regioselectivity, due to the inductive effect of the bromine atom, to an exclusive proton abstraction in position 5. Furthermore, the second metalation occurs only at position



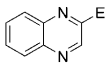
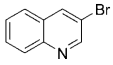
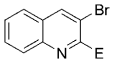
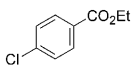
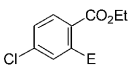
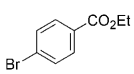
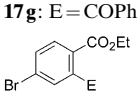
Scheme 3. Double functionalization of the quinoxalines **2a** and **2b**.

8 giving the corresponding ketone **20** by means of a copper-mediated benzoylation in 82% yield (Scheme 3). Therefore, the use of a bromine substituent in position 6 reveals a route to functionalization of the aromatic ring of quinoxalines and may be of general synthetic value.

Additional experiments were performed to obtain more information about the reaction mechanism. Thus, the metalation and functionalization of some of the aromatics and heterocycles listed in Table 1 using directly the zinc bisamide $(TMP)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (**9**)[9] were studied and the metalation rates were compared with those of the $ZnCl_2$–$(TMP)_2Mg{\cdot}2\,LiCl$ protocol. In general, the metalation time dramatically increased when **9** was used (Table 2). A remarkable example is the metalation of 5-bromopyrimidine (**10b**; Table 2, entry 3). In this case, the metalation using the $ZnCl_2$–$(TMP)_2Mg{\cdot}2\,LiCl$ protocol occurs 10 times faster than using freshly prepared $(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2\,LiCl$ (**9**). Moreover, the full conversion of the halo esters **12a** and **12b** into the corresponding zinc reagents with **9** was only achieved after 110 h (Table 2, entries 5–7). The same reaction can be completed within 12 h by using the $ZnCl_2$–$(TMP)_2Mg{\cdot}2\,LiCl$ protocol (Table 1, entries 14–17). These results suggest that the formation of a zinc bisamide intermediate (pathway b, Scheme 1) does not occur, and that the more reactive base **1** performs the metalation rapidly on the precomplexed aromatic or heterocyclic system, which is immediately converted into the corresponding zinc reagent. Kinetic studies were also performed by changing the ratio between base **1** and $ZnCl_2$. Interestingly, when 1.1 equiv of **1** and 0.5 equiv of $ZnCl_2$ were used, full metalation of ethyl 4-chlorobenzoate (**12a**) was achieved within 1 h, thus showing that this reaction can be accelerated by increasing the amount of $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**; Figure 1).

We also investigated the preparation and application of other mixed bases[17] derived from $(TMP)_2Mg{\cdot}2\,LiCl$ and $ZnCl_2$. Thus, mixed-metal bases like $(TMP)_3ZnMgCl{\cdot}0.5\,MgCl_2{\cdot}3\,LiCl$ and $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$ were prepared by stirring 1 equiv of $ZnCl_2$ with 1.5 and 2 equiv of $(TMP)_2Mg{\cdot}2\,LiCl$, respectively (30 min at 25 °C), and their activities were investigated for the metalation of ethyl 4-chlorobenzoate (**12a**; Figure 2). Remarkably, the base $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$ (0.55 equiv) showed high activity leading to the complete metalation of **12a** within 1 h. After transmetalation with CuCN·2 LiCl, the reaction with benzoyl chloride provided ketone **17g** in 76% yield (Scheme 4). This result is comparable to the yield of **17g** obtained by using $(TMP)_2Mg{\cdot}2\,LiCl$ (1.1 equiv) in the presence of $ZnCl_2$ (0.55 equiv). Therefore, $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$ could be one of the active intermediates in this reaction (Figure 2 and Scheme 4). When 1.1 equiv of $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$ was used the metalation of **12a** appeared to be even faster, but after the subsequent reaction with benzoyl chloride in the presence of CuCN·2 LiCl only

Table 2. Products of type **14–17** obtained by direct metalation of the substrates **2–12** with $(TMP)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (**9**) at 25 °C followed by the reaction with electrophiles.

Entry	Substrate	t [h][a]	E–X	Product	Yield [%][b]
					
1	**2a**	5 (2)	p-$IC_6H_4CO_2Et$	**14f**: E = p-$C_6H_4CO_2Et$	82[c]
2	**2a**	5 (2)	m-$IC_6H_4CF_3$	**14h**: E = m-$C_6H_4CF_3$	88[d]
					
3	**10b**	5 (0.5)	p-IC_6H_4CN	**15g**: E = p-C_6H_4CN	75[d]
					
4	**11**	2 (0.5)	p-IC_6H_4CN	**16c**: E = p-C_6H_4CN	95[d]
					
5	**12a**	110 (12)	PhCOCl	**17g**: E = COPh	85[c]
					
6	**12b**	110 (12)	m-$IC_6H_4CF_3$	**17h**: E = m-$C_6H_4CF_3$	83[d]
7	**12b**	110 (12)	p-$IC_6H_4CO_2Et$	**17i**: E = p-$C_6H_4CO_2Et$	78[d]

[a] Metalation times using $(TMP)_2Zn{\cdot}2\,MgCl_2{\cdot}2\,LiCl$ (**9**); in parentheses are the metalation times using $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**) in the presence of $ZnCl_2$. [b] Isolated yield of analytically pure product. [c] A transmetalation CuCN·2 LiCl (1.1 equiv) was performed. [d] Obtained by a palladium-catalyzed cross-coupling.

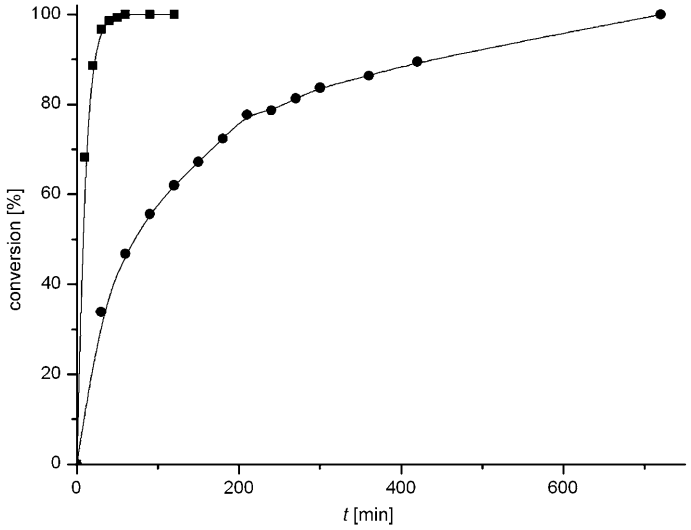


Figure 1. Influence of the $(TMP)_2Mg{\cdot}2\,LiCl/ZnCl_2$ ratio on the metalation rate of the ethyl 4-chlorobenzoate (**12a**) at 25 °C: ■ = 1.10 equiv $(TMP)_2Mg{\cdot}2\,LiCl$ + 0.5 equiv $ZnCl_2$ in situ; ● = 0.55 equiv $(TMP)_2Mg{\cdot}2\,LiCl$ + 0.5 equiv $ZnCl_2$ in situ.

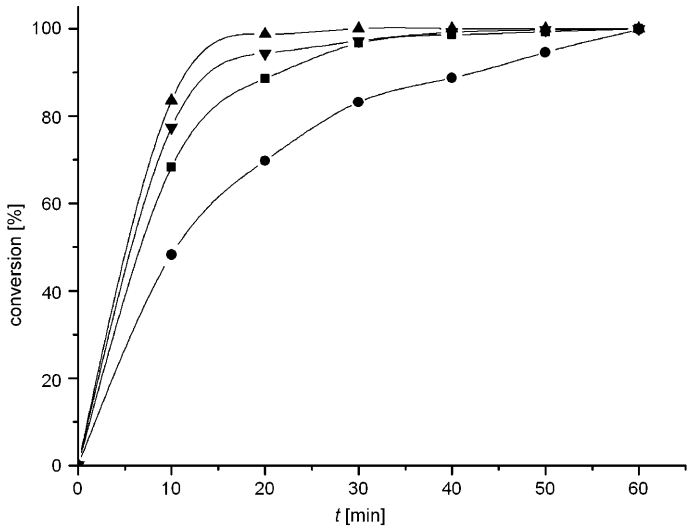
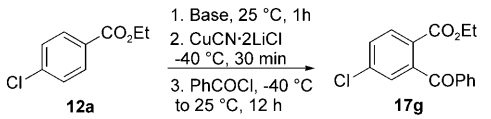


Figure 2. Metalation of substrate **12a** using different mixed bases: ■ = 1.1 equiv $(TMP)_2Mg{\cdot}2\,LiCl$ + 0.5 equiv $ZnCl_2$ in situ; ● = 1.1 equiv $(TMP)_3ZnMgCl{\cdot}0.5\,MgCl_2{\cdot}3\,LiCl$; ▲ = 1.1 equiv $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$; ▼ = 0.55 equiv $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$.

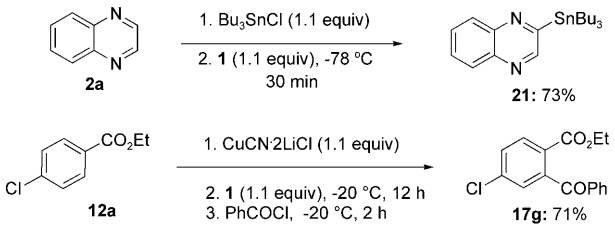


1.10 equiv $(TMP)_2Mg{\cdot}2LiCl$ + 0.5 equiv $ZnCl_2$ in situ	86%
0.55 equiv $(TMP)_4Zn(MgCl)_2{\cdot}4LiCl$	76%
1.10 equiv $(TMP)_3ZnMgCl{\cdot}0.5MgCl_2{\cdot}3LiCl$	13%
1.10 equiv $(TMP)_4Zn(MgCl)_2{\cdot}4LiCl$	traces

Scheme 4. Metalation of substrate **12a** using different mixed bases followed by a copper-mediated reaction with benzoyl chloride.

the formation of 1-benzoyl-2,2,6,6-tetramethylpiperidine was observed. Similarly, the base $(TMP)_3ZnMgCl{\cdot}0.5\,MgCl_2{\cdot}3\,LiCl$ (1.1 equiv) displayed a good kinetic basicity, but after a copper-mediated benzoylation ketone **17g** was isolated in only 13% yield (Scheme 4). Attempts to improve these reactions by using less than 0.5 equiv of the mixed-metal bases $(TMP)_3ZnMgCl{\cdot}0.5\,MgCl_2{\cdot}3\,LiCl$ and $(TMP)_4Zn(MgCl)_2{\cdot}4\,LiCl$ led to lower metalation rates but not to improved yields of **17g**.

We have also investigated the preparation of other organometallics by performing selective deprotonations with $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**) in the presence of various other organometallic compounds. Thus, **1** (1.1 equiv) was added dropwise to a mixture of quinoxaline (**2a**) and n-Bu_3SnCl (1.1 equiv) in THF at −78 °C. After stirring for 30 min, stannane **21** was isolated in 73% yield (Scheme 5). Similarly, ethyl 4-chlorobenzoate (**12a**) is smoothly deprotonated with **1** in the presence of CuCN·2 LiCl (1.1 equiv), giving the functionalized ketone **17g** in 71% yield after a subsequent reaction with benzoyl chloride.



Scheme 5. Metalation of **2a** and **12a** with $(TMP)_2Mg{\cdot}2\,LiCl$ (**1**) in the presence of other salts.

Conclusion

In summary, we have reported a simple method to deprotonate and functionalize a broad range of reactive aromatics and heterocycles by using the powerful base $(TMP)_2Mg{\cdot}2\,LiCl$ in the presence of $ZnCl_2$. The deprotonation reaction can be drastically accelerated by increasing the $(TMP)_2Mg{\cdot}2\,LiCl$-to-$ZnCl_2$ ratio. Mechanistic studies indicate that a precomplexation of the aromatic or heteroaromatic substrate facilitates the deprotonation with $(TMP)_2Mg{\cdot}2\,LiCl$. Finally, the methodology proved to be also efficient for preparing other reactive organometallics such as copper or tin derivatives through an in situ trapping by other salts. Applications toward the synthesis of biologically active molecules are currently being investigated in our laboratories.

Experimental Section

General: All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes that were used to transfer anhydrous sol-

vents or reagents were purged with argon prior to use. THF was freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy (25°C) and capillary GC. Column chromatography was performed by using silica gel (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated. (TMP)H and liquid acid chlorides were distilled prior to use.

Typical procedure 1 (TP 1)—Preparation of the reagent (TMP)$_2$Mg·2 LiCl: In an argon-flushed Schlenk flask, 2,2,6,6-tetramethylpiperidine ((TMP)H) (5.07 mL, 30 mmol) was dissolved in 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. After the addition was complete, the reaction mixture was warmed to 0°C and was stirred at this temperature for 30 min. Freshly titrated (TMP)MgCl·LiCl (1.0 M in THF, 30 mL, 30 mmol) was then added dropwise to the Li(TMP) 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 then removed under vacuum to afford a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the complete dissolution of the salts. The freshly prepared solution of (TMP)$_2$Mg·2 LiCl (**1**) in THF was titrated prior to use at 0°C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.6 M in THF was obtained.

Typical procedure 2 (TP 2)—Zincation of polyfunctionalized aromatics and heterocycles with (TMP)$_2$Mg·2 LiCl: In a dry, argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, the given starting material (1 mmol) was dissolved in THF (2 mL), and $ZnCl_2$ (1 M solution in THF, 0.5 mL, 0.5 mmol) was added. (TMP)$_2$Mg·2 LiCl (0.6 M in THF, 0.92 mL, 0.55 mmol) was added dropwise and the reaction mixture was stirred at 25°C for the indicated time. Complete metalation was detected by using GC analysis of reaction aliquots, which were quenched with I_2 in dry THF.

Typical procedure 3 (TP 3)—Preparation of the reagent (TMP)$_2$Zn·2 MgCl$_2$·2 LiCl (9): In an argon-flushed Schlenk flask, $ZnCl_2$ (53.0 mmol, 7.22 g) was dried under vacuum at 140°C for 4 h. After cooling to 25°C, dry THF (25 mL) and freshly titrated (TMP)MgCl·LiCl (100 mmol, 1.00 M, 100 mL) were added slowly. The resulting mixture was stirred for 15 h at 25°C. The freshly prepared (TMP)$_2$Zn·2 MgCl$_2$·2 LiCl (**9**) solution was titrated prior to use at 0°C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.4 M in THF was obtained.

Typical procedure 4 (TP 4)—Zincation of polyfunctionalized aromatics and heterocycles with (TMP)$_2$Zn·2 MgCl$_2$·2 LiCl: A dry, argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with a solution of the corresponding arene (1.0 mmol) in dry THF (1 mL). After setting the desired temperature (Table 1), the zinc base (0.55 mmol) was added dropwise and was stirred at the same temperature. The completion of the metalation was checked by using GC analysis of reaction aliquots quenched with a solution of I_2 in dry THF.

Synthesis of 2-iodoquinoxaline[5e] **(3)**: By following **TP 2**, the metalation of quinoxaline (**2b**; 130 mg, 1 mmol) was completed within 2 h at 25°C. Iodine (506 mg, 2 mmol) dissolved in THF (2 mL) was added to the reaction and the reaction mixture was stirred at 25°C for 1 h and was quenched with aqueous saturated NH_4Cl solution (10 mL). After extraction with diethyl ether (3×20 mL), the combined organic layers were washed with saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 10:1) to give **3** as a pale yellow solid (230 mg, 94%). M.p. 107.5–108.8°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.99 (s, 1H), 8.08–8.03 (m, 2H), 7.80–7.76 ppm (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.06, 144.79, 140.97, 130.86, 130.42, 129.50, 128.80, 118.08 ppm; IR (ATR): $\tilde{\nu}$ = 3057, 3039, 1562, 1527, 1486, 1459, 1318, 1235, 1131, 1064, 947, 898, 849, 758 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 256 (77) $[M]^+$, 130 (10), 129 (100), 102 (43), 75 (15); HRMS (EI): *m*/*z* calcd for $C_8H_5N_2I$: 255.9497; found: 255.9485.

Synthesis of 2-(4-triisopropylsilanyloxyphenyl)quinoxaline (14a): By following **TP 2**, the metalation of quinoxaline (**2b**; 130 mg, 1 mmol) was completed within 2 h at 25°C. A solution of [Pd(dba)$_2$] (15 mg) and P(*o*-furyl)$_3$ (12.5 mg) in THF (2 mL) was added, followed by triisopropylsilyl-4-iodobenzene (564 mg, 1.5 mmol). The reaction mixture was stirred at 25°C for 1 h and was quenched with aqueous saturated NH_4Cl solution (10 mL). After extraction with diethyl ether (3×20 mL), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by using flash chromatography on silica gel (pentane/diethyl ether 4:1) furnished **14a** as a pale yellow oil (265 mg, 71%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.30 (d, *J* = 9.6 Hz, 1H), 8.14–8.11 (m, 4H), 7.79–7.70 (m, 2H), 7.09–7.06 (m, 2H), 1.35–1.03 ppm (m, 21H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.41, 151.55, 143.09, 142.26, 141.09, 130.17, 129.50, 129.35, 129.04, 129.01, 128.94, 120.62, 17.91, 17.71, 12.71, 12.30 ppm; IR (ATR): $\tilde{\nu}$ = 2942, 2864, 1602, 1544, 1513, 1487, 1462, 1422, 1313, 1269, 1229, 1169, 1134, 1047, 1011, 996, 956, 906, 881, 840, 759, 737, 729, 682 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 379 (17), 378 (51) $[M]^+$, 336 (30), 335 (100), 308 (14), 307 (53), 293 (15), 280 (21), 279 (84), 266 (11), 265 (49), 249 (11), 205 (15), 140 (34), 133 (10); HRMS (EI): *m*/*z* calcd for $C_{23}H_{30}ON_2Si$: 378.2127; found: 378.2132.

Synthesis of 2-cyclohex-2-enylquinoxaline (14b):[18] By following **TP 2**, the metalation of quinoxaline (**2b**; 130 mg, 1 mmol) was completed within 2 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2 LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and 3-bromocyclohexene (242 mg, 1.5 mmol) were added. The mixture was allowed to warm to 25°C overnight. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by using flash chromatography on silica gel (pentane/diethyl ether 5:1) to give **14b** as a colorless oil (137 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1H), 8.11–8.07 (m, 2H), 7.76–7.71 (m, 2H), 6.10–6.03 (m, 1H), 5.94–5.90 (m, 1H), 3.90–3.83 (m, 1H), 2.23–2.17 (m, 3H), 1.94–1.72 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.11, 145.14, 142.05, 141.38, 130.08, 129.89, 129.10, 129.03, 129.01, 127.01, 42.94, 30.31, 24.85, 21.29 ppm; IR (ATR): $\tilde{\nu}$ = 3176, 3020, 2929, 2859, 2835, 1558, 1491, 1446, 1366, 1294, 1204, 1176, 1126, 1016, 969, 918, 882, 758, 723 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 210 (82) $[M]$,$^+$ 209 (40), 196 (10), 195 (37), 183 (14), 182 (28), 181 (100), 169 (24), 168 (15), 154 (15), 145 (12), 144 (97), 130 (15), 129 (22), 103 (13), 102 (30), 77 (28), 76 (33), 75 (16), 63 (13), 53 (10), 52 (10), 51 (23), 50 (15); HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}N_2$: 210.1157; found: 210.1145.

Synthesis of 1-(6-bromoquinoxalin-5-yl)-2,2-dimethylpropan-1-one (14c): By following **TP 2**, the metalation of 6-bromoquinoxaline (**2b**; 208 mg, 1.0 mmol) was completed within 5 min at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2 LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and pivaloyl chloride (0.19 mL, 1.5 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 4:1) to give **14c** as a colorless solid (238 mg, 81%). M.p. 108.7–110.0°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 8.84 (s, 1H), 8.00 (d, *J* = 9 Hz, 1H), 7.92 (d, *J* = 9 Hz, 1H), 1.38 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.25, 145.16, 143.01, 141.42, 134.35, 130.49, 119.11, 44.79, 27.88 ppm; IR (ATR): $\tilde{\nu}$ = 2969, 2930, 1694, 1587, 1566, 1475, 1464, 1363, 1356, 1216, 1209, 1154, 1116, 1082, 1022, 946, 889, 870, 835, 805, 788, 738, 688 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 292 (3) $[M]^+$, 228 (17), 237 (97), 236 (18), 235 (100), 213 (11), 210 (11), 209 (20), 208 (11), 207 (19), 129 (10), 128 (11); HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}ON_2Br$: 292.0211; found: 292.0195.

Synthesis of (6-bromoquinoxalin-5-yl)phenylmethanone (14d): By following **TP 2**, the metalation of 6-bromoquinoxaline (**2b**; 208 mg, 1.0 mmol) was completed within 5 min at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2 LiCl (1 M in THF, 1.1 mL, 1.1 mmol) and benzoyl chloride (0.18 mL, 1.5 mmol) were added. The mixture was allowed to warm to 25°C overnight. The reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 1:1) to

give **14d** as a colorless solid (532 mg, 86%). M.p. 169.6–172.4°C (decomp); ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.86 (d, J=0.6 Hz, 1H), 8.74 (d, J=0.6 Hz, 1H), 8.10 (d, J=9 Hz, 1H), 7.97 (d, J=9 Hz, 1H), 7.81 (d, J=7.2 Hz, 2H), 7.59 (t, J=7.2 Hz, 1H), 7.44 ppm (t, J=7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=194.79, 145.75, 145.53, 142.04, 141.45, 140.03, 136.05, 134.18, 134.07, 131.29, 130.09, 129.78, 128.85, 128.43, 120.97 ppm; IR (ATR): $\tilde{\nu}$=3065, 3026, 3002, 1669, 1594, 1579, 1479, 1468, 1446, 1372, 1352, 1316, 1290, 1268, 1258, 1216, 1198, 1179, 1150, 1112, 1018, 928, 868, 845, 835, 794, 781, 711, 690 cm^{-1}; MS (70 eV, EI): m/z (%): 314 (29), 312 (30) $[M]^+$, 286 (13), 285 (60), 284 (13), 283 (61), 206 (17), 205 (100), 105 (13), 77 (32); HRMS (EI): m/z calcd for $C_{15}H_9ON_2Br$: 311.9898; found: 311.9877.

Synthesis of phenylpyrazin-2-ylmethanol (14e):[19] By following **TP 2**, the metalation of pyrazine (**2c**; 160 mg, 2.0 mmol) was completed within 30 min at 25°C. Benzaldehyde (0.303 mL, 3 mmol) was added at 25°C and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. Purification by using flash chromatography (pentane/diethyl ether 80:1; then diethyl ether) furnished **14e** as a pale yellow oil (221 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.61 (s, 2H), 8.52–8.48 (m, 2H), 7.42–7.32 (m, 5H), 5.88 (s, 1H), 4.23 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=156.94, 143.44, 143.32, 142.87, 141.86, 128.83, 128.29, 126.88, 74.19 ppm; IR (ATR): $\tilde{\nu}$=3254, 3058, 1493, 1452, 1400, 1301, 1226, 1190, 1146, 1060, 1016, 857, 810, 752, 698 cm^{-1}; MS (70 eV, EI): m/z (%): 186 (100) $[M]^+$, 185 (16), 169 (15), 168 (11), 107 (36), 105 (20), 81 (37), 80 (66), 79 (60), 78 (11), 77 (50), 53 (14), 52 (12), 51 (14); HRMS (EI): m/z calcd for $C_{11}H_{10}ON_2$: 186.0793; found: 186.0781.

Synthesis of 4-quinoxalin-2-ylbenzoic acid ethyl ester (14f): By following **TP 2**, the metalation of quinoxaline (**2a**; 260 mg, 2.0 mmol) was completed within 2 h at 25°C. A solution of $[Pd(dba)_2]$ (30 mg) and P(o-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (828 mg, 3.0 mmol). The reaction mixture was stirred at 25°C for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 3:1) to give **14f** as a colorless solid (455 mg, 82%). M.p. 88.8–90.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.39 (s, 1H), 8.33–8.16 (m, 6H), 7.85–7.80 (m, 2H), 4.46 (q, J=7.2 Hz, 2H), 1.47 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.15, 150.70, 143.12, 142.30, 141.81, 131.84, 130.57, 130.30, 130.12, 129.78, 129.17, 127.43, 61.27, 14.35 ppm; IR (ATR): $\tilde{\nu}$=2923, 1713, 1607, 1363, 1271, 1183, 1126, 1099, 1048, 1017, 958, 861, 772, 758, 752, 698, 668, 615 cm^{-1}; MS (70 eV, EI): m/z (%): 279 (15), 278 (74) $[M]^+$, 250 (32), 233 (100), 206 (12), 205 (32), 102 (12), 76 (14); HRMS (EI): m/z calcd for $C_{17}H_{14}O_2N_2$: 278.1055; found: 278.1030.

Synthesis of 5,6-dibromoquinoxaline (14g): By following **TP 2**, the metalation of 6-bromoquinoxaline (**2b**; 208 mg, 1 mmol) was completed within 5 min at 25°C. $BrCl_2CCCl_2Br$ (487 mg, 1.5 mmol) was added at 25°C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 5:1) to give **14g** as a colorless solid (202 mg, 70%). M.p. 182.0–184.3°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.99 (d, J=1.8 Hz, 1H), 8.91 (d, J=1.8 Hz, 1H), 8.03 (d, J=9 Hz, 1H), 8.00 ppm (d, J=9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=145.96, 145.41, 142.55, 141.96, 134.51, 129.67, 128.05, 127.11 ppm; IR (ATR): $\tilde{\nu}$=3076, 3044, 1591, 1548, 1469, 1430, 1352, 1338, 1188, 1112, 1030, 965, 880, 865, 830, 776, 640, 616 cm^{-1}; MS (70 eV, EI): m/z (%): 290 (50), 289 (10), 288 (100) $[M]^+$, 286 (53), 261 (18), 236 (12), 234 (24), 232 (12); HRMS (EI): m/z calcd for $C_8H_6N_2Br_2$: 287.8721; found: 287.8677.

Synthesis of 4-(2-bromopyrimidin-4-yl)benzonitrile (15a): By following **TP 2**, the metalation of 2-bromopyrimidine (**10a**; 318 mg, 2.0 mmol) was completed within 12 h at 25°C. A solution of $[Pd(dba)_2]$ (30 mg) and P(o-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (687 mg, 3.0 mmol), and the reaction mixture was stirred overnight at 25°C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/ethyl acetate 1:1) to give **15a** as a pale yellow solid (479 mg, 91%). M.p. 229.5–231.1°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.69 (d, J=5.1 Hz, 1H), 8.25–8.21 (m, 2H), 7.86–7.83 (m, 2H), 7.74 ppm (d, J=5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=164.69, 160.24, 153.91, 138.99, 132.85, 127.98, 115.92, 115.35 ppm; IR (ATR): $\tilde{\nu}$=3079, 3049, 2229, 1562, 1532, 1498, 1429, 1341, 1314, 1184, 1170, 1099, 1061, 983, 836, 830, 821, 767, 753, 673 cm^{-1}; MS (70 eV, EI): m/z (%): 261 (36), 259 (37) $[M]^+$, 181 (15), 180 (100), 199 (100), 128 (30), 127 (12), 102 (15), 101 (10), 76 (10), 75 (14), 53 (12); MS (70 eV, EI): m/z calcd for $C_{11}H_6N_3Br$: 258.9745; found: 258.9746.

Synthesis of 4-(2-bromopyrimidin-4-yl)benzoic acid ethyl ester (15b):[20] By following **TP 2**, the metalation of 2-bromopyrimidine (**10a**; 318 mg, 2.0 mmol) was completed within 12 h at 25°C. A solution of $[Pd(dba)_2]$ (30 mg) and P(o-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (828 mg, 3.0 mmol), and the reaction mixture was stirred at 25°C for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 2:1) to give **15b** as a colorless solid (444 mg, 72%). M.p. 129.2–130.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.65 (d, J=5.1 Hz, 1H), 8.22–8.15 (m, 4H), 7.75 (d, J=5.1 Hz, 1H), 4.44 (q, J=7.2 Hz, 2H), 1.45 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.82, 165.80, 159.91, 153.77, 138.81, 133.38, 130.22, 127.38, 115.98, 61.43, 14.31 ppm; IR (ATR): $\tilde{\nu}$=3081, 2991, 2902, 1712, 1563, 1531, 1429, 1347, 1277, 1164, 1129, 1117, 1102, 1062, 1021, 983, 848, 801, 780, 754, 712, 694, 653, 632 cm^{-1}; MS (70 eV, EI): m/z (%): 308 (31), 307 (17), 306 (32) $[M]^+$, 305 (12), 280 (55), 278 (54), 264 (17), 263 (97), 262 (18), 261 (100), 235 (23), 233 (24), 199 (43), 181 (10), 154 (34), 129 (11), 128 (15), 127 (43), 102 (14), 101 (28), 100 (11), 91 (12), 77 (13), 76 (19), 75 (24), 74 (11), 51 (12); HRMS (EI): m/z calcd for $C_{13}H_{11}O_2N_2Br$: 306.0000; found: 305.9989.

Synthesis of 2-bromo-4-cyclohex-2-enylpyrimidine (15c): By following **TP 2**, the metalation of 2-bromopyrimidine (**10a**; 318 mg, 2 mmol) was completed within 12 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromocyclohexene (484 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 3:1) to give **15c** as a colorless oil (333 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.46 (d, J=5.1 Hz, 1H), 7.22 (d, J=5.1 Hz, 1H), 6.03–5.98 (m, 1H), 5.75–5.71 (m, 1H), 3.57–3.52 (m, 1H), 2.13–2.09 (m, 3H), 1.75–1.65 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=177.57, 159.06, 153.02, 130.84, 125.87, 118.03, 43.24, 29.65, 24.78, 20.53 ppm; IR (ATR): $\tilde{\nu}$=3022, 2928, 2859, 1562, 1528, 1420, 1335, 1162, 908, 889, 838, 802, 776, 732, 723, 686, 673, 645 cm^{-1}; MS (70 eV, EI): m/z (%): 240 (14), 239 (21), 238 (14) $[M]^+$, 237 (21), 225 (20), 223 (21), 212 (12), 211 (59), 210 (12), 209 (57), 199 (11), 174 (31), 172 (33), 160 (12), 159 (100), 157 (13), 130 (13), 79 (22), 78 (11), 77 (21), 53 (14), 52 (14), 51 (14); HRMS (EI): m/z calcd for $C_{10}H_{11}N_2Br$: 238.0106; found: 238.0097.

Synthesis of 2-bromo-4-(2-methylallyl)pyrimidine (15d): By following **TP 2**, the metalation of 2-bromopyrimidine (**10a**; 318 mg, 2 mmol) was completed within 12 h at 25°C The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product

was purified by means of column chromatography (pentane/diethyl ether 5:1) to give **15d** as a colorless oil (303 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.39 (d, J=5.1 Hz, 1H), 7.17 (d, J=5.1 Hz, 1H), 4.88 (m, 1H), 4.74 (m, 1H), 3.40 (d, J=0.6 Hz, 2H), 1.66 ppm (t, J=1.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.07, 158.94, 152.93, 140.92, 119.21, 114.82, 46.05, 22.24 ppm; IR (ATR): $\tilde{\nu}$=3080, 2974, 2938, 1652, 1566, 1530, 1427, 1334, 1205, 1164, 1095, 1021, 985, 894, 852, 817, 771, 732, 717, 692 cm^{-1}; MS (70 eV, EI): m/z (%): 214 (15), 213 (100), 212 (17) $[M]^+$, 211 (100), 200 (14), 199 (100), 198 (28), 197 (100), 196 (13), 174 (46), 172 (48), 132 (13), 131 (12), 118 (16), 106 (15), 92 (37), 65 (11); HRMS (EI): m/z calcd for $C_8H_9N_2Br$: 211.9949; found: 211.9915.

Synthesis of 5-bromo-4-cyclohex-2-enylpyrimidine (15e): By following **TP 2**, the metalation of 5-bromopyrimidine (**10b**, 318 mg, 2 mmol) was completed within 0.5 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromocyclohexene (484 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 8:1) to give **15e** as a colorless oil (333 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.04 (s, 1H), 8.71 (s, 1H), 6.02–5.97 (m, 1H), 5.71–5.66 (m, 1H), 4.02–3.96 (m, 1H), 2.15–2.04 (m, 3H), 1.90–1.85 (m, 1H), 1.72–1.62 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=171.14, 158.59, 157.06, 129.61, 126.24, 121.05, 41.88, 28.00, 24.60, 21.34 ppm; IR (ATR): $\tilde{\nu}$=3027, 2932, 1557, 1516, 1436, 1387, 1272, 1154, 1015, 891, 770, 720, 676, 658, 614, 569 cm^{-1}; MS (70 eV, EI): m/z (%): 240 (27), 239 (26), 238 (28) $[M]^+$, 237 (25), 225 (15), 223 (15), 212 (27), 211 (100), 210 (28), 209 (100), 199 (11), 198 (11), 197 (12), 196 (10), 174 (32), 172 (32), 159 (23), 131 (13), 130 (11), 118 (10), 79 (11), 77 (13), 51 (10); HRMS (EI): m/z calcd for $C_{10}H_{11}N_2Br$: 238.0106; found: 238.0105.

Synthesis of 5-bromo-4-(2-methylallyl)pyrimidine (15f): By following **TP 2**, the metalation of 5-bromopyrimidine (**10b**; 318 mg, 2 mmol) was completed within 0.5 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 4:1) to give **15f** as a colorless oil (279 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=9.06 (s, 1H), 8.77 (s, 1H), 4.95 (m, 1H), 4.70 (m, 1H), 3.66 (s, 2H), 1.82 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.54, 158.72, 158.71, 156.79, 156.78, 140.56, 121.84, 113.97, 44.97, 22.70 ppm; IR (ATR): $\tilde{\nu}$=2973, 2916, 1650, 1556, 1522, 1439, 1386, 1276, 1142, 1022, 892, 758, 720 cm^{-1}; MS (70 eV, EI): m/z (%): 214 (10), 213 (79), 212 (10) $[M]^+$, 211 (78), 199 (99), 198 (19), 197 (100), 196 (11), 174 (41), 172 (43), 133 (11), 132 (20), 131 (19), 118 (28), 117 (10), 106 (10), 104 (11), 77 (14), 52 (15), 51 (22); HRMS (EI): m/z calcd for $C_8H_{10}N_2Br$: 211.9949; found: 211.9855.

Synthesis of 4-(3-bromoquinolin-2-yl)benzoic acid ethyl ester (16a): By following **TP 2**, the metalation of 3-bromoquinoline (**11**; 416 mg, 2.0 mmol) was completed within 0.5 h at 25°C. A solution of $[Pd(dba)_2]$ (30 mg) and P(*o*-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (828 mg, 3.0 mmol), and the reaction mixture was stirred at 25°C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 5:1) to give **16a** as a colorless solid (582 mg, 82%). M.p. 132.2–133.3°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.54 (s, 1H), 8.22–8.14 (m, 3H), 7.86–7.76 (m, 4H), 7.65–7.60 (m, 1H), 4.45 (q, J=7.2 Hz, 2H), 1.45 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.31, 157.18, 146.54, 144.03, 140.14, 130.72, 130.31, 129.58, 129.56, 129.29, 128.39, 127.82, 126.52, 116.45, 61.12, 14.36 ppm; IR (ATR): $\tilde{\nu}$=3066, 2974, 1713, 1612, 1571, 1546, 1484, 1476, 1398, 1366, 1290, 1275, 1243, 1181, 1122, 1107, 1072, 1024, 954, 913, 878, 850, 767, 748, 714, 696 cm^{-1}; MS (70 eV, EI): m/z (%): 357 (31), 355 (33) $[M]^+$, 312 (33), 310 (35), 284 (22), 282 (22), 277 (21), 276 (100), 248 (36), 204 (13), 203 (48), 202 (33), 201 (12), 176 (13), 101 (20), 75 (13); HRMS (EI): m/z calcd for $C_{18}H_{14}O_2NBr$: 355.0208; found: 355.0200.

Synthesis of 3-bromo-2-(2-methylallyl)quinoline (16b): By following **TP 2**, the metalation of 3-bromoquinoline (**11**; 416 mg, 2 mmol) was completed within 0.5 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 10:1) to give **16b** as a colorless oil (366 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.36 (s, 1H), 8.09 (d, J=9.0 Hz, 1H), 7.75–7.70 (m, 2H), 7.57–7.52 (m, 1H), 4.92–4.91 (m, 1H), 4.56–4.54 (m, 1H), 3.90 (s, 2H), 1.90 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.12, 146.47, 142.45, 139.09, 129.70, 129.07, 128.05, 126.93, 126.44, 119.03, 112.52, 46.10, 23.15 ppm; IR (ATR): $\tilde{\nu}$=3078, 3059, 2970, 2913, 1650, 1586, 1486, 1442, 1424, 1401, 1373, 1306, 1221, 1195, 1140, 1125, 984, 887, 858, 802, 780, 745, 679 cm^{-1}; MS (70 eV, EI): m/z (%): 263 (25), 262 (80), 261 (25) $[M]^+$, 260 (79), 249 (14), 248 (96), 247 (33), 246 (100), 245 (19), 223 (30), 221 (34), 182 (11), 181 (14), 180 (29), 167 (55), 166 (17), 142 (10), 141 (13), 140 (38), 139 (10), 127 (14), 115 (29), 114 (14), 113 (11), 101 (11), 91 (10), 90 (10), 89 (12), 84 (10), 75 (16), 63 (12), 51 (10); HRMS (EI): m/z calcd for $C_{13}H_{12}NBr$: 261.0153; found: 261.0156.

Synthesis of 5-chlorobiphenyl-2,4′-dicarboxylic acid diethyl ester (17a): By following **TP 2**, the metalation of ethyl 4-chlorobenzoate (**12a**; 369 mg, 2.0 mmol) was completed within 12 h at 25°C. A solution of $[Pd(dba)_2]$ (30 mg) and P(*o*-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (828 mg, 3.0 mmol), and the reaction mixture was stirred at 25°C overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 6:1) to give **17a** as a pale yellow oil (598 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.12–8.09 (m, 2H), 7.87 (d, J=8.4 Hz, 1H), 7.46–7.36 (m, 4H), 4.43 (q, J=7.2 Hz, 2H), 4.11 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H), 1.04 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.15, 166.32, 144.92, 143.48, 137.48, 131.62, 130.52, 129.70, 129.32, 129.22, 128.32, 127.90, 61.23, 61.06, 14.35, 13.71 ppm; IR (ATR): $\tilde{\nu}$=3069, 2980, 2904, 1710, 1610, 1591, 1556, 1465, 1386, 1365, 1266, 1241, 1177, 1099, 1032, 1015, 858, 770, 670 cm^{-1}; MS (70 eV, EI): m/z (%): 334 (22), 333 (14), 332 (63) $[M]^+$, 289 (35), 288 (19), 287 (100), 276 (12), 261 (13), 260 (13), 259 (36), 217 (16), 215 (48), 186 (11), 152 (28), 151 (21), 150 (19); HRMS (EI): m/z calcd for $C_{18}H_{17}O_4Cl$: 332.0815; found: 332.0823.

Synthesis of 4-chloro-2-(2-methylallyl)benzoic acid ethyl ester (17b): By following **TP 2**, the metalation of ethyl 4-chlorobenzoate (**10a**; 369 mg, 2.0 mmol) was completed within 12 h at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 160:1) to give **17b** as a colorless oil (365 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.85–7.82 (m, 1H), 7.29–7.25 (m, 1H), 4.84–4.83 (m, 1H), 4.51–4.50 (m, 1H), 4.35 (q, J=7.2 Hz, 2H), 3.71 (s, 2H), 1.76 (s, 3H), 1.39 ppm (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.87, 144.54, 143.02, 137.76, 131.92, 131.16, 129.03, 126.39, 112.08, 61.02, 41.46, 22.77, 14.23 ppm; IR (ATR): $\tilde{\nu}$=3080, 2981, 2937, 2907, 1719, 1592, 1566, 1478, 1446, 1366, 1252, 1128, 1102, 1074, 1020, 887, 868, 836, 772, 692 cm^{-1}; MS (70 eV, EI): m/z (%): 240 (16), 238 (46) $[M]^+$, 225 (22), 223 (66), 197 (25), 196 (12), 195 (100), 194 (23), 193 (79),

192 (39), 191 (10), 176 (10), 167 (11), 165 (25), 158 (15), 157 (38), 130 (32), 129 (71), 128 (42), 127 (23), 125 (13), 115 (23), 89 (13); HRMS (EI): m/z calcd for $C_{13}H_{15}O_2Cl_1$: 238.0760; found: 238.0740.

Synthesis of 2,4-dibromobenzoic acid ethyl ester (17c):[21] By following **TP 2**, the metalation of ethyl 4-bromobenzoate (**12b**; 369 mg, 2.0 mmol) was completed within 12 h at 25 °C. $BrCl_2CCCl_2Br$ (974 mg, 3.0 mmol) was added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. Purification by using flash chromatography (pentane/diethyl ether 160:1) furnished **17c** as a semisolid (468 mg, 76 %). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.44–7.42 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.34 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.19, 136.70, 132.35, 131.03, 130.36, 126.18, 122.53, 61.78, 14.18 ppm; IR (ATR): $\tilde{\nu}$ = 3085, 2980, 1726, 1574, 1549, 1462, 1365, 1281, 1241, 1109, 1083, 1034, 869, 853, 830, 766, 743, 679, 657 cm^{-1}; MS (70 eV, EI): m/z (%): 310 (12), 308 (25) $[M]^+$, 306 (13), 282 (21), 280 (42), 278 (22), 265 (51), 264 (12), 263 (100), 261 (54), 237 (11), 235 (22), 233 (11), 156 (10), 154 (10), 75 (18), 74 (13); HRMS (EI): m/z calcd for $C_9H_{10}O_2Br_2$: 307.8871; found: 307.8865.

Synthesis of 2-benzoyl-4-bromobenzoic acid ethyl ester (17d): By following **TP 2**, the metalation of ethyl 4-bromobenzoate (**12b**; 369 mg, 2.0 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2 LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 4:1) to give **17d** as a colorless solid (501 mg, 76 %). M.p. 90.8–92.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 1H), 7.76–7.74 (m, 2H), 7.70 (dd, J = 8.4, 1.8 Hz, 1H), 7.58–7.55 (m, 1H), 7.53 (d, J = 1.8 Hz, 1H), 7.46–7.43 (m, 2H), 4.07 (q, J = 7.2 Hz, 2H), 1.04 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 195.13, 165.10, 143.22, 136.62, 133.42, 132.66, 131.71, 130.58, 129.37, 128.60, 128.08, 127.40, 61.75, 13.56 ppm; IR (ATR): $\tilde{\nu}$ = 2981, 1711, 1677, 1582, 1554, 1471, 1450, 1362, 1266, 1243, 1135, 1097, 1020, 948, 898, 858, 842, 778, 759, 711, 681, 689, 697 cm^{-1}; MS (70 eV, EI): m/z (%): 334 (10), 332 (10) $[M]^+$, 289 (14), 287 (14), 257 (18), 255 (18), 229 (27), 227 (27), 180 (10), 152 (23), 151 (12), 105 (100), 77 (63), 76 (10), 75 (17), 51 (19); HRMS (EI): m/z calcd for $C_{16}H_{13}O_3Br$: 332.0048; found: 332.0048.

Synthesis of 2-benzoyl-3-fluorobenzoic acid ethyl ester (17e): By following **TP 2**, the metalation of ethyl 3-fluorobenzoate (**12c**; 336 mg, 2 mmol) was completed within 3 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2 LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 8:1) to give **17e** as a colorless solid (433 mg, 80 %). M.p. 103.8–105.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (dd, J = 7.8, 1.2 Hz, 1H), 7.85–7.82 (m, 2H), 7.63–7.35 (m, 5H), 4.17 (q, J = 7.2 Hz, 2H), 1.10 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.53, (d, $^3J_{C,F}$ = 1.1 Hz), 164.65 (d, $^4J_{C,F}$ = 1.5 Hz), 159.15 (d, $^1J_{C,F}$ = 247 Hz), 137.08, 133.53, 130.94 (d, $^3J_{C,F}$ = 3.9 Hz), 130.60, 130.49, 129.56 (d, $^2J_{C,F}$ = 20 Hz), 129.43, 129.02, 128.65, 126.24 (d, $^3J_{C,F}$ = 3.9 Hz), 120.20 (d, $^2J_{C,F}$ = 20 Hz), 61.82, 13.59 ppm; IR (ATR): $\tilde{\nu}$ = 3073, 2990, 2944, 2908, 1714, 1673, 1608, 1598, 1581, 1478, 1448, 1366, 1272, 1198, 1151, 1026, 962, 928, 811, 762, 708, 660, 589, 569 cm^{-1}; MS (70 eV, EI): m/z (%): 272 (44) $[M]^+$, 228 (18), 227 (38), 199 (14), 195 (49), 170 (16), 168 (10), 167 (100), 151 (12), 105 (60), 77 (31); HRMS (EI): m/z calcd for $C_{16}H_{13}O_3F$: 272.0849; found: 272.0842.

Synthesis of 2-bromo-3-fluorobenzoic acid ethyl ester (17f): By following **TP 2**, the metalation of ethyl 3-fluorobenzoate (**12c**; 336 mg, 2 mmol) was completed within 3 h at 25 °C. $BrCl_2CCCl_2Br$ (974 mg, 3.0 mmol) was added at 25 °C and the resulting mixture stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 10:1) to give **17f** as a colorless oil (360 mg, 74 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 1H), 7.37–7.21 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 1.41 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.42 (d, $^4J_{C,F}$ = 2.8 Hz), 159.47 (d, $^1J_{C,F}$ = 247 Hz), 134.77, 128.41 (d, $^3J_{C,F}$ = 8.0 Hz), 126.38 (d, $^3J_{C,F}$ = 3.4 Hz), 118.89 (d, $^2J_{C,F}$ = 23 Hz), 109.19 (d, $^2J_{C,F}$ = 22 Hz), 61.92, 14.16 ppm; IR (ATR): $\tilde{\nu}$ = 2984, 2906, 1728, 1572, 1462, 1435, 1367, 1289, 1269, 1183, 1142, 1091, 1019, 945, 863, 802, 754, 695 cm^{-1}; MS (70 eV, EI): m/z (%): 248 (23), 246 (24) $[M]^+$, 220 (38), 218 (38), 204 (11), 203 (96), 202 (12), 201 (100), 175 (29), 173 (29), 94 (35); HRMS (EI): m/z calcd for $C_9H_8O_2BrF$: 245.9692; found: 245.9692.

Synthesis of 2-benzoyl-4-chlorobenzoic acid ethyl ester (17g): By following **TP 2**, the metalation of ethyl 4-chlorobenzoate (**12a**; 369 mg, 2 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2 LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 6:1) to give **17g** as a yellow solid (500 mg, 86 %). M.p. 78.9–80.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 1H), 7.73–7.77 (m, 2H), 7.52–7.57 (m, 2H), 7.41–7.46 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 1.04 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 165.2, 143.3, 139.2, 136.7, 133.7, 131.9, 129.9, 129.6, 128.9, 128.0, 127.8, 62.0, 13.8 ppm; IR (ATR): $\tilde{\nu}$ = 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585 cm^{-1}; MS (70 eV, EI): m/z (%): 288 (24) $[M]^+$, 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13); HRMS (EI): m/z calcd for $C_{16}H_{13}ClO_3$: 288.0553; found: 288.0550.

Synthesis of 2′,6′-difluorobiphenyl-4-carboxylic acid ethyl ester (18a):[12c] By following **TP 2**, the metalation of 1,3-difluorobenzene (**13**; 228 mg, 2 mmol) was completed within 12 h at 25 °C. A solution of $[Pd(dba)_2]$ (30 mg) and P(*o*-furyl)$_3$ (25 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (828 mg, 3.0 mmol) and the reaction mixture was stirred at 25 °C overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 80:1) to give **18a** as a colorless solid (471 mg, 90 %). M.p. 59.4–61.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13–8.11 (m, 2H), 7.54 (dt, J = 9, 1.8 Hz, 2H), 7.33–7.28 (m, 1H), 6.70 (t, J = 8.4 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.40 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.24, 159.95 (d, $^1J_{C,F}$ = 250 Hz), 159.90 (d, $^1J_{C,F}$ = 250 Hz), 133.76, 130.32 (t, $J_{C,F}$ = 2.1 Hz), 130.15, 129.55 (t, $J_{C,F}$ = 10 Hz), 129.37, 117.58 (t, $J_{C,F}$ = 18 Hz), 111.76 (d, $J_{C,F}$ = 21 Hz), 111.73 (d, $J_{C,F}$ = 21 Hz), 61.04, 14.32 ppm; IR (ATR): $\tilde{\nu}$ = 2980, 1711, 1624, 1585, 1564, 1464, 1404, 1369, 1266, 1230, 1180, 1107, 1099, 1065, 995, 854, 792, 787, 770, 723, 670 cm^{-1}; MS (70 eV, EI): m/z (%): 263 (10), 262 (57) $[M]^+$, 234 (41), 217 (100), 189 (42), 188 (53), 169 (15); HRMS (EI): m/z calcd for $C_{15}H_{12}O_2F_2$: 262.0805; found: 262.0797.

Synthesis of 2,6-difluorobenzophenone (18b):[22] By following **TP 2**, the metalation of 1,3-difluorobenzene (**13**; 228 mg, 2 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2 LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the sol-

vent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 80:1) to give **18b** as a colorless oil (359 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.88 (m, 2H), 7.68–7.62 (m, 1H), 7.54–7.42 (m, 3H), 7.06–6.99 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.93, 159.86 (d, $^1J_{C,F}$ = 252 Hz), 159.76 (d, $^1J_{C,F}$ = 252 Hz), 136.84, 134.22, 131.91 (t, $J_{C,F}$ = 9.80 Hz), 129.64, 128.77, 117.05 (t, $J_{C,F}$ = 22 Hz), 112.06–111.72 ppm (m); IR (ATR): $\tilde{\nu}$ = 3064, 1672, 1622, 1583, 1462, 1449, 1316, 1275, 1266, 1233, 1180, 1145, 1004, 925, 783, 732, 696, 686 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 219 (14), 218 (93) $[M]^+$, 141 (63), 113 (20), 105 (100), 77 (46), 63 (11), 51 (14); HRMS (EI): *m*/*z* calcd for $C_{13}H_8OF_2$: 218.0543; found: 218.0527.

Synthesis of 4-(3-iodoquinoxalin-2-yl)benzoic acid ethyl ester (19): By following **TP 2**, the metalation of 4-quinoxalin-2-ylbenzoate (**12f**; 139 mg, 0.5 mmol) was completed within 15 min at 25°C. Iodine (253 mg, 1 mmol) dissolved in THF (2 mL) was added and the reaction mixture was stirred for 30 min at 25°C. Then the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was evaporated under vacuum. The residue was purified by using flash chromatography on silica gel (pentane/diethyl ether 4:1) to furnish **19** as a colorless solid (147 mg, 73%). M.p. 159.7–161.8°C (decomp); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.22–8.20 (m, 2H), 8.12–8.10 (m, 2H), 7.82–7.80 (m, 4H), 4.44 (q, J = 7.2 Hz, 2H), 1.44 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.05, 156.18, 143.68, 143.12, 140.38, 131.34, 131.00, 130.97, 129.72, 129.41, 129.38, 128.49, 118.63, 61.26, 14.34 ppm; IR (ATR): $\tilde{\nu}$ = 2968, 2921, 2852, 1713, 1605, 1549, 1523, 1506, 1463, 1405, 1364, 1333, 1276, 1181, 1098, 1065, 1022, 959, 882, 854, 762, 718, 699 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 404 (15) $[M]^+$, 278 (25), 277 (100), 250 (12), 249 (56), 233 (12), 204 (11), 102 (22), 76 (12); HRMS (EI): *m*/*z* calcd for $C_{17}H_{13}O_2N_2I$: 404.0022; found: 404.0016.

Synthesis of (7,8-dibromoquinoxalin-5-yl)phenylmethanone (20): By following **TP 2**, the metalation of 5,6-dibromoquinoxaline (**14g**; 144 mg, 0.5 mmol) was completed (treated with 0.5 equiv of $ZnCl_2$ and 0.75 equiv of **1**) within 15 min at 25°C. The reaction mixture was cooled to −40°C, then CuCN·2LiCl (1 M in THF, 0.55 mL, 0.55 mmol) and benzoyl chloride (0.09 mL, 0.75 mmol) were added. The mixture was allowed to warm to 25°C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 3:1) to give **20** as a colorless solid (160 mg, 82%). M.p. 180.8–182.5°C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (d, J = 1.8 Hz, 1H), 8.81 (d, J = 1.8 Hz, 1H), 8.07 (s, 1H), 7.83–7.80 (m, 2H), 7.66–7.61 (m, 1H), 7.48 ppm (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.17, 146.42, 145.46, 141.57, 140.62, 139.54, 137.00, 134.01, 132.95, 130.12, 129.13, 128.67, 128.64, 127.51 ppm; IR (ATR): $\tilde{\nu}$ = 3050, 3026, 1655, 1595, 1576, 1548, 1475, 1450, 1428, 1358, 1319, 1297, 1237, 1213, 1198, 1179, 1053, 1027, 1022, 962, 879, 866, 780, 728, 706, 684, 674 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 394 (42), 393 (21), 392 (87) $[M]^+$, 391 (22), 390 (45), 365 (34), 364 (12), 363 (67), 361 (35), 313 (10), 287 (18), 286 (16), 285 (100), 284 (15), 283 (94), 204 (15), 203 (31), 150 (10), 127 (16), 105 (34), 77 (76), 51 (17); HRMS (EI): *m*/*z* calcd for $C_{15}H_{10}ON_2Br_2$: 391.8983; found: 391.8962.

Synthesis of 2-tributylstannanylquinoxaline (21):[23] In a dry argon-flushed 10 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, quinoxaline (**2a**, 230 mg, 2 mmol) was dissolved in THF (2 mL) and tributyltin chloride (0.780 g, 0.650 mL, 2.4 mmol) was added. The solution was cooled to −78°C. $(TMP)_2Mg$·2LiCl (**1**; 0.6 M in THF, 1.84 mL, 1.10 mmol) was added dropwise and the reaction mixture was stirred for 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 5:1 + 1% NEt_3) to give **21** as a yellow oil (675 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1H), 8.00–8.15 (m, 2H), 7.64–7.74 (m, 2H), 1.56–1.67 (m, 6H), 1.33 (m, 6H), 1.2–1.21 (m, 6H), 0.88 ppm (t, ^3J = 7.2 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 150.0 (t, $^2J_{C,Sn}$ = 41.0 Hz), 145.1, 141.5, 129.7, 129.6, 129.2, 129.1, 29.1 (t, $^3J_{C,Sn}$ = 10.3 Hz), 27.3 (t, $^2J_{C,Sn}$ = 28.6 Hz), 13.7, 10.2 ppm (t, $^1J_{C,Sn}$ = 170.3 Hz); IR (ATR): $\tilde{\nu}$ = 3080, 3012, 2952, 2870, 2836, 2753, 2683, 1696, 1681, 1638, 1613, 1571, 1546, 1538, 1495, 1473, 1464, 1432, 1422, 1374, 1323, 1263, 1201, 1143, 1127, 1068, 1022, 965, 955, 950, 924, 895, 778, 764, 752, 725, 683, 666 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 420 (1) $[M]^+$, 364 (30), 363 (35), 362 (30), 361 (29), 360 (19), 359 (12), 307 (26), 306 (11), 305 (29), 304 (12), 303 (19), 253 (18), 251 (51), 250 (21), 249 (100), 248 (35), 247 (70), 246 (20), 245 (31), 148 (32), 131 (37), 121 (13), 119 (11); HRMS (EI): *m*/*z* calcd for $C_{20}H_{32}N_2Sn$: 420.1587; found: 420.1581.

Synthesis of 4-quinoxalin-2-ylbenzoic acid ethyl ester (14f): By following **TP 4**, the metalation of quinoxaline (**2b**; 230 mg, 2 mmol) was completed within 5 h at 25°C. A solution of $[Pd(dba)_2]$ (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (615 mg, 2.2 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 3:1) to give **14f** as a colorless solid (455 mg, 82%). M.p. 88.8–90.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (s, 1H), 8.33–8.16 (m, 6H), 7.85–7.80 (m, 2H), 4.46 (q, J = 7.2 Hz, 2H), 1.47 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.15, 150.70, 143.12, 142.30, 141.81, 131.84, 130.57, 130.30, 130.12, 129.78, 129.17, 127.43, 61.27, 14.35 ppm; IR (ATR): $\tilde{\nu}$ = 2923, 1713, 1607, 1363, 1271, 1183, 1126, 1099, 1048, 1017, 958, 861, 772, 758, 752, 698, 668, 615 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 279 (15), 278 (74) $[M]^+$, 250 (32), 233 (100), 206 (12), 205 (32), 102 (12), 76 (14); HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}O_2N_2$: 278.1055; found: 278.1030.

Synthesis of 2-(3-trifluoromethylphenyl)quinoxaline (14h): By following **TP 4**, the metalation of quinoxaline (**2b**; 230 mg, 2 mmol) was completed within 5 h at 25°C. A solution of $[Pd(dba)_2]$ (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol). The reaction mixture was stirred at 25°C for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 3:1) to give **14h** as a colorless solid (482 mg, 88%). M.p. 119.0–121.8°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.33 (s, 1H), 8.50 (s, 1H) 8.36 (d, J = 7.9 Hz, 1H), 8.18–8.13 (m, 2H), 7.82–7.75 (m, 3H), 7.68 ppm (t, J = 7.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 150.13, 142.70, 142.18, 141.81, 137.51, 131.69 (q, $^2J_{C,F}$ = 32 Hz), 130.61, 130.53 (q, $^4J_{C,F}$ = 1 Hz), 130.11, 129.68, 129.61, 129.15, 126.68 (q, $^3J_{C,F}$ = 3.7 Hz), 124.85 (q, $^1J_{C,F}$ = 272 Hz), 124.42 ppm (q, $^3J_{C,F}$ = 4.0 Hz); IR (ATR): $\tilde{\nu}$ = 1546, 1487, 1366, 1338, 1327, 1309, 1279, 1263, 1231, 1223, 1209, 1187, 1179, 1160, 1140, 1130, 1110, 1096, 1076, 1048, 1013, 973, 961, 952, 937, 919, 889, 885, 877, 838, 809, 795, 763, 706, 690, 651, 637, 632, 624, 615, 591, 561 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 275 (14), 278 (100) $[M]^+$, 247 (30), 178 (5), 76 (19); HRMS (EI): *m*/*z* calcd for $C_{17}H_{14}O_2N_2$: 274.0718; found: 274.0703.

Synthesis of 4-(5-bromopyrimidin-4-yl)benzonitrile (15g): By following **TP 4**, the metalation of 5-bromopyrimidine (**10a**; 318 mg, 2.0 mmol) was completed within 5 h at 25°C. A solution of $[Pd(dba)_2]$ (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 25°C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 4:1) to give **15g** as a colorless solid (390 mg, 75%). M.p. 158.9–160.9°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.19 (s, 1H), 8.97 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.80 ppm (d, J = 8.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.34, 160.55, 157.05, 140.82, 132.06, 130.03, 119.06, 118.15, 114.02 ppm; IR (ATR): $\tilde{\nu}$ = 2231, 1558, 1498, 1438, 1405, 1392, 1283, 1228, 1172, 1152, 1058, 1025, 1017, 926, 842, 815, 774,

746, 724, 668, 664, 643, 579, 572, 568, 559 cm^{-1}; MS (70 eV, EI): *m/z* (%): 261 (30), 259 (30) [M^+], 181 (14), 180 (100), 153 (25), 126 (10), 74 (11), 59 (15); HRMS (EI): *m/z* calcd for $C_{17}H_{14}O_2N_2$: 258.9745; found: 258.9735.

Synthesis of 4-(3-bromoquinolin-2-yl)benzonitrile (16c): By following **TP 2**, the metalation of 3-bromoquinoline (**11**; 416 mg, 2.0 mmol) was completed within 2.5 h at 25 °C. A solution of [Pd(dba)$_2$] (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 4-iodobenzonitrile (504 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 5:1) to give **16c** as a colorless solid (662 mg, 95%). M.p. 130.4–132.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 8.19–8.16 (m, 2H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.82–7.74 (m, 4H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 1.42 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.28, 157.13, 146.42, 143.88, 140.20, 130.71, 130.34, 129.54, 129.48, 129.27, 128.37, 127.83, 126.51, 116.42, 61.11, 14.33 ppm; IR (ATR): $\tilde{\nu}$ = 3064, 2988, 2973, 1712, 1673, 1651, 1612, 1586, 1571, 1546, 1484, 1475, 1457, 1411, 1397, 1387, 1365, 1309, 1289, 1274, 1262, 1242, 1201, 1180, 1153, 1145, 1121, 1106, 1098, 1072, 1023, 971, 954, 913, 884, 878, 857, 850, 824, 791, 780, 767, 748, 714, 697, 636, 630, 622, 613, 606, 597, 581, 576, 570, 565, 560, 552 cm^{-1}; MS (70 eV, EI): *m/z* (%): 357 (38), 356 (12) 355 (40) [M]$^+$, 312 (38), 310 (34), 281 (21), 277 (20), 276 (100) 248 (32), 203 (35), 101 (10); HRMS (EI): *m/z* calcd for $C_{17}H_{14}O_2N_2$: 355.0208; found: 355.0194.

Synthesis of 2-benzoyl-4-chlorobenzoic acid ethyl ester (17g): By following **TP 4**, the metalation of ethyl 4-chlorobenzoate (**12a**; 369 mg, 2 mmol) was completed within 110 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2 LiCl (1 M in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C and was stirred overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 6:1) to give **17g** as a yellow solid (500 mg, 86%). M.p. 78.9–80.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.77–7.73 (m, 2H), 7.57–7.52 (m, 2H), 7.46–7.41 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.04 ppm (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 165.2, 143.3, 139.2, 136.7, 133.7, 131.9, 129.9, 129.6, 128.9, 128.0, 127.8, 62.0, 13.8 ppm; IR (ATR): $\tilde{\nu}$ = 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585 cm^{-1}; MS (70 eV, EI): *m/z* (%): 288 (24) [M]$^+$, 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13); HRMS (EI): *m/z* calcd for $C_{16}H_{13}ClO_3$: 288.0553; found: 288.0550.

Synthesis of 5-bromobiphenyl-2,4′-dicarboxylic acid diethyl ester (17h): By following **TP 4**, the metalation of ethyl 4-bromobenzoate (**12b**; 458 mg, 2 mmol) was completed within 110 h at 25 °C. A solution of [Pd(dba)$_2$] (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by 1-iodo-3-trifluoromethylbenzene (598 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 60 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 15:1) to give **17h** as a yellowish oil (619 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.9 Hz, 1H) 7.54–7.46 (m, 4H), 4.06 (q, *J* = 7.2 Hz, 2H), 0.98 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.1, 142.9, 141.0, 133.5, 131.8, 131.6 (q, $^4J_{C,F}$ = 1.3 Hz), 131.0, 130.4 (q, $^2J_{C,F}$ = 32 Hz), 129.7, 128.5, 126.0, 125.2 (q, $^3J_{C,F}$ = 3.9 Hz), 124.3 (q, $^3J_{C,F}$ = 3.9 Hz), 123.8 (q, $^1J_{C,F}$ = 272 Hz), 61.2, 13.5 ppm; IR (ATR): $\tilde{\nu}$ = 2982, 1715, 1585, 1557, 1492, 1444, 1432, 1384, 1365, 1328, 1272, 1238, 1164, 1122, 1094, 1072, 1035, 1016, 905, 885, 860, 834, 803, 778, 753, 701, 688, 657, 626, 615, 608, 591, 568, 560, 554 cm^{-1}; MS (70 eV, EI): *m/z* (%): 374 (42), 372 (38) [$M-^{79}$Br]$^+$, 346 (26), 345 (11), 344 (25), 330 (17), 329 (94), 328 (16), 327 (100), 248 (38), 221 (11), 220 (68), 219 (28), 201 (18), 170 (10), 43 (12); HRMS (EI): *m/z* calcd for $C_{16}H_{12}BrF_3O_2$: 371.9973; found: 371.9955.

Synthesis of 5-bromo-3′-trifluoromethylbiphenyl-2-carboxylic acid ethyl ester (17i): By following **TP 4**, the metalation of ethyl 4-bromobenzoate (**12b**; 458 mg, 2 mmol) was completed within 110 h at 25 °C. A solution of [Pd(dba)$_2$] (56 mg) and P(*o*-furyl)$_3$ (46 mg) in THF (2 mL) was added, followed by ethyl 4-iodobenzoate (615 mg, 2.2 mmol). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with diethyl ether (3×20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum. The crude product was purified by means of column chromatography (pentane/diethyl ether 20:1) to give **17i** as a yellowish oil (586 mg, 78%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08–8.04 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.57 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.36–7.33 (m, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.00 ppm (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.25, 166.29, 144.78, 143.52, 133.37, 131.63, 130.86, 130.12, 129.65, 129.30, 128.30, 127.17, 125.88, 61.23, 61.04, 14.32, 13.67 ppm; IR (ATR): $\tilde{\nu}$ = 2979, 1710, 1609, 1585, 1552, 1464, 1445, 1408, 1385, 1365, 1309, 1266, 1241, 1178, 1132, 1096, 1029, 1013, 887, 858, 835, 798, 771, 760, 700, 649, 642, 635, 623, 614, 608, 602, 583, 576, 573 cm^{-1}; MS (70 eV, EI): *m/z* (%): 378 (74), 376 (70) [$M-^{79}$Br]$^+$, 350 (12), 348 (13), 334 (21), 333 (100), 332 (26), 331 (99), 322 (11), 320 (11), 305 (34), 304 (17), 303 (39), 298 (11), 261 (39), 259 (43), 253 (19), 180 (29), 152 (42), 151 (42), 144 (12), 139 (11), 89 (17) 75 (11); HRMS (EI): *m/z* calcd for $C_{16}H_{12}BrF_3O_2$: 376.0310; found: 376.0309.

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