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Deprotonative Metalation of Aromatic Compounds by Using an Amino-Based Lithium Cuprate

Tan Tai Nguyen, Nada Marquise, Floris Chevallier, and Florence Mongin*[a]

Abstract: Deprotonative cupration of aromatic compounds by using amino-based lithium cuprates was optimized with 2,4-dimethoxypyrimidine and 2-methoxypyridine as the substrates and benzoyl chloride as the electrophile. $[(tmp)_2CuLi]$ (+2 LiCl) (tmp = 2,2,6,6-tetramethylpiperidino) was identified as the best reagent and its use was extended to anisole, 1,4-dimethoxybenzene, other substituted pyridines, furan, thiophene and derivatives, and *N*-Boc-indole (Boc = *tert*-butyloxycarbonyl). Of the electrophiles employed to attempt the interception of the generated aryl cuprates, aroyl chlorides, iodomethane, and diphenyl disulfide efficiently reacted. In addition, different oxidative agents were identified to afford symmetrical biaryls. Finally, palladium-catalyzed coupling with aryl halides was optimized and allowed the synthesis of different aryl derivatives in medium to good yields.

Keywords: bimetallic bases · copper · deprotonation · lithium · synthesis design

Introduction

Lithium bases have been largely employed to functionalize aromatic compounds.[1] Nevertheless, one limit of the method is the low compatibility of aryllithiums generated with reactive functions and sensitive rings, which require very low reaction temperatures or in situ electrophilic trappings. By combining lithium compounds with soft organometallics, more recently bases have been designed for the deprotonation of sensitive compounds.[2] Reactions at higher temperatures and metal-adjustable trapping are other advantages expected from these approaches.

Because of their unique behavior, cuprates have been the subject of many studies in organic and organometallic chemistry.[3] For a long time, the amino ligands of cuprates were mainly considered as nontransferable groups and allowed various applications.[4] In 2007, Wheatley and Uchiyama and co-workers showed that it was possible to perform deprotonative cupration of different aromatic compounds by amino ligand transfer from a lithium cuprate.[5] Among the different bases tested, the authors identified the Lipshutz-type compound $[MeCu(tmp)(CN)Li_2]$ (tmp = 2,2,6,6-tetramethylpiperidino) as the best reagent when two equivalents were employed in THF at 0 °C.

We recently developed tmp-based lithium–zinc[6] and lithium–cadmium[7] combinations for the deprotonative metalation of sensitive aromatic compounds. For this purpose, the mixed lithium–metal bases were prepared by treating three equivalents of [Li(tmp)] with either $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or $CdCl_2$·TMEDA.

To obtain a similar lithium–copper(I) base, $[(tmp)_2CuLi] + 2\,LiCl$,[8] we recently documented a protocol using air-stable $CuCl_2$·TMEDA.[9] For this purpose, the Cu^{II} salt was reduced to Cu^{I} by using butyllithium (1 equiv) and the base was obtained after the addition of two equivalents of [Li(tmp)] to the copper(I) species.[10] The reactivity of this lithium–copper(I) base toward various aromatic compounds was studied and was good in some cases. Herein, the details of our investigations into the choice of base and reaction conditions are described. In addition, different kinds of trapping for the aromatic cuprates are recorded.

Results and Discussion

To study the reactivity of this lithium–copper(I) base as a deprotonating agent for aromatic compounds, it is important to have at our disposal an electrophile efficient enough to trap the arylmetal species generated. It is acknowledged that cuprates can be trapped by acid chlorides to provide ketones and we thus considered this possibility.[5a,11]

To optimize the reactions conditions, we first chose 2,4-dimethoxypyrimidine (Table 1). This substrate can be considered as a moderately sensitive one: diazines are admittedly renowned for their ability to undergo nucleophilic attack,[12] but the presence of the methoxy groups reduces the π deficiency of the ring. As a consequence, 2,4-dimethoxypyrimidine can be metalated by using hindered lithium amides either at 0 °C in diethyl ether[13] or at −75 °C in THF[14] with complete regioselectivity for the position adjacent to the methoxy group.

[a] T. T. Nguyen, N. Marquise, Dr. F. Chevallier, Prof. F. Mongin
Chimie et Photonique Moléculaires, UMR 6510 CNRS
Université de Rennes 1. Bâtiment 10A, Case 1003
Campus Scientifique de Beaulieu, 35042 Rennes Cedex (France)
Fax: (+33) 2-2323-6955
E-mail: florence.mongin@univ-rennes1.fr

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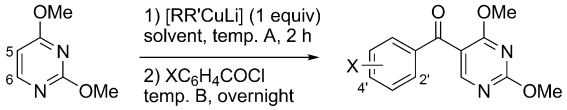
Table 1. Deprotocupration of 2,4-dimethoxypyrimidine followed by trapping with PhCOCl or ClC_6H_4COCl.



1a (X = H)
1b (X = 4-Cl)
1c (X = 2-Cl)

Entry	R, R′	Solvent	Temperature		Product (Yield [%])
			A	B	
1	TMP, TMP	THF	RT	60 °C	**1a** (45) or **1b** (52)
2	Bu, TMP	THF	RT	60 °C	**1a** (33, 29[a])
3	Me_3SiCH_2, TMP	THF	RT	60 °C	**1a** (10, 9[a])
4	Bu, Bu	THF	RT	60 °C	–[b]
5	TMP, TMP	THF	40 °C	60 °C	**1a** (57, 70[c])
6	TMP, TMP	THF	60 °C	60 °C	**1a** (52)
7	TMP, TMP	THF	RT	RT	**1a** (60, 47[d])
8	TMP, TMP	THF	0 °C	RT	**1a** (55)
9[e]	TMP, TMP	THF	40 °C	RT	**1c** (58[c])
10	TMP, TMP	HexH + TMEDA (5 equiv)	RT	RT	**1a** (29, 37[f])
11	TMP, TMP	PhMe + TMEDA (5 equiv)	RT	RT	**1a** (63[g])
12	TMP, TMP	Et_2O	RT	RT	**1a** (99)

[a] Yield obtained if temperature B = RT. [b] Degradation was observed. [c] Metalation for 3 h instead of 2 h. [d] Metalation for 1 h instead of 2 h. [e] Base prepared from CuCl and [Li(tmp)] (2 equiv) in the presence of TMEDA (1 equiv). [f] Conducting the reaction in hexane. [g] 6-Benzoyl-2,4-dimethoxypyrimidine (**1′a**) was also formed in an estimated yield of 6%.

The metalation ability of $[(tmp)_2CuLi]$ (+2 LiCl) (1 equiv) was first compared with that of amino organocuprates [BuCu(tmp)Li] (+2 LiCl) and $[Me_3SiCH_2Cu(tmp)Li]$ (+2 LiCl), and of diorganocuprate $[Bu_2CuLi]$ (+2 LiCl).[8] It is clear from the deprotonation experiments performed in THF at room temperature for 2 h that $[(tmp)_2CuLi]$ (+2 LiCl) is the best base. Under these conditions, ketones **1a** and **1b** were isolated in 45 and 52% yield, after trapping of the intermediate aryl cuprates with benzoyl and 4-chlorobenzoyl chloride, respectively, at 60 °C (Table 1, entry 1). Replacing one tmp ligand with a butyl or a (trimethylsilyl)-methyl group resulted in lower yields, as previously noted with the corresponding lithium–zinc[6] and lithium–cadmium[7] combinations, and no improvement was observed when conducting the trapping step at room temperature instead of at reflux (Table 1, entries 2 and 3). Degradation reactions, which took place with amino organocuprate bases, intensified with $[Bu_2CuLi]$ (+2 LiCl) and prevented isolation of the desired product (Table 1, entry 4).

A careful study of the temperatures of both metalation and the trapping steps was then undertaken. Yields of 45, 57, and 52% were obtained by performing the deprotonation step at room temperature, 40 °C and 60 °C, respectively (Table 1, entries 1, 5, and 6). These results indicate that the best metalation temperature for 2,4-dimethoxypyrimidine is 40–60 °C. The quenching temperature also had an impact on the yield. Indeed, after deprotonation at room temperature, carrying out this step at 60 °C and room temperature led to 45 and 60% yield (55% if the deprotonation was performed at 0 °C), respectively (Table 1, entries 1, 7, and 8). The impact of the deprotonation times on the yields was also noted, for example, deprotonation at 40 °C gave derivative **1a** in 70% yield after reaction for 3 h versus 57% yield after reaction for 2 h (Table 1, entry 5), and deprotonation at room temperature afforded ketone **1a** in 47% yield after 1 h versus 60% yield after 2 h (Table 1, entry 7). Under the best reaction conditions, ketone **1c** was prepared in 58% yield (Table 1, entry 9).

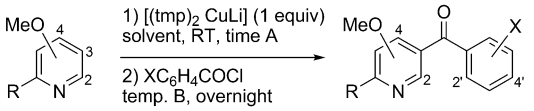
Since solvent has an important impact on the structure and reactivity of organometallics, the effect of different media on the course of this reaction was studied. THF was first chosen because it was traditionally the solvent of choice for metalation reactions. Nevertheless, examples in the literature have shown that hexane containing TMEDA was a better solvent than THF for performing metalation reactions.[15] In our case, the reactions carried out in hexane, or in hexane containing 5 equivalents of TMEDA,[6a] led to lower conversions, giving **1a** in 37 and 29% yield, respectively, after trapping (Table 1, entry 10). Using toluene containing 5 equivalents of TMEDA afforded the expected ketone **1a** in 63% yield, but regioisomer **1′a**, which resulted from metalation at the 6 position next to the nitrogen ring, was competitively formed (estimated yield: 6%; Table 1, entry 11). Diethyl ether, which is less coordinating than THF and often employed as a solvent in reactions involving cuprates, was similarly tested, and surprisingly afforded **1a** in 99% yield (Table 1, entry 12). The solvent can have an impact on the aggregation state of the base and also on its ability to exist as contacted ion pairs or solvent-separated ion pairs.[16] Labile Lewis bases, such as ethers and TMEDA, could help in breaking up the aggregates and make the base more available for interactions with substrate heteroatoms, thus facilitating the metalation reaction. Nevertheless, THF (more basic than diethyl ether), is known to favor cuprates as solvent-separated ion pairs, whereas cuprates as contacted ion pairs, which are known to favor deprotometalation,[2] predominate in diethyl ether.[16] Thus, it seems that the solvent has to be basic enough to allow the disaggregation of the base, but not too complexing to avoid solvent-separated ion pairs.

Nevertheless, one also has to consider LiCl, which is present in the reaction medium (2 equiv). Wheatley and Uchiyama and co-workers have shown that Lipshutz-type species, including LiX (X = CN), were more efficient reagents than the corresponding Gilman-type species.[5b] In our case, the formation of Lipshutz-type species by LiX (X = Cl) inclusion could be responsible for the good reactivity observed. The

moderate yield observed in hexane could in turn be related with the lack of solubility of LiCl in hexane.

The reaction conditions were optimized by using 2,4-dimethoxypyrimidine as a substrate. Depending on the substituents and the nature of the aromatic ring (presence or absence of coordinating atoms, electron effects, etc.), these conditions were more or less appropriate. We thus turned to methoxypyridines to see if the results obtained with 2,4-dimethoxypyrimidine could be extended to these substrates (Table 2).

Table 2. Deprotocupration of methoxypyridines followed by trapping with PhCOCl or XC_6H_4COCl.



2a (2-OMe, R = H, X = H)
2b (2-OMe, R = OMe, X = 4-CF_3)
2c (2-OMe, R = OMe, X = 2-Cl)
2d (4-OMe, R = H, X = 2-Cl)

Entry	Substrate, R	Solvent	Time A [h]	Temperature B	Product (Yield [%])
1	2-OMe, H	THF	2	RT	**2a** (82, 40[a])
2	2-OMe, OMe	THF	2	RT	**2b** (60)
3[b]	2-OMe, OMe	THF	2	RT	**2c** (91)
4	2-OMe, H	THF	2	60 °C	**2a** (66)
5	2-OMe, H	THF	2	0 °C	**2a** (66[c])
6	2-OMe, H	THF	0.5	RT	**2a** (72)
7	2-OMe, H	THF	6	RT	**2a** (62[d])
8	2-OMe, H	Et_2O	2	RT	**2a** (71)
9	2-OMe, H	PhMe + TMEDA (5 equiv)	2	RT	**2a** (49)
10	2-OMe, H	Et_2O + Me_2S (5 equiv)	2	RT	**2a** (81, 77[e])
11	2-OMe, H	Et_2O + Me_2S (5 equiv)	0.5	RT	**2a** (52[d])
12[f]	2-OMe, H	Et_2O	2	RT	**2a** (54)
13[f]	2-OMe, H	THF	2	RT	**2a** (33)
14	4-OMe, H	THF	2	RT	**2d** (57)

[a] Using 0.5 equiv of base. [b] The base was prepared from CuCl and [Li(tmp)] (2 equiv) in the presence of TMEDA (1 equiv). [c] The 3,6-disubstituted derivative **2′a** was also formed in 10% yield. [d] The 3,6-disubstituted derivative **2′a** was also formed in 5% yield. [e] Metalation for 1 h instead of 2 h. [f] The base was prepared from [$CuBr(Me_2S)$] and [Li(tmp)] (2 equiv).

2-Methoxypyridine is amenable to lithiation at the 3-position using either organolithium compounds containing a catalytic amount of diisopropylamine in THF at 0 °C[17] or mesityllithium in THF at 0 °C.[18] Concerning 2,6-dimethoxypyridine, butyllithium has been employed in THF at −40 °C.[19] In contrast, metalation of 2-methoxypyridine occurs at C6 upon treatment with BuLi–[Li(dmae)] (DMAE = 2-dimethylaminoethoxide).[20]

Treatment of 2-methoxypyridine with [$(tmp)_2CuLi$] (+2 LiCl) (1 equiv) in THF at room temperature for 2 h and subsequent trapping with benzoyl chloride at room temperature provided derivative **2a**, resulting from reaction at the 3-position in 82% yield. The quantity of base was essential for the success of the reaction; indeed, using 0.5 equivalent led to a 42% drop in the yield (Table 2, entry 1). 2,6-Dimethoxypyridine was similarly converted into ketones **2b** and **2c**, using 4-(trifluoromethyl)benzoyl chloride and 2-chlorobenzoyl chloride, respectively, as the electrophiles (Table 2, entries 2 and 3).

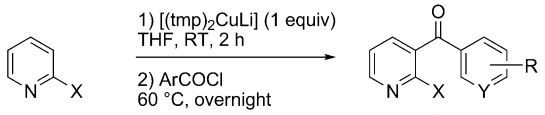
Carrying out the quenching step of the 3-metalated 2-methoxypyridine at 60 °C instead of room temperature caused a decrease in the yield (Table 2, entry 4), as previously observed with 2,4-dimethoxypyrimidine, that could be due to a low compatibility at this temperature between the unreacted metal amide and the generated ketone. On the contrary, when the trapping temperature was lowered to 0 °C, 3,6-disubstituted derivative **2′a** was formed in 10% yield in addition to the expected ketone **2a**. Compound **2′a** could result from metalation of **2a** by unreacted amino ligands during the trapping step (Table 2, entry 5). Choosing reduced or extended reaction times gave lower yields (Table 2, entries 6 and 7). In the case of 2-methoxypyridine, the use of diethyl ether and toluene containing 5 equivalents of TMEDA was less efficient than with 2,4-dimethoxypyrimidine, giving **2a** in 71 and 49% yield, respectively (Table 2, entries 8 and 9). Dimethyl sulfide was sometimes used as cosolvent for reactions involving cuprates,[21] therefore, the reaction was also attempted with diethyl ether containing 5 equivalents of dimethyl sulfide, under the same reaction conditions. Derivative **2a** was obtained in a yield (81%) similar to that obtained in THF. As already observed in THF, the conversion was less complete with shorter reaction times (Table 2, entries 10 and 11).

The positive impact of dimethyl sulfide on the course of the reaction led us to consider [$CuBr(Me_2S)$] as a copper(I) source. For this purpose, 2-methoxypyridine was treated at room temperature with a base prepared in situ from [$CuBr(Me_2S)$] and 2 equivalents of [Li(tmp)] for 2 h before trapping with benzoyl chloride. Diethyl ether and THF were tested as solvents: the former was the best (54% yield instead of 33% with the latter, Table 2, entries 12 and 13), but the method with $CuCl_2$·TMEDA remained superior.

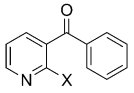
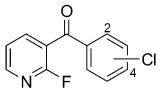
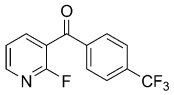
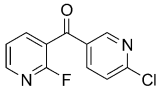
The best conditions were finally applied to the conversion of 4-methoxypyridine into the ketone **2d**, albeit in a more modest yield of 57% (Table 2, entry 14).

2-Fluoro-, 2-chloro-, and 2-bromopyridine were compared with 2-methoxypyridine with regards to their behavior toward [$(tmp)_2CuLi$] (+2 LiCl) (1 equiv) in THF at room temperature (Table 3). Whereas 2-fluoro- and 2-chloropyridine afforded the expected benzoyl derivatives **3a** and **4a** in high yields, similar to that obtained for 2-methoxypyridine, a low 20% yield of **5a** was noted for 2-bromopyridine. At-

Table 3. Deprotocupration of 2-fluoro-, 2-chloro-, and 2-bromopyridine followed by trapping with an aroyl chloride.



3-5

Entry	X	Product	(Yield [%])
1	F		**3a** (85[a])
2	Cl		**4a** (83)
3	Br		**5a** (20)
4	F		**3b**: 2-Cl (76)
5	F		**3c**: 4-Cl (83)
6	F		**3d** (92)
7	F		**3e** (72)

[a] Degradation occurs if the metalation step is performed at 40 °C.

tempts to perform the reaction at 0 °C or using diethyl ether as the solvent did not result in any improvement (Table 3, entries 1–3). Such a problem could be related to the instability of 2-bromopyridine with a metal at C3.[22]

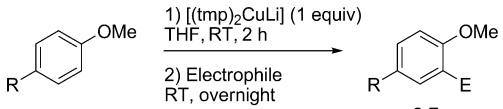
Starting from 2-fluoropyridine, the method was extended to the synthesis of ketones **3b–e** using electrophiles 2- and 4-chlorobenzoyl chloride, 4-(trifluoromethyl)benzoyl chloride, and 6-chloronicotinoyl chloride (Table 3, entries 4–7). Attempts to deprotometalate ketone **4a** were unsuccessful.

Pyridin-2-yl and -4-yl cuprates have previously been reported.[23] However, the metalation of different 3-substituted (methoxy, fluoro, chloro) pyridines was not successful, regardless of the conditions used. Precomplexing the 3-substituted pyridine with BF_3•Et_2O before the deprotonation step[24] did not result in isolation of an aryl ketone.

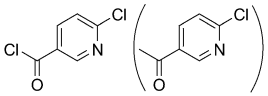
To evaluate the scope of the reaction, we turned to anisole, which has been the subject of many studies concerning deprotometalation,[1–,2d] and the 4-methoxy derivative (Table 4). These substrates do not have a complexing nitrogen and have less acidic hydrogen atoms. Upon treatment with 1 equivalent of [(tmp)$_2$CuLi] (+2 LiCl) in THF at room temperature for 2 h and subsequent trapping with different aroyl chlorides, the expected ketones **6a–c** were obtained in 54–68 % yield (Table 4, entries 1–3).

The reaction with elemental iodine instead of an aroyl chloride to trap the metalated species resulting from 1,4-dimethoxybenzene and anisole proceeded in low yields (compounds **6d** and **7d** were isolated in 19–20 % yield; Table 4, entries 4 and 5). Starting from anisole, concomitant formation of 2,2′-dimethoxybiphenyl and *N*-(2-methoxyphenyl)-2,2,6,6-tetramethylpiperidine was observed, probably through reactions occurring during the trapping step with iodine, which can behave as an oxidative agent.[25] Indeed,

Table 4. Deprotocupration of anisole and 1,4-dimethoxybenzene followed by electrophilic trapping.



6,7

Entry	R	Electrophile (E)	Product (Yield [%])
1	OMe	PhCOCl (PhCO)	**6a** (68[a])
2	OMe	4-ClC_6H_4COCl (4-ClC_6H_4CO)	**6b** (57)
3	OMe		**6c** (54[b])
4	OMe	I_2 (I)	**6d** (19)
5	H	I_2 (I)	**7d** (20)
6	OMe	CH_2=$CHCH_2$Br (CH_2=$CHCH_2$)	**6e** (41)

[a] A more complex reaction mixture was formed when using more than one equivalent of base. [b] By performing the deprotonation step at 40 °C.

these derivatives were not observed when using aroyl chlorides, water, or allyl bromide as electrophiles. The 2-allylated compound **6e** was synthesized from 1,4-dimethoxybenzene in 41 % yield (Table 4, entry 6).

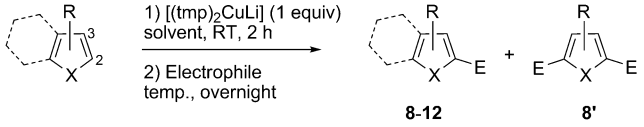
We then used five-membered heterocycles in the reaction with [(tmp)$_2$CuLi] (+2 LiCl). Upon treatment with 1 equivalent of base at room temperature in THF for 2 h, followed by subsequent interception with benzoyl and 4-chlorobenzoyl chloride at 60 °C, thiophene was converted into the corresponding ketones **8a** and **8b** (Table 5, entries 1 and 2). Compounds **9** and **10** were similarly prepared starting from furan and *N*-Boc indole (Table 5, entries 3 and 4). When diethyl ether was employed in the presence or absence of dimethyl sulfide instead of THF, 2-monosubstituted thiophene **8a** was also formed after trapping with benzoyl chloride at room temperature, together with the 2,5-disubstituted thiophene **8′a** (Table 5, entries 5 and 6).

Ethyl thiophene-2-carboxylate was regioselectively deprotonated next to sulfur to give, after subsequent trapping at room temperature with benzoyl chloride or iodine, functionalized derivatives **11a** and **11b** in moderate to medium yields (Table 5, entries 7 and 8). Turning to ethyl thiophene-3-carboxylate, the reaction was more difficult at room temperature; by lowering the deprotonation temperature to 0 °C, an improved yield of 40 % of **12** resulted after interception with benzoyl chloride at room temperature (Table 5, entry 9).

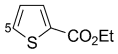
Similar to alkynyl, cyano, and methyl groups, 2-thienyl is, in general, considered to be a nontransferable or "dummy" ligand of cuprates. This could partly explain the moderate yields obtained upon reaction of such substrates.

The trapping step of the different heteroaryl cuprates was then studied (Table 6). From 2,4-dimethoxypyrimidine, the expected methylated and allylated derivatives **13a** and **13b** were isolated in low to good yields (Table 6, entries 1 and 2). Using nitrobenzene as an oxidant resulted in homocoupled pyrimidine **13′** (Table 6, entry 3).

Table 5. Deprotocupration of thiophene derivatives and furan followed by electrophilic trapping.



8-12 8'

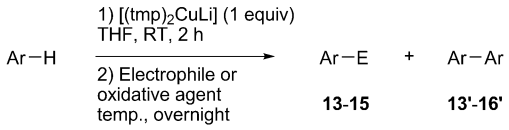
Entry	Substrate	Solvent	Electrophile (E), T [°C]	Product (Yield [%])
1		THF	PhCOCl (PhCO), 60	**8a** (48)
2		THF	4-ClC_6H_4COCl (4-ClC_6H_4CO), 60	**8b** (58)
3		THF	PhCOCl (PhCO), 60	**9** (53)
4		THF	PhCOCl (PhCO), 60	**10** (50[a])
5		Et_2O + Me_2S (5 equiv)	PhCOCl (PhCO), RT	**8a** (53), **8'a** (18)
6		Et_2O	PhCOCl (PhCO), RT	**8a** (31), **8'a** (29)
7		THF	PhCOCl (PhCO), RT	**11a** (49)
8		THF	I_2 (I), RT	**11b** (23)
9		THF	PhCOCl (PhCO), RT	**12** (26, 40[b])

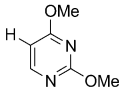
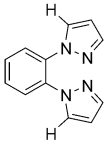
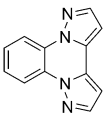
[a] After removal of the *tert*-butyloxycarbonyl (Boc) group with trifluoroacetic acid (TFA) in CH_2Cl_2 at RT.[26] [b] Performing the metalation step at 0°C instead of RT.

From 2-methoxypyridine, the expected 3-iodo derivative **14a** was isolated in a moderate yield of 28% due to the major formation of the coupled product **14′** (Table 6, entry 4). When 2-phenyloxirane was employed, two regioisomeric alcohols resulting from attack at the less (**14b**) and more (**14b′**) hindered position of the epoxide were formed in 22 and 12% yield, respectively (Table 6, entry 5), and no improvement was observed in the presence of BF_3·Et_2O. In contrast, diphenyl disulfide efficiently trapped pyridyl cuprate to afford sulfide **14c** (67% yield, Table 6, entry 6).

Dimethylsulfamoyl chloride, 4-chlorobenzenesulfonyl chloride, and tetramethylthiuram disulfide did not behave as electrophiles, but as oxidative agents, leading to homocoupled pyridine **14′**. Diarylsulfone **14d** was the only trapping product detected, but isolated in a negligible yield of 3% (Table 6, entry 7–9). Reactions involving conjugate addition were possible by using ethyl phenylpropiolate, ethyl pentylpropiolate, or methyl methylpropiolate as the electrophiles at room

Table 6. Deprotocupration of aromatic compounds followed by different electrophilic trapping or oxidation.



Entry	Ar−H	Electrophile (E) or oxidative agent, T [°C]	Product (Yield [%])	
1		MeI (Me), 30C	**13a** (62)	
2		CH_2=$CHCH_2Br$ (CH_2=$CHCH_2$), RT	**13b** (19)	
3		$PhNO_2$, RT		**13'** (22)
4		I_2 (I), RT	**14a** (28)	**14′** (39)
5		2-phenyloxirane (PhCH(OH)CH_2 or $HOCH_2CH$(Ph)), RT	**14b** (22) **14b'** (12)	
6		$(PhS)_2$ (PhS), RT	**14c** (67)	
7		Me_2NSO_2Cl, RT		**14'** (72)
8		4-$ClC_6H_4SO_2Cl$ (4-$ClC_6H_4SO_2$), RT	**14d** (3)	**14'** (58)
9		$[Me_2NC(S)S]_2$, RT		**14'** (88)
10		PhC≡CCO_2Et [(*Z*)-C(Ph)=$CHCO_2Et$], RT	**14e** (39[a])	
11		PeC≡CCO_2Et [(*E*)-C(Pe)=$CHCO_2Et$], RT	**14f** (26)	
12		MeC≡CCO_2Me [(*Z*/*E*)-C(Me)=$CHCO_2Me$], RT	(*Z*)-**14g** (30) (*E*)-**14g'** (17)	
13		I_2 (I), RT	**15** (31)	**15′** (5[b])
14		Me_3SiCl, 50		**15'** (52)
15		$PhNO_2$, RT		**15'** (84, 73[c])
16		chloranil, 60		**15'** (94, 58[d])
17[e]		$PhNO_2$, RT		**16′** (10)

[a] The *E* isomer **14e′** was also identified in the crude (estimated yield: 10%). [b] Yield estimated from the crude mixture. [c] By using the oxidative agent at 60°C. [d] By using the oxidative agent at RT. [e] By using two equivalents of base.

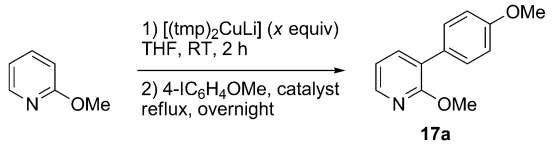
temperature to afford **14e–g** in moderate yields ranging from 26 to 39% (Table 6, entries 10–12).[27]

As observed with 2-methoxypyridine, the conversion of 2-fluoropyridine into the corresponding 3-iodo derivative **14** proceeded in a moderate yield (Table 6, entry 13). The dimer yield progressively increased when using iodine, trimethylsilyl chloride, nitrobenzene, and chloranil[28] as oxidative agents. Whereas nitrobenzene gave the best yield at room temperature, chloranil was more successfully employed at 60°C (Table 6, entry 14–16). To perform an intramolecular double-deprotonation–cyclization, we treated 1,1′-(1,2-phenylene)bis(1*H*-pyrazole) with 2 equivalents of $[(tmp)_2CuLi]$ (+2 LiCl) in THF at room temperature for 2 h before subsequent treatment with nitrobenzene. Under these conditions, the expected cyclized derivative was isolated, albeit in a low yield of 10% (Table 6, entry 17).

It was then decided to evaluate the involvement of the generated aryl cuprates in palladium-catalyzed cross-coupling reactions. Because this possibility has not been developed to synthesize biaryl compounds, we first chose to test the efficiency of different catalyst systems using 2-methoxypyridine as the cuprate precursor and 4-iodoanisole as the aryl halide (Table 7).

The first reactions of our optimization study were carried

Table 7. Optimization of the palladium-catalyzed cross-coupling reaction of 3-metalated 2-methoxypyridine and 4-iodoanisole.



17a

Entry	*x* equiv	Catalyst[a]	Yield [%]
1	1 (0.5)	$[PdCl_2(PPh_3)_2]$ (2 mol%), PPh_3 (4 mol%)	40 (37)
2	1 (0.5)	$[PdCl_2(PPh_3)_2]$ (2 mol%), dppf (2 mol%)	23[b] (64)
3	0.5	$[PdCl_2(PPh_3)_2]$ (2 mol%)	47[c]
4	0.5	$[Pd(PPh_3)_4]$ (2 mol%)	42[d]
5	0.5	$Pd(OAc)_2$ (2 mol%), dppf (2 mol%)	43
6	0.5	$[Pd(dba)_2]$ (2 mol%), dppf (2 mol%)	57

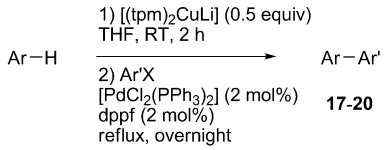
[a] dppf = 1,1′-bis(diphenylphosphino)ferrocene, dba = dibenzylideneacetone. [b] Compound **17a′** was also isolated in 8% yield. [c] Dimer **14′** was also isolated in 9% yield. [d] Dimer **14′** was also isolated in 12% yield.

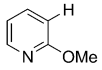
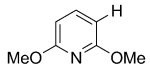
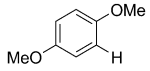
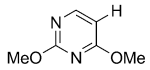
out after deprotocupration using one equivalent of base and employing catalytic amounts of $[PdCl_2(PPh_3)_2]$ combined either with triphenylphosphine (Table 7, entry 1) or with dppf (Table 7, entry 2), at the reflux temperature of THF. A moderate yield of 40% of the expected product **17a** was obtained with triphenylphosphine; in the presence of the bidentate ligand, the expected coupling product **17a** was produced in a low yield of 23%, partly due to the concomitant formation of **17a′**. It appeared to us that the latter was formed by metalation of **17a** during the trapping step followed by cross-coupling, as a result of the excess base used in the metalation step. This led us to explore the use of 0.5 equivalent of base. With triphenylphosphine the yield remained moderate (Table 7, entry 1), but with dppf, it could be improved to 64% (Table 7, entry 2); a yield that was intermediate between those obtained after trapping with benzoyl chloride using 0.5 (40) and 1 equivalent (82%) of base (Table 2, entry 1).

The formation of **14′** was observed in 9 and 12% yield, respectively, using $[PdCl_2(PPh_3)_2]$ without additional ligand and $[Pd(PPh_3)_4]$ (Table 7, entries 3 and 4). Palladium(II) acetate, for which mixtures with tertiary phosphines are known to spontaneously generate palladium(0) complexes,[29] was also tested as a precatalyst, combined with dppf, but a lower yield of 43% was recorded (Table 7, entry 5). Finally, $[Pd(dba)_2]$ as a palladium source with the same bidentate ligand gave a yield comparable with that obtained with $[PdCl_2(PPh_3)_2]$ (Table 7, entry 6) discarding a possible inefficient reduction of palladium(II) chloride.

With these optimized conditions in hand, different experiments were conducted to evaluate the scope of this reaction (Table 8). Starting from 2-methoxypyridine, 4-bromoanisole

Table 8. Deprotocupration of aromatic compounds followed by palladium-catalyzed cross-coupling.



Entry	Ar−H	Ar′−X	Product (Yield [%])
1		4-IC_6H_4OMe	**17a** (64)
2		4-BrC_6H_4OMe	**17a** (46)
3		4-BrC_6H_4F	**17b** (47)
4		4-$BrC_6H_4CO_2Et$	**17c** (64)
5		2-BrPy	**17d** (63)
6		4-IC_6H_4OMe	**18a** (51)
7		2-BrPy	**18b** (54)
8		4-IC_6H_4OMe	**19a** (39[a])
9		2-BrPy	**19b** (36[a])
10		4-IC_6H_4OMe	**20a** (42, 46[a])
11		2-BrPy	**20b** (44)

[a] The metalation step was performed at 40°C.

was used under the conditions employed in Table 7, entry 2, with 0.5 equivalent of base. Biaryl derivative **17a** was isolated in 46% yield, versus 64% yield when employing 4-iodoanisole (Table 8, entries 1 and 2). Biaryl **17b** was similarly prepared in 47% yield by employing 1-bromo-4-fluorobenzene (Table 8, entry 3). Electron-deficient aryl bromides, such as ethyl 4-bromobenzoate and 2-bromopyridine, were coupled with 3-metalated 2-methoxypyridine in higher yields; a result that could be explained by a mechanism involving an addition–elimination step instead of classical oxidative addition.[30] Biaryls **17c** and **17d** were thus obtained in satisfying yields of 64 and 63%, respectively (Table 8, en-

tries 4 and 5). 2,6-Dibromopyridine was converted into 3-(4-anisyl) and -(pyridin-2-yl) derivatives **18a** and **18b** in 51 and 54%, respectively (Table 8, entries 6 and 7). Due to the lower acidity or higher sensitivity to nucleophiles, respectively, 1,4-dimethoxybenzene and 2,4-dimethoxypyrimidine were similarly reacted to afford the corresponding coupling products **19a** and **19b** (Table 8, entries 8 and 9) and **20a** and **20b** (Table 8, entries 10 and 11).

Conclusion

We have examined the possible use of amino-based lithium cuprates for the deprotometalation of aromatic compounds. As previously observed with lithium–zinc,[6e] lithium–cadmium,[7g] and lithium–cobalt combinations,[31] the best base was the "all-tmp" one. In most cases, the reaction could be performed at room temperature in THF with one equivalent of base.

One limitation concerning the interception step of the generated aryl cuprates with electrophiles is their easy oxidation, leading to symmetrical biaryl compounds. Nevertheless, successful methylation, aroylation, sulfanylation, and palladium-catalyzed coupling reactions were recorded. The scope of the method could be considerably extended with addition reactions to activated alkenes and alkynes; currently, this possibility only led to modest yields using activated alkynes to trap the aryl cuprates.

The use of ever-efficient lithium–metal combinations, which allow other kinds of functionalization, is currently under investigation.

Experimental Section

General: All reactions were performed in Schlenk tubes under an argon atmosphere. THF was distilled over sodium/benzophenone. NMR spectra were acquired on Bruker AC-300 spectrometer (300 and 75 MHz for ^{1}H and ^{13}C, respectively) or Bruker Avance I500 spectrometers (500 and 125 MHz for ^{1}H and ^{13}C, respectively). High-resolution mass spectra measurements were performed at the CRMPO in Rennes (Centre Régional de Mesures Physiques de l'Ouest) using a Waters Q-TOF 2 instrument. Liquid chromatography separations were achieved on silica gel Merck Geduran Si 60 (40–63 mesh). $CuCl_2$·TMEDA was prepared according to a described procedure.[9b]

2-Iodo-1,4-dimethoxybenzene (**6d**),[31] 2-iodoanisole (**7d**),[7a] 3-iodo-2-methoxypyridine (**14a**),[31] 2,2′-dimethoxy-3,3′-bipyridine (**14′**),[31] and 2-fluoro-3-iodopyridine (**15**),[6e] have previously been described.

General procedure for the deprotocupration: Electrophilic trapping of aromatic compounds: BuLi (about 1.6 M hexanes solution, 2.0 mmol) was successively added to a stirred, cooled (0 °C) suspension of $CuCl_2$·TMEDA (0.5 g, 2.0 mmol) in THF (5 mL) then 15 min later, a solution of [Li(tmp)] prepared in THF (2 mL) at 0 °C from 2,2,6,6-tetramethylpiperidine (0.68 mL, 4.0 mmol) and BuLi (about 1.6 M hexanes solution, 4.0 mmol) was also added. The mixture was stirred for 15 min at this temperature before the introduction of the substrate (2.0 mmol). After the required reaction time at the required temperature, the electrophile (4.0 mmol) was added at 0 °C. The mixture was stirred for 16 h at the required temperature before the addition of brine (5 mL) and extraction with Et_2O (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure before purification by column chromatography on silica gel (the eluent is given in the product description). When I_2 was used as the electrophile, the mixture was treated by an aqueous saturated solution of $Na_2S_2O_3$ (5 mL) before extraction.

2,4-Dimethoxypyrimidin-5-yl phenyl ketone (1a):[10] Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.95 (s, 3H), 4.07 (s, 3H), 7.42–7.49 (m, 2H), 7.58 (tt, J = 7.3, 1.3 Hz, 1H), 7.74–7.78 (m, 2H), 8.46 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.5 (CH_3), 55.5 (CH_3), 114.5 (C), 128.5 (2 CH), 129.7 (2 CH), 133.3 (CH), 137.6 (C), 161.2 (CH), 166.3 (C), 169.3 (C), 192.2 ppm (C=O); HRMS (ESI): m/z calcd for $C_{13}H_{13}N_2O_3$: 245.0926 $[M+H]^+$, $C_{13}H_{12}N_2NaO_3$: 267.0746 $[M+Na]^+$; found: 245.0929, 267.0746.

4-Chlorophenyl 2,4-dimethoxypyrimidin-5-yl ketone (1b):[10] Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 145–146 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.96 (s, 3H), 4.08 (s, 3H), 7.41–7.46 (m, 2H), 7.68–7.73 (m, 2H), 8.48 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.5 (CH_3), 55.5 (CH_3), 114.1 (C), 128.8 (2 CH), 130.9 (2 CH), 136.0 (C), 139.7 (C), 161.3 (CH), 166.5 (C), 169.1 (C), 190.9 ppm (C=O); HRMS (ESI): m/z calcd for $C_{13}H_{12}{}^{35}ClN_2O_3$: 279.05365 $[M+H]^+$, 301.0356 $[M+Na]^+$; found: 279.0546, 301.0354.

2-Chlorophenyl 2,4-dimethoxypyrimidin-5-yl ketone (1c): Eluent: heptane/EtOAc (80:20); orange powder; m.p. 74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.91 (s, 3H), 4.06 (s, 3H), 7.31–7.44 (m, 4H), 8.62 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.7 (CH_3), 55.7 (CH_3), 114.1 (C), 127.0 (CH), 129.4 (CH), 129.9 (CH), 131.3 (C), 131.6 (CH), 139.4 (C), 163.4 (CH), 167.0 (C), 169.6 (C), 190.8 ppm (C=O); HRMS (ESI): m/z calcd for $C_{13}H_{11}{}^{35}ClN_2NaO_3$: 301.0356 $[M+Na]^+$; found: 301.0356.

2-Methoxypyridin-3-yl phenyl ketone (2a): Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 85–86 °C (lit.[24b] 80.2–81.5 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.88 (s, 3H), 7.01 (dd, J = 7.3, 5.0 Hz, 1H), 7.43–7.48 (m, 2H), 7.59 (tt, J = 7.3, 1.3 Hz, 1H), 7.72 (dd, J = 7.3, 2.0 Hz, 1H), 7.78–7.81 ppm (m, 2H), 8.32 (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.8 (CH_3), 116.6 (CH), 122.7 (C), 128.5 (2 CH), 129.9 (2 CH), 133.5 (CH), 137.2 (C), 139.0 (CH), 149.4 (CH), 161.3 (C), 194.9 ppm (C=O). These data are consistent with that reported in the literature.[24b]

Diphenyl 2-methoxypyridine-3,6-diyl diketone (2′a): Eluent: heptane/EtOAc (80:20); brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.87 (s, 3H), 7.43–7.53 (m, 4H), 7.57–7.65 (m, 2H), 7.75 (d, 1H, J = 7.5 Hz), 7.79–7.85 (m, 2H), 7.88 (d, 1H, J = 7.5 Hz), 8.14–8.19 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.2 (CH_3), 117.6 (CH), 125.4 (C), 128.2 (2 CH); 128.7 (2 CH), 129.9 (2 CH), 131.1 (2 CH), 133.1 (CH), 133.9 (CH), 136.3 (C), 136.7 (C), 139.6 (CH), 154.0 (C), 160.1 (C), 192.6 (C=O), 194.2 ppm (C=O); HRMS (ESI): m/z calcd for $C_{20}H_{15}NNaO_3$: 340.0950 $[M+Na]^+$; found: 340.0949.

2,6-Dimethoxypyridin-3-yl 4-(trifluoromethyl)phenyl ketone (2b): Eluent: heptane/EtOAc (90:10); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.84 (s, 3H), 3.99 (s, 3H), 6.41 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.83 ppm (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.7 (CH_3), 54.1 (CH_3), 102.4 (CH), 112.8 (C), 123.9 (q, C, J(C,F) = 272 Hz), 125.2 (q, 2CH, J(C,F) = 4 Hz), 129.6 (2CH), 133.5 (q, C, J(C,F) = 32 Hz), 142.1 (C), 143.7 (CH), 161.9 (C), 165.7 (C), 193.3 ppm (C=O); HRMS (ESI): m/z calcd for $C_{15}H_{13}F_3NO_3$: 312.0847 $[M+H]^+$, 334.0667 $[M+Na]^+$; found: 312.0846, 334.0670.

2-Chlorophenyl 2,6-dimethoxypyridin-3-yl ketone (2c): Eluent: heptane/EtOAc (90:10); yellow powder; m.p. 55 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.81 (s, 3H), 3.98 (s, 3H), 6.37 (d, J = 8.4 Hz, 1H), 7.31–7.37 (m, 4H), 7.98 ppm (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.0 (CH_3), 54.2 (CH_3), 102.7 (CH), 113.1 (C), 126.8 (CH), 128.7 (CH), 129.6 (CH), 130.6 (CH), 130.9 (C), 141.1 (C), 144.1 (CH), 163.0 (C), 166.3 (C), 192.1 ppm (C=O); HRMS (ESI): m/z calcd for $C_{14}H_{12}{}^{35}ClNNaO_3$: 300.0403 $[M+Na]^+$; found: 300.0403.

2-Chlorophenyl 4-methoxypyridin-3-yl ketone (2d): Eluent: heptane/EtOAc (20:80); yellow powder; m.p. 107 °C; ^{1}H NMR (C_6D_6, 500 MHz): δ = 2.96 (s, 3H), 6.26 (brs, 1H), 6.83 (m, 2H), 7.05 (m, 1H), 7.25 (m, 1H), 8.87 (brs, 1H), 9.44 ppm (brs, 1H); ^{13}C NMR (C_6D_6, 125 MHz): δ = 55.0 (CH_3), 108.8 (C), 126.7 (CH), 128.3 (CH), 130.1 (CH), 130.1 (CH),

131.3 (CH), 132.1 (C), 140.8 (C), 152.7 (CH), 154.5 (CH), 164.1 (C), 192.3 ppm (C=O); HRMS (ESI): *m/z* calcd for $C_{13}H_{11}{}^{35}ClNO_2$: 248.0478 $[M+H]^+$, 270.0298 $[M+Na]^+$; found: 248.0478, 270.0298.

2-Fluoropyridin-3-yl phenyl ketone (3a): Eluent: heptane/EtOAc (80:20); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.36$ (ddd, $J=7.4$, 4.9, 1.9 Hz, 1H), 7.45–7.54 (m, 2H), 7.64 (tt, $J=7.4$, 1.9 Hz, 1H), 7.78–7.85 (m, 2H), 8.03 (ddd, $J=9.1$, 7.4, 2.0 Hz, 1H), 8.42 ppm (d, 1H, $J=4.2$ Hz). These data are consistent with those reported in the literature:[32] beige oil; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=121.6$ (d, C, J(C,F)=30 Hz), 121.7 (d, CH, J(C,F)=5 Hz), 128.7 (2 CH), 129.7 (d, 2 CH, J(C,F)=1 Hz), 134.0 (CH), 136.5 (d, C, J(C,F)=1 Hz), 141.8 (d, CH, J(C,F)=3 Hz), 150.4 (d, CH, J(C,F)=15 Hz), 160.1 (d, C, J(C,F)=243 Hz), 191.7 ppm (d, C=O, J-(C,F)=5 Hz).

2-Chloropyridin-3-yl phenyl ketone (4a): Eluent: heptane/EtOAc (90:10); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.38$ (dd, $J=7.5$, 4.9 Hz, 1H), 7.42–7.50 (m, 2H), 7.61 (tt, $J=7.4$, 1.3 Hz, 1H), 7.72 (dd, $J=7.5$, 2.0 Hz, 1H), 7.75–7.81 (m, 2H), 8.52 ppm (dd, $J=4.9$, 2.0 Hz, 1H). These data are consistent with those reported in the literature:[33] yellow oil; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=122.3$ (CH), 128.9 (2CH), 130.0 (2 CH), 134.3 (CH), 134.9 (C), 135.7 (C), 138.0 (CH), 147.7 (C), 150.9 (CH), 193.3 ppm (C=O)

2-Bromopyridin-3-yl phenyl ketone (5a): Eluent: heptane/EtOAc (90:10); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.39$ (dd, $J=7.5$, 4.9 Hz, 1H), 7.46–7.54 (m, 2H), 7.64 (tt, $J=7.4$, 1.3 Hz, 1H), 7.75 (dd, $J=7.5$, 2.0 Hz, 1H), 7.78–7.82 (m, 2H), 8.56 ppm (dd, $J=4.9$, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=122.4$ (CH), 129.0 (2CH), 130.1 (2CH), 134.3 (CH); 135.1 (C), 135.9 (C), 138.1 (CH), 147.9 (C), 151.0 (CH), 193.5 ppm (C=O). These data are consistent with those reported in the literature:[34] yellow oil.

2-Fluoropyridin-3-yl 2-chlorophenyl ketone (3b): Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.30$–7.50 (m, 5H), 8.19 (ddd, $J=9.3$, 7.5, 2.0 Hz, 1H), 8.36–8.42 ppm (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=121.2$ (d, CH, J(C,F)=26 Hz), 122.1 (d, C, J(C,F)=5 Hz), 127.2 (CH), 129.8 (CH), 130.3 (CH), 131.6 (d, C, J(C,F)=2 Hz), 132.5 (CH), 138.3 (C), 142.2 (d, CH, J(C,F)=2 Hz), 151.9 (d, CH, J-(C,F)=15 Hz), 160.9 (d, C, J(C,F)=247 Hz), 191.0 ppm (d, C=O, J-(C,F)=6 Hz); HRMS (ESI): *m/z* calcd for $C_{12}H_7{}^{35}ClFNNaO$: 258.0098 $[M+Na]^+$; found: 258.0098.

2-Fluoropyridin-3-yl 4-chlorophenyl ketone (3c):[10] Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 90°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.37$ (ddd, $J=7.6$, 4.9, 1.9 Hz, 1H), 7.44–7.50 (m, 2H), 7.73–7.79 (m, 2H), 8.04 (ddd, $J=9.4$, 7.5, 2.0 Hz, 1H), 8.43 ppm (ddd, $J=4.9$, 2.1, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=121.3$ (d, C, J(C,F)=30 Hz), 121.9 (d, CH, J(C,F)=4 Hz), 129.2 (2 CH), 131.1 (d, 2 CH, J-(C,F)=1 Hz), 135.0 (d, C, J(C,F)=1 Hz), 140.7 (C), 142.0 (d, CH, J-(C,F)=3 Hz), 150.9 (d, CH, J(C,F)=15 Hz), 160.1 (d, C, J(C,F)=243 Hz), 190.7 ppm (d, C=O, J(C,F)=5 Hz); HRMS (ESI): *m/z* calcd for $C_{12}H_8{}^{35}ClFNO$: 236.0278 $[M+H]^+$, 258.0098 $[M+Na]^+$; found: 236.0281, 258.0096.

2-Fluoropyridin-3-yl 4-(trifluoromethyl)phenyl ketone (3d): Eluent: heptane/EtOAc (80:20); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.40$ (ddd, $J=7.4$, 4.9, 1.9 Hz, 1H), 7.75 (d, $J=8.2$ Hz, 2H), 7.90 (d, $J=8.2$ Hz, 2H), 8.09 (ddd, $J=9.0$, 7.4, 2.0 Hz, 1H), 8.45 ppm (ddd, $J=4.9$, 2.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=120.6$ (d, C, J(C,F)=29 Hz), 121.9 (d, CH, J(C,F)=5 Hz), 123.7 (q, C, J(C,F)=273 Hz), 125.7 (q, 2 CH, J-(C,F)=4 Hz), 129.8 (d, 2 CH, J(C,F)=1 Hz), 134.8 (q, C, J(C,F)=33 Hz), 139.5 (C), 142.1 (d, CH, J(C,F)=3 Hz), 151.2 (d, CH, J(C,F)=15 Hz), 160.1 (d, C, J(C,F)=243 Hz), 190.8 ppm (d, C=O, J(C,F)=5 Hz). These data are consistent with those reported in the literature:[35] beige oil.

2-Chloropyridin-5-yl 2-fluoropyridin-3-yl ketone (3e): Eluent: heptane/EtOAc (70:30); orange solid; m.p. 94°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.40$ (ddd, $J=7.4$, 4.9, 1.9 Hz, 1H), 7.46 (d, 1H, $J=8.3$ Hz), 8.04–8.12 (m, 2H), 8.43–8.45 (m, 1H), 8.72 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=119.9$ (d, C, J(C,F)=29 Hz), 122.1 (d, CH, J(C,F)=5 Hz), 124.5 (CH), 131.0 (C), 139.1 (d, CH, J(C,F)=1 Hz), 142.1 (d, CH, J-(C,F)=3 Hz), 150.8 (d, CH, J(C,F)=2 Hz), 151.5 (d, CH, J(C,F)=15 Hz), 156.0 (C), 159.8 (d, C, J(C,F)=243 Hz), 189.0 ppm (d, C=O, J-(C,F)=5 Hz); HRMS (ESI): *m/z* calcd for $C_{11}H_6{}^{35}ClFN_2NaO$: 259.0050 $[M+Na]$; found: 259.0050.

2,5-Dimethoxyphenyl phenyl ketone (6a): Eluent: heptane/EtOAc (90:10); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.66$ (s, 3H), 3.78 (s, 3H), 6.92 (d, $J=9.0$ Hz, 1H), 6.92 (d, $J=3.0$ Hz, 1H), 7.01 (dd, $J=9.0$, 3.0 Hz, 1H), 7.39–7.47 (m, 2H), 7.55 (tt, $J=7.3$, 1.3 Hz, 1H), 7.79–7.85 ppm (m, 2H). These data are consistent with those reported in the literature:[36] yellow oil; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.8$ (CH_3), 56.2 (CH_3), 112.9 (CH), 114.3 (CH), 117.2 (CH), 128.2 (2 CH), 129.4 (C), 129.8 (2 CH), 133.0 (CH), 137.5 (C), 151.4 (C), 153.4 (C), 196.1 ppm (C=O)

4-Chlorophenyl 2,5-dimethoxyphenyl ketone (6b): Eluent: heptane/EtOAc (98:2); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.66$ (s, 3H), 3.79 (s, 3H), 6.91 (d, $J=9.0$ Hz, 1H), 6.91 (d, $J=3.0$ Hz, 1H), 7.01 (dd, $J=9.0$, 3.0 Hz, 1H), 7.40 (d, $J=8.7$ Hz, 2H), 8.74 ppm (d, $J=8.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=55.9$ (CH_3), 56.3 (CH_3), 113.1 (CH), 114.5 (CH), 117.8 (CH), 128.6 (2 CH), 128.9 (2 CH), 131.2 (C), 136.2 (C), 139.4 (C), 151.5 (C), 153.6 (C), 195.0 ppm (C=O). These data are consistent with those reported in the literature:[37] yellow oil.

6-Chloropyridin-3-yl 2,5-dimethoxyphenyl ketone (6c): Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 90°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.65$ (s, 3H), 3.80 (s, 3H), 6.93 (d, $J=9.0$ Hz, 1H), 7.0 (d, $J=3.1$ Hz, 1H), 7.07 (dd, $J=9.0$, 3.1 Hz, 1H), 7.41 (dd, $J=8.3$, 0.6 Hz, 1H), 8.07 (dd, $J=8.3$, 2.4 Hz, 1H), 8.67 ppm (d, $J=2.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=56.0$ (CH_3), 56.1 (CH_3), 113.1 (CH), 114.5 (CH), 119.3 (CH), 124.2 (CH), 127.6 (C), 132.4 (C), 139.2 (CH), 151.6 (CH), 151.7 (C), 153.9 (C), 155.1 (C), 193.5 ppm (C=O); HRMS (ESI): *m/z* calcd for $C_{14}H_{13}{}^{35}ClNO_3$: 278.0584 $[M+H]^+$, 300.0403 $[M+Na]^+$; found: 278.0581, 300.0402.

***N*-(2-Methoxyphenyl)-2,2,6,6-tetramethylpiperidine**: Eluent: CH_2Cl_2; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=0.78$ (s, 6H), 1.23 (s, 6H), 1.49–1.64 (m, 6H), 3.75 (s, 3H), 6.82–6.88 (m, 2H), 7.13–7.19 (m, 1H), 7.29 ppm (dd, $J=8.3$, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=18.6$ (CH_2), 26.0 (2 CH_3), 31.5 (2 CH_3), 41.8 (CH_2), 54.4 (2 C), 55.1 (CH_3), 111.0 (CH), 119.3 (CH), 126.4 (CH), 134.2 (CH), 136.0 (C), 160.3 ppm (C); HRMS (EI): *m/z* calcd for $C_{16}H_{25}NO$: 247.1936 $[M]^+$; found: 247.1941.

2-Allyl-1,4-dimethoxybenzene (6e): Eluent: heptane/EtOAc (95:5); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=3.38$ (d, $J=6.6$ Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 5.05 (t, $J=1.4$ Hz, 1H), 5.07–5.13 (m, 1H), 6.00 (ddt, $J=16.7$, 10.4, 6.6 Hz, 1H), 6.68–6.85 ppm (m, 3H). These data are consistent with those reported in the literature:[38] colorless oil; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=34.4$ (CH_2), 55.7 (CH_3), 56.2 (CH_3), 111.4 (CH), 111.5 (CH), 115.7 (CH_2), 116.2 (CH), 129.9 (C), 136.9 (CH), 151.7 (C), 153.7 ppm (C).

Phenyl thiophen-2-yl ketone (8a): Eluent: heptane/CH_2Cl_2 (70:30); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.17$ (dd, $J=4.9$, 3.8 Hz, 1H), 7.46–7.54 (m, 2H), 7.56–7.63 (m, 1H), 7.65 (dd, 1H, $J=3.8$ and 1.1 Hz), 7.73 (dd, 1H, $J=4.9$ and 1.1 Hz), 7.84–7.90 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=128.0$ (CH), 128.5 (2 CH), 129.2 (2 CH), 132.3 (CH), 134.3 (CH), 134.8 (CH), 138.2 (C), 143.7 (C), 188.3 ppm (C=O). These data are consistent with those obtained from a commercial sample.

Furan-2-yl phenyl ketone (9): Eluent: heptane/Et_2O (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=6.59$ (dd, $J=3.6$, 1.7 Hz, 1H), 7.23 (dd, $J=3.6$, 0.8 Hz, 1H), 7.45–7.53 (m, 2H), 7.55–7.63 (m, 1H), 7.71 (dd, $J=1.7$, 0.8 Hz, 1H), 7.93–8.00 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=112.3$ (CH), 120.8 (CH), 128.5 (2 CH), 129.4 (2 CH), 132.7 (CH), 137.3 (C), 147.3 (CH), 152.3 (C), 182.7 ppm (C=O). These data are consistent with those reported the literature.[39]

Indol-2-yl phenyl ketone (10): Eluent: heptane/CH_2Cl_2 (50:50); pale yellow solid; m.p. 153°C (lit.[40] 149–150°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=7.14$–7.22 (m, 2H), 7.39 (td, $J=8.2$, 1.1 Hz, 1H), 7.49–7.59 (m, 3H), 7.64 (tt, $J=7.3$, 1.4 Hz, 1H), 7.73 (dd, $J=8.1$, 0.8 Hz, 1H), 7.99–8.05 (m, 2H), 9.68 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=112.4$ (CH), 113.0 (CH), 121.2 (CH), 123.3 (CH), 126.7 (CH), 127.8 (C), 128.6 (2 CH), 129.4 (2 CH), 132.5 (CH), 134.5 (C), 137.8 (C), 138.1 (C), 187.4 ppm (C=O). These data are consistent with those reported in the literature.[40]

4-Chlorophenyl thiophen-2-yl ketone (8b): Eluent: heptane/CH_2Cl_2 (70:30); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.17 (dd, J = 5.0, 3.8 Hz, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.62 (dd, J = 3.8, 1.1 Hz, 1H), 7.74 (dd, J = 5.0, 1.1 Hz, 1H), 7.82 ppm (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 128.2 (CH), 128.9 (2 CH), 130.7 (2 CH), 134.7 (CH), 134.9 (CH), 136.5 (C), 138.8 (C), 143.3 (C), 187.0 ppm (C=O). These data are consistent with the literature:[39] pale yellow solid; m.p. 99 °C.

Diphenyl thiophene-2,5-diyl diketone (8′a): Eluent: heptane/CH_2Cl_2 (70:30); beige powder; m.p. 107 °C (lit.[41] 114.5–115 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49–7.56 (m, 4H), 7.64 (tt, J = 7.5, 1.4 Hz, 2H), 7.68 (s, 2H), 7.89–7.94 ppm (m, 4H). These data are consistent with those reported in the literature:[41] ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 128.8 (4CH), 129.5 (4CH), 133.1 (2CH), 133.9 (2CH), 137.4 (2C), 148.6 (2C), 188.2 ppm (2C=O); HRMS (ESI): m/z calcd for $C_{18}H_{13}O_2S$: 293.0636 $[M+H]^+$, 315.0456 $[M+Na]^+$; found: 236.0281, 315.0454.

Ethyl 5-benzoylthiophene-2-carboxylate (11a): Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.48–7.56 (m, 2H), 7.59–7.67 (m, 1H), 7.61 (d, J = 4.0 Hz, 1H), 7.79 (d, J = 4.0 Hz, 1H), 7.85–7.90 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4 (CH_3), 62.0 (CH_2), 128.7 (2 CH), 129.5 (2 CH), 133.0 (CH), 133.1 (CH), 134.0 (CH), 137.5 (C), 140.5 (C), 147.8 (C), 161.8 (C), 188.2 ppm (C=O); HRMS (ESI): m/z calcd for $C_{14}H_{13}O_3S$: 261.0585 $[M+H]^+$, 283.0404 $[M+Na]^+$; found: 261.0583, 283.0403.

Ethyl 5-iodothiophene-2-carboxylate (11b): Eluent: heptane/CH_2Cl_2 (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.36 (t, J = 7.1 Hz, 3H), 4.33 (q, J = 7.1 Hz, 2H), 7.25 (d, J = 3.9 Hz, 1H), 7.42 ppm (d, J = 3.9 Hz, 1H). These data are consistent with those reported in the literature:[42] ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4 (CH_3), 61.5 (CH_2), 82.6 (C), 134.4 (CH), 137.8 (CH), 139.8 (C), 161.0 ppm (C=O).

Ethyl 2-benzoylthiophene-3-carboxylate (12): Eluent: heptane/EtOAc (80:20); beige oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, J = 7.2 Hz, 3H), 3.92 (q, J = 7.2 Hz, 2H), 7.41–7.53 (m, 4H), 7.58 (tt, J = 7.4, 1.3 Hz, 1H), 7.78–7.84 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 13.6 (CH_3), 61.3 (CH_2), 127.9 (CH), 128.7 (2CH), 129.1 (CH), 129.5 (2CH), 133.5 (CH), 134.0 (C), 137.8 (C), 145.3 (C), 162.6 (C=O), 189.9 ppm (C=O); HRMS (ESI): m/z calcd for $C_{14}H_{12}NaO_3S$: 283.0405 $[M+Na]^+$; found: 283.0407.

2,4-Dimethoxy-5-methylpyrimidine (13a): Eluent: heptane/EtOAc (80:20); white powder; m.p. 64–65 °C (lit.[43] 61.9–63.2 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.01 (s, 3H), 3.92 (s, 3H), 3.95 (s, 3H), 7.94 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.0 (CH_3), 53.9 (CH_3), 54.7 (CH_3), 111.2 (C), 156.9 (CH), 164.2 (C), 169.7 ppm (C). These data are consistent with those reported in the literature.[43]

5-Allyl-2,4-dimethoxypyrimidine (13b):[10] Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.22 (m, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 5.00–5.08 (m, 2H), 5.82–5.97 (m, 1H), 7.98 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 29.8 (CH_2), 54.0 (CH_3), 54.8 (CH_3), 113.6 (C), 116.5 (CH_2), 135.2 (CH), 157.0 (CH), 164.4 (C), 169.4 ppm (C); HRMS (ESI): m/z calcd for $C_9H_{12}N_2NaO_2$: 203.0796 $[M+Na]^+$; found: 203.0800.

2,2′,4,4′-Tetramethoxy-5,5′-bipyrimidine (13′):[10] Eluent: heptane/EtOAc (80:20); red powder; m.p. 209 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.97 (s, 6H), 4.03 (s, 6H), 8.20 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.3 (2CH_3), 55.0 (2CH_3), 108.3 (2C), 158.8 (2CH), 165.1 (2C), 168.7 ppm (2C); HRMS (ESI): m/z calcd for $C_{12}H_{15}N_4O_4$: 279.1093 $[M+H]^+$, 301.0913 $[M+Na]^+$; found: 279.1095, 301.0916.

2-(2-Methoxypyridin-3-yl)-1-phenylethanol (14b): Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.49 (s, 1H), 2.88–3.10 (m, 2H), 3.95 (s, 3H), 4.98 (dd, J = 7.4, 5.0 Hz, 1H), 6.78 (dd, J = 7.2, 5.0 Hz, 1H), 7.20–7.40 (m, 6H), 8.04 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 40.6 (CH_2), 53.6 (CH_3), 73.6 (CH), 116.9 (CH), 121.1 (C), 125.9 (2CH), 127.6 (CH), 128.4 (2CH), 139.7 (CH), 144.2 (C), 145.2 (CH), 162.4 ppm (C); HRMS (ESI): m/z calcd for $C_{14}H_{16}NO_2$: 230.1181 $[M+H]^+$, 252.1000 $[M+Na]$; found: 230.1182, 252.1000.

2-(2-Methoxypyridin-3-yl)-2-phenylethanol (14b′): Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.92 (s, 1H), 3.91 (s, 3H), 4.06–4.20 (m, 2H), 4.50 (t, J = 7.0 Hz, 1H), 6.84 (dd, J = 7.3, 5.0 Hz, 1H), 7.19–7.38 (m, 5H), 7.45 (dd, J = 7.3, 1.8 Hz, 1H), 8.03 ppm (dd, J = 5.0, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 46.8 (CH), 53.6 (CH_3), 64.9 (CH_2), 116.9 (CH), 124.4 (C), 126.9 (CH), 128.6 (2CH), 128.7 (2CH), 136.9 (CH), 140.5 (C), 145.0 (CH), 161.9 ppm (C); HRMS (ESI): m/z calcd for $C_{14}H_{16}NO_2$: 230.1181 $[M+H]$, 252.1000 $[M+Na]^+$; found: 230.1182, 252.1000.

2-Methoxy-3-(phenylthio)pyridine (14c): Eluent: heptane/EtOAc (90:10); orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.01 (s, 3H), 6.75 (dd, J = 7.5, 4.9 Hz, 1H), 7.16 (dd, J = 7.5, 1.8 Hz, 1H), 7.32–7.45 (m, 5H), 7.99 ppm (dd, J = 4.9, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.0 (CH_3), 117.4 (CH), 121.2 (C), 128.3 (CH), 129.6 (2CH), 132.2 (C), 133.2 (2CH), 137.6 (CH), 144.3 (CH), 160.4 ppm (C); HRMS (ESI): m/z calcd for $C_{12}H_{12}NOS$: 218.0640 $[M+H]^+$, 240.0459 $[M+Na]^+$; found: 218.0641, 240.0460.

4-Chlorophenyl 2-methoxypyridin-3-yl sulfone (14d): Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.94 (s, 3H), 7.07 (dd, J = 7.6, 5.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 8.34 (dd, J = 5.0, 1.9 Hz, 1H), 8.39 ppm (dd, J = 7.6, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.4 (CH_3), 117.1 (CH), 123.8 (C), 129.2 (2CH), 130.4 (2CH), 138.9 (C), 139,4 (CH), 140.3 (C), 152.7 (CH), 159.9 (C); HRMS (ESI): m/z calcd for $C_{12}H_{11}{}^{35}ClNO_3S$: 284.0148 $[M+H]^+$, 305.9968 $[M+Na]^+$; found: 284.0149, 305.9968.

(*Z*)-Ethyl 3-(2-methoxypyridin-3-yl)-3-phenylpropenoate (14e): Eluent: heptane/EtOAc (80:20); orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.12 (t, J = 7.1 Hz, 3H), 3.85 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.47 (s, 1H), 6.93 (dd, J = 7.3, 5.0 Hz, 1H), 7.29–7.37 (m, 6H), 8.21 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.0 (CH_3), 53.5 (CH_3), 60.0 (CH_2), 116.3 (CH), 119.1 (CH), 122.5 (C), 127.4 (2CH), 128.5 (2CH), 129.5 (CH), 138.5 (CH), 139.4 (C), 146.5 (CH), 151.0 (C), 160.8 (C), 165.6 ppm (C=O); HRMS (ESI): m/z calcd for $C_{17}H_{18}NO_3$: 284.1287 $[M+H]^+$, 306.1106 $[M+Na]^+$; found: 284.1288, 306.1106.

(*E*)-Ethyl 3-(2-methoxypyridin-3-yl)-3-phenylpropenoate (14e′): Compound **14e′** was identified by the NMR spectrum: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.10 (t, J = 7.1 Hz, 3H), 3.89 (s, 3H), 4.05 (q, J = 7.1 Hz, 2H), 6.51 (s, 1H), 6.83 (dd, J = 7.4, 5.0 Hz, 1H), 7.15–7.23 (m, 2H), 7.28–7.37 (m, 4H), 8.11 (dd, J = 5.0, 1.9 Hz, 1H).

(*E*)-Ethyl 3-(2-methoxypyridin-3-yl)octenoate (14f): Eluent: heptane/EtOAc (80:20); orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.76–0.86 (m, 3H), 1.20–1.36 (m, 6H), 1.29 (t, J = 7.1 Hz, 3H), 2.98–3.06 (m, 2H), 3.94 (s, 3H), 4.19 (q, J = 7.1 Hz, 2H), 5.82 (s, 1H), 6.89 (dd, J = 7.2, 5.0 Hz, 1H), 7.39 (dd, J = 7.2, 1.9 Hz, 1H), 8.12 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.1 (CH_3), 14.4 (CH_3), 22.6 (CH_2), 28.2 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 53.6 (CH_3), 60.0 (CH_2), 116.7 (CH), 120.1 (CH), 125.9 (C), 137.8 (CH), 146.6 (CH), 159.1 (C), 160.1 (C), 166.3 ppm (C=O); HRMS (ESI): m/z calcd for $C_{16}H_{24}NO_3$: 278.1756 $[M+H]^+$, 300.1576 $[M+Na]^+$; found: 278.1758, 300.1579.

(*Z*)-Methyl 3-(2-methoxypyridin-3-yl)butenoate (14g): Eluent: heptane/EtOAc (80:20); orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.12 (d, J = 1.5 Hz, 3H), 3.52 (s, 3H), 3.91 (s, 3H), 5.96 (q, J = 1.5 Hz, 1H), 6.86 (dd, J = 7.2, 5.1 Hz, 1H), 7.31 (dd, J = 7.2, 1.9 Hz, 1H), 8.10 ppm (dd, J = 5.1, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 25.6 (CH_3), 51.1 (CH_3), 53.5 (CH_3), 116.4 (CH), 119.2 (CH), 124.1 (C), 136.6 (CH), 146.1 (CH), 151.7 (C), 159.7 (C), 165.8 ppm (C=O); HRMS (ESI): m/z calcd for $C_{11}H_{13}NNaO_3$: 230.0793 $[M+Na]^+$; found: 230.0795.

(*E*)-Methyl 3-(2-methoxypyridin-3-yl)butenoate (14g′): Eluent: heptane/EtOAc (80:20); orange oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.47 (d, J = 1.4 Hz, 3H), 3.72 (s, 3H), 3.95 (s, 3H), 5.95 (q, J = 1.4 Hz, 1H), 6.87 (dd, J = 7.3, 5.0 Hz, 1H), 7.42 (dd, J = 7.3, 1.9 Hz, 1H), 8.12 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.2 (CH_3), 51.2 (CH_3), 53.6 (CH_3), 116.8 (CH), 119.7 (CH), 126.8 (C), 137.1 (CH), 146.8 (CH), 154.4 (C), 160.6 (C), 167.0 ppm (C=O); HRMS (ESI): m/z calcd for $C_{11}H_{13}NNaO_3$: 230.0793 $[M+Na]^+$; found: 230.0792.

2,2′-Difluoro-3,3′-bipyridine (15′):[10] Eluent: heptane/EtOAc (80:20); beige powder; m.p. 153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.31–7.36 (m, 2H), 7.88–7.96 (m, 2H), 8.30 ppm (dd, J = 4.9, 1.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 116.7 (m, 2C), 121.7 (m, 2CH), 142.0 (t, 2CH, J(C,F) = 3 Hz), 148.1 (m, 2CH), 160.4 (d, 2C, J(C,F) = 241 Hz); HRMS (ESI): m/z calcd for $C_{10}H_7F_2N_2$: 193.0577 $[M+H]^+$, 215.0397 $[M+Na]^+$; found: 193.0583, 215.0397.

1,1′-(Benzene-1,2-diyl)-2,2′-bi(1*H*-pyrazole) (16′): Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 189 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.80 (d, J = 2.0 Hz, 2H), 7.50 (dd, J = 6.2, 3.4 Hz, 2H), 7.95 (d, J = 2.0 Hz, 2H), 8.41 ppm (dd, J = 6.2, 3.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 101.1 (2CH), 116.5 (2CH), 126.0 (2C), 126.6 (2CH), 130.5 (2C), 141.9 ppm (2CH); HRMS (ESI): m/z calcd for $C_{12}H_9N_4$: 209.0827 $[M+H]^+$; found: 209.0829.

General procedure for the deprotocupration: Cross-coupling: BuLi (about 1.6 M hexanes solution, 2.0 mmol) was successively added to a stirred, cooled (0 °C) suspension of $CuCl_2$·TMEDA (0.5 g, 2.0 mmol) in THF (5 mL) then 15 min later a solution of [Li(tmp)] prepared in THF (2 mL) at 0 °C from 2,2,6,6-tetramethylpiperidine (0.68 mL, 4.0 mmol) and BuLi (about 1.6 M hexanes solution, 4.0 mmol) was added. The mixture was stirred for 15 min at this temperature before the introduction of the substrate (4.0 mmol). After 2 h at RT, the halide (4.0 mmol) was added, as well as $[PdCl_2(PPh_3)_2]$ (55 mg, 80 μmol) and dppf (44 mg, 80 μmol), and the mixture was heated at reflux for 16 h. After cooling, water (0.5 mL) and EtOAc (20 mL) were added, the solution was filtered through Celite, the mixture was dried over Na_2SO_4, filtered, and concentrated under reduced pressure before purification by column chromatography on silica gel (the eluent is given in the product description).

2-Methoxy-3-(4-methoxyphenyl)pyridine (17a): Eluent: heptane/EtOAc (80:20); white powder; m.p. 112–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.85 (s, 3H), 3.98 (s, 3H), 6.92–7.00 (m, 3H), 7.51 (d, J = 8.9 Hz, 2H), 7.59 (dd, J = 7.3, 1.9 Hz, 1H), 8.14 (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6 (CH_3), 55.4 (CH_3), 113.8 (2CH), 117.2 (CH), 124.4 (C), 129.2 (C), 130.4 (2CH), 138.3 (CH), 145.3 (CH), 159.2 (C), 161.0 ppm (C); HRMS (ESI): m/z calcd for $C_{13}H_{14}NO_2$: 216.1024 $[M+H]$, 238.0844 $[M+Na]$; found: 216.1026, 238.0845.

2-Methoxy-3-[4-methoxy-3-(4-methoxyphenyl)phenyl]pyridine (17a′): Eluent: heptane/EtOAc (80:20); white powder; m.p. 82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.85 (s, 3H), 3.86 (s, 3H), 4.0 (s, 3H), 6.94–7.01 (m, 3H), 7.04 (d, J = 8.3 Hz, 1H), 7.49–7.56 (m, 4H), 7.63 (dd, J = 7.3, 1.9 Hz, 1H), 8.15 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.7 (CH_3), 55.4 (CH_3), 55.8 (CH_3), 111.1 (CH), 113.6 (2CH), 117.2 (CH), 124.4 (C), 129.0 (CH), 129.3 (C), 130.3 (C), 130.7 (2CH), 130.8 (C), 131.6 (CH), 138.3 (CH), 145.3 (CH), 156.1 (C), 158.9 (C), 161.0 (C); HRMS (ESI): m/z calcd for $C_{20}H_{20}NO_3$: 322.1443 $[M+H]^+$, 344.1263 $[M+Na]$, 360.1002 $[M+K]^+$; found: 322.1443, 344.1266, 360.1010.

3-(4-Fluorophenyl)-2-methoxypyridine (17b): Eluent: heptane/EtOAc (90:10); pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.98 (s, 3H), 6.96 (dd, J = 7.3, 5.0 Hz, 1H), 7.11 (t, J = 8.8 Hz, 2H), 7.48–7.60 (m, 3H), 8.17 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6 (CH_3), 115.2 (d, 2CH, J(C,F) = 21 Hz), 117.2 (CH), 123.7 (C), 130.9 (d, 2CH, J(C,F) = 8 Hz), 132.8 (d, C, J(C,F) = 3 Hz), 138.5 (CH), 145.9 (CH), 160.9 (C), 162.4 ppm (d, C, J(C,F) = 247 Hz); HRMS (ESI): m/z calcd for $C_{12}H_{12}N_2NaO_2$: 239.0796 $[M+Na]$; found: 239.0795.

Ethyl 4-(2-methoxypyridin-3-yl)benzoate (17c): Eluent: heptane/EtOAc (80:20); yellow powder; m.p. 82 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.40 (t, J = 7.1 Hz, 3H), 3.97 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.99 (dd, J = 7.3, 5.0 Hz, 1H), 7.60–7.66 (m, 3H), 8.09 (d, J = 8.5 Hz, 2H), 8.19 ppm (dd, J = 5.0, 1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.5 (CH_3), 53.7 (CH_3), 61.1 (CH_2), 117.2 (CH), 123.7 (C), 129.2 (2CH), 129.5 (2CH), 138.7 (CH), 141.5 (C), 146.6 (CH), 160.9 (C), 166.5 ppm (C=O); HRMS (ESI): m/z calcd for $C_{15}H_{16}NO_3$: 258.1130 $[M+H]^+$, 280.0950 $[M+Na]^+$; found: 258.1133, 280.0950.

2-Methoxy-3-(pyridin-2-yl)pyridine (17d): Eluent: heptane/EtOAc (80:20); yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.02 (s, 3H), 7.02 (dd, J = 7.1, 5.3 Hz, 1H), 7.21 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.71 (ddd, J = 8.0, 7.6, 1.9 Hz, 1H), 8.0 (dt, J = 8.0, 1.0 Hz, 1H), 8.17–8.23 (m, 2H), 8.68 ppm (ddd, J = 4.8, 1.8, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.6 (CH_3), 117.5 (CH), 122.3 (CH), 123.1 (C), 124.7 (CH), 136.1 (CH), 139.5 (CH), 147.1 (CH), 149.6 (CH), 154.2 (C), 161.1 ppm (C); HRMS (ESI): m/z calcd for $C_{11}H_{11}N_2O$: 187.0871 $[M+H]^+$ and 209.0691 $[M+Na]^+$; found: 187.0872, 209.0691.

2,6-Dimethoxy-3-(4-methoxyphenyl)pyridine (18a): Eluent: heptane/Et_2O (90:10); white powder; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.84 (s, 3H), 3.96 (s, 3H), 3.97 (s, 3H), 6.38 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.9 Hz, 2H), 7.54 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.5 (CH_3), 53.7 (CH_3), 55.4 (CH_3), 101.0 (CH), 113.8 (2 CH), 115.5 (C), 129.4 (C), 130.1 (2 CH), 141.3 (CH), 158.6 (C), 159.3 (C), 162.0 ppm (C). These data are consistent with those reported in the literature.[44]

2,6-Dimethoxy-3-(pyridin-2-yl)pyridine (18b): Eluent: heptane/EtOAc (80:20); pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.96 (s, 3H), 4.02 (s, 3H), 6.44 (d, J = 8.2 Hz, 1H), 7.13 (ddd, J = 7.4, 4.9, 1.1 Hz, 1H), 7.67 (ddd, J = 8.0, 7.5, 1.9 Hz, 1H), 7.94 (dt, J = 8.0, 1.0 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.63 ppm (ddd, J = 4.9, 1.9, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 53.4 (CH_3), 53.6 (CH_3), 101.8 (CH), 114.2 (C), 121.2 (CH), 123.9 (CH), 135.9 (CH), 142.2 (CH), 149.2 (CH), 154.3 (C), 159.8 (C), 162.9 ppm (C); HRMS (ESI): m/z calcd for $C_{12}H_{13}N_2O_2$: 217.0977 $[M+H]^+$, 239.0796 $[M+Na]^+$; found: 217.0983, 239.0797.

2,4′,5-Trimethoxybiphenyl (19a):[45] Eluent: heptane/EtOAc (90:10); pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.81–6.87 (m, 1H), 6.89–6.95 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.50 ppm (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.4 (CH_3), 55.9 (CH_3), 56.4 (CH_3), 112.6 (CH), 112.7 (CH), 113.6 (2CH), 116.7 (CH), 130.6 (2CH), 130.9 (C), 131.5 (C), 150.9 (C), 153.9 (C), 158.9 ppm (C).

2-(2,5-Dimethoxyphenyl)pyridine (19b): Eluent: heptane/EtOAc (80:20); brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.77 (s, 3H), 3.81 (s, 3H), 6.87–6.95 (m, 2H), 7.18 (ddd, J = 7.3, 4.9, 0.9 Hz, 1H), 7.39 (dd, J = 2.2, 1.2 Hz, 1H), 7.67 (td, J = 7.9, 1.8 Hz, 1H), 7.84 (d, J = 7.9 Hz, 1H), 8.69 ppm (d, J = 4.9 Hz, 1H). These data are consistent with those reported in the literature:[46] ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.8 (CH_3), 56.4 (CH_3), 113.1 (CH), 115.7 (CH), 115.8 (C), 121.8 (CH), 125.1 (CH), 129.8 (C), 135.7 (CH), 149.4 (CH), 151.3 (C), 154.0 (C), 155.8 ppm (C).

2,4-Dimethoxy-5-(4-methoxyphenyl)pyrimidine (20a): Eluent: heptane/EtOAc (80:20); white powder; m.p. 104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.83 (s, 3H), 4.00 (s, 3H), 4.02 (s, 3H), 6.95 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.9 Hz, 2H), 8.21 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.2 (CH_3), 54.9 (CH_3), 55.4 (CH_3), 114.0 (2CH), 116.0 (C), 125.6 (C), 130.0 (2CH), 157.2 (CH), 159.3 (C), 164.3 (C), 168.2 ppm (C); HRMS (ESI): m/z calcd for $C_{13}H_{15}N_2O_3$: 247.1083 $[M+H]$, 269.0902 $[M+Na]^+$; found: 247.1085, 269.0900.

2,4-Dimethoxy-5-(pyridin-2-yl)pyrimidine (20b): Eluent: heptane/EtOAc (80:20); white powder; m.p. 83 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.02 (s, 3H), 4.05 (s, 3H), 7.19 (ddd, J = 7.4, 4.9, 1.2 Hz, 1H), 7.69 (td, J = 7.5, 1.9 Hz, 1H), 7.80 (dt, J = 8.0, 1.0 Hz, 1H), 8.64 (ddd, J = 4.8, 1.8, 1.0 Hz, 1H), 8.87 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.3 (CH_3), 55.1 (CH_3), 114.7 (C), 122.3 (CH), 124.1 (CH), 136.4 (CH), 149.6 (CH), 151.9 (C), 159.9 (CH), 165.1 (C), 168.3 ppm (C); HRMS (ESI): m/z calcd for $C_{11}H_{12}N_3O_2$: 218.0929 $[M+H]^+$, 240.0749 $[M+Na]^+$; found: 218.0943, 240.0749.

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