Preparation of Polyfunctionalized 2,6-Dimethoxypyrimidine Derivatives via Chemo- and Regioselective Direct Zinc Insertion

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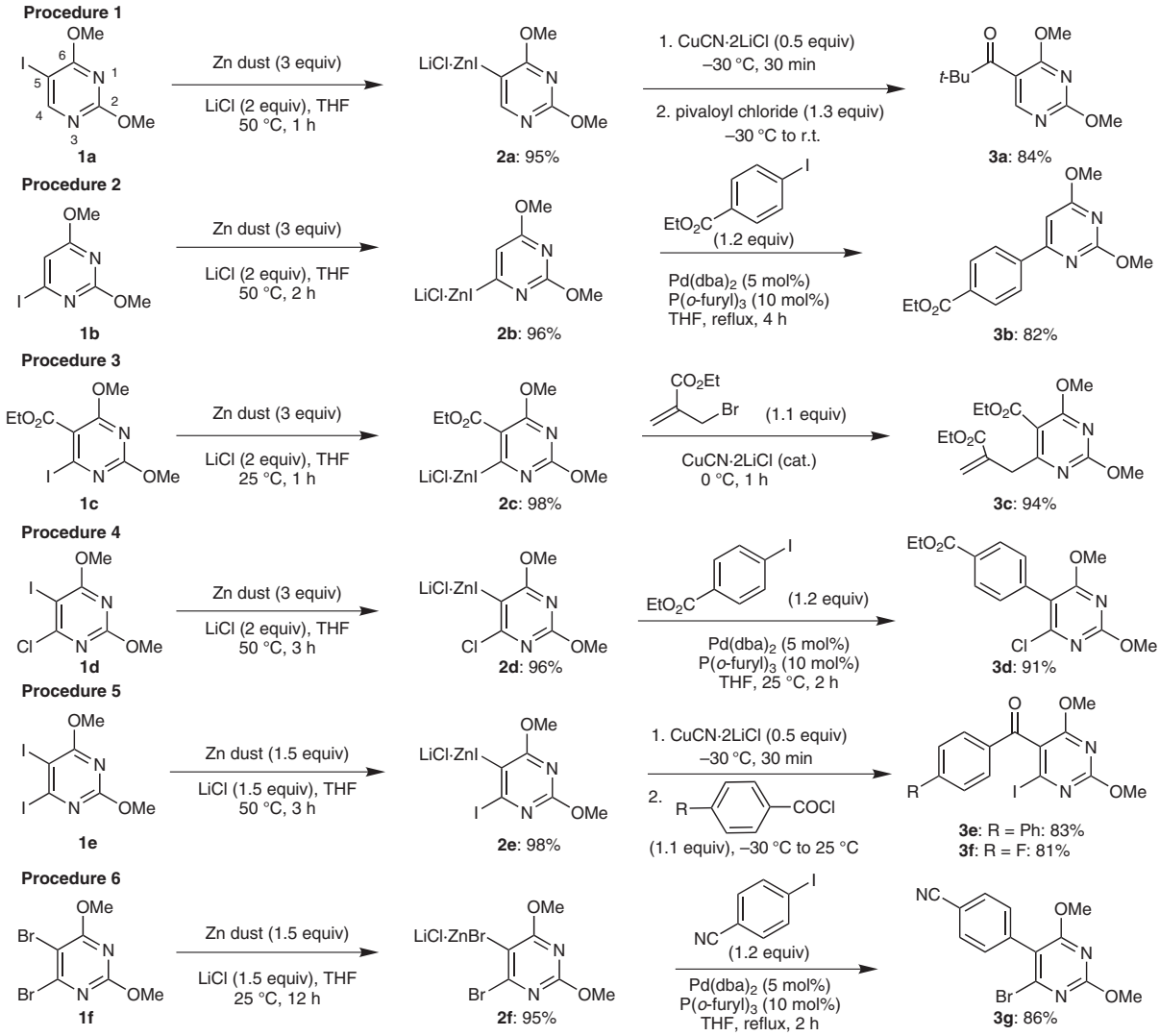
Abstract: The functionalization at the C4 and/or C5 positions of 2,6-dimethoxypyrimidine derivatives via direct chemo- and regioselective zinc insertions is described. The insertion of commercially available zinc dust into C–I and C–Br bonds, in the presence of LiCl, proceeded under mild reaction conditions. The reactions of the resulting organozinc reagents with electrophiles gave the expected products in good yields. This procedure represents a new method for the polyfunctionalization of uracil derivatives.

Key words: insertion, organozinc compounds, zinc, pyrimidine, uracil



Scheme 1

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Introduction

Organozinc compounds are important organometallic intermediates in modern organic synthesis. They tolerate a wide range of functional groups and display an excellent reactivity in the presence of appropriate catalysts (Pd, Cu, Ti…).[1] The direct insertion of zinc into organic halides is the most general method for the preparation of functionalized organozinc halides. The zinc insertion into an sp^2 C–X bond is more difficult than into an sp^3 C–X bond and requires either the use of polar solvents[2] (such as hexamethylphosphoramide, *N*,*N*-dimethylformamide, dimethyl sulfoxide, acetonitrile or tetramethylurea), elevated reaction temperatures, or the use of highly activated zinc (Rieke zinc).[3]

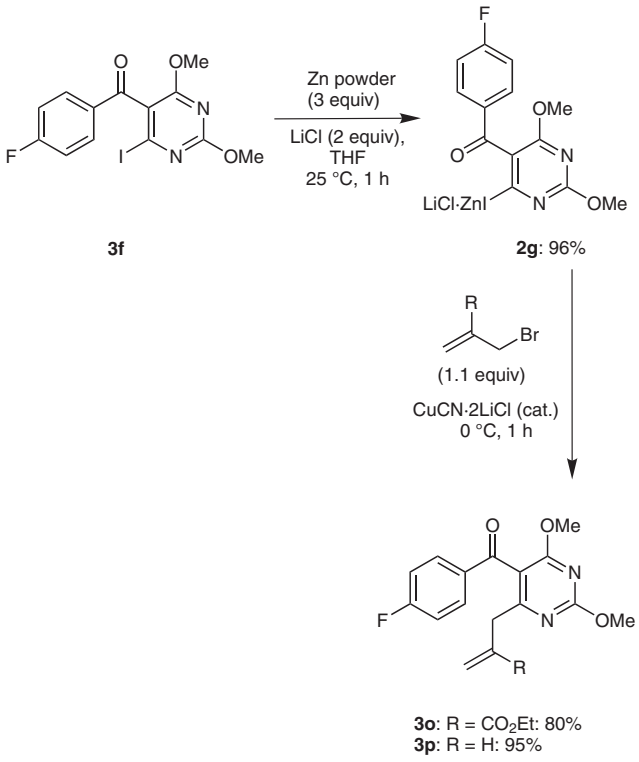
Recently, we have found that LiCl considerably accelerates the bromine–magnesium exchange reaction on aryl and heteroaryl bromides.[4] We have reported a protocol for the preparation of functionalized aryl- and alkylzinc compounds by the direct insertion of commercially available Zn powder in the presence of LiCl in THF.[5] This method allows a simple, high yielding preparation of a broad range of functionalized aryl- and heteroarylzinc reagents. These results encouraged us to study the zinc insertion with various uracil derivatives. This class of heterocycles is present in DNA and related natural products.[6] Generally, the functionalization of uracil derivatives requires protection steps and functional groups are implemented by directed lithiation[7] or bromine–lithium exchange reaction[8] starting from 2,6-dialkoxy-5-halogenopyrimidines. Recently, we also reported a chemo- and regioselective functionalization of uracil derivatives at C4 and C5 positions, starting from 5-bromo-4-halogeno-2,6-dimethoxypyrimidines by a LiCl-catalyzed Br–Mg exchange reaction using *i*-PrMgCl·LiCl.[9]

Herein, we wish to describe our results for the preparation of zincated uracil derivatives by direct regioselective zinc insertion starting from halogenated 2,6-dimethoxypyrimidines, as well as the reactions of the resulting organozinc reagents with electrophiles.

Results and Discussion

First, we treated 5-iodo-2,6-dimethoxypyrimidine[10] (**1a**, **Procedure 1**, Scheme 1) with commercial zinc dust (3 equiv)[11] in the presence of LiCl (2 equiv) in THF. After 1 hour at 50 °C, a full conversion[12] of **1a** was observed and the corresponding organozinc compound **2a** was obtained in 95% yield.[13] Subsequently, the transmetalation with CuCN·2LiCl (0.5 equiv) and the reaction with pivaloyl chloride (1.3 equiv, –30 to 25 °C) gave cleanly the expected ketone **3a** in 84% yield. The zinc insertion into 4-iodo-2,6-dimethoxypyrimidine (**1b**)[14] was performed at 50 °C for 2 hours (**Procedure 2**) to give the zinc organometallic **2b** in 96% yield. After a palladium-catalyzed cross-coupling[15] with ethyl 4-iodobenzoate (1.2 equiv), under reflux conditions (4 h), the expected biphenyl derivative **3b** was obtained in 82% yield. The zinc insertion into 4-iodo-2,6-dimethoxypyrimidine-5-carboxylic acid ethyl ester required milder reaction conditions (**Procedure 3**). Thus, treatment of the iodoester **1c**[14] with zinc dust (3 equiv) in the presence of LiCl (2 equiv) in THF gave the corresponding zinc reagent **2c** after stirring at 25 °C for 1 hour. A copper-catalyzed allylation [CuCN·2LiCl (5 mol%)] with ethyl (2-bromomethyl)acrylate (1.1 equiv, 0 °C, 1 h) led to the diester **3c** in 94% yield. Starting from 4-chloro-5-iodo-2,6-dimethoxypyrimidine (**1d**),[14] the zinc insertion provided **4b** in 98% yield (**Procedure 4**). A Negishi cross-coupling reaction with ethyl 4-iodobenzoate [$Pd(dba)_2$ (5 mol%), P(*o*-furyl)$_3$ (10 mol%), THF, 25 °C, 2 h] led to the desired functionalized pyrimidine **3d** in 91% yield.

Various electrophiles such as aryl iodides, acyl chlorides and 3-iodo-2-cyclohexenone, react with the organozinc derivative **2d**, and a variety of polyfunctionalized 2,6-dimethoxypyrimidines could be prepared in moderate to high yields (45–96%, entries 1–5, Table 1). The palladium-catalyzed cross-coupling[15] with 4-iodobenzonitrile provided the expected product **3h** in 89% yield (entry 1). The acylation reactions in the presence of CuCN·2LiCl (0.5 equiv) led to the products **3i–k** in moderate to good yields (entries 2–4). The 1,4-addition-elimination of **2d** with 3-iodocyclohex-2-en-1-one[16] gave the expected product **3l** in 96% isolated yield (entry 5). Interestingly, the zinc insertion into dihalogenated 2,6-dimethoxypyrimidine displays an excellent regioselectivity. Thus, treatment of 4,5-diiodo-2,6-dimethoxy-pyrimidine (**1e**)[14] with Zn/LiCl (1.5 equiv, 50 °C, 3 h, **Procedure 5**, Scheme 1)

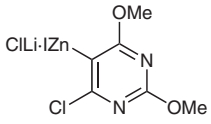
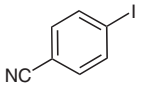
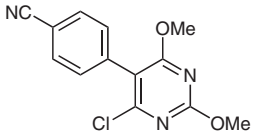
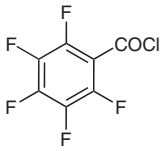
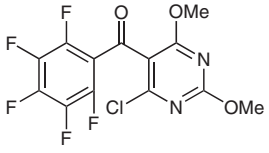
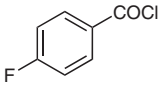
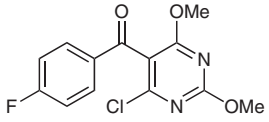
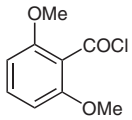
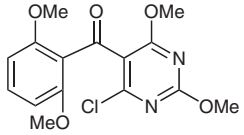
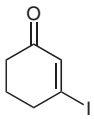
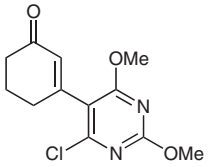
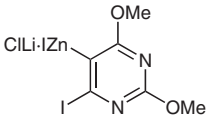
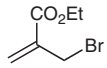
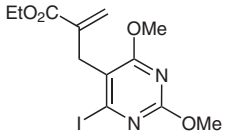
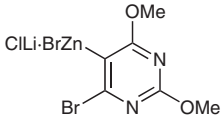
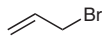
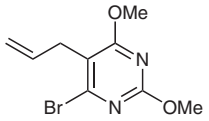


3f **2g**: 96%

3o: R = CO_2Et: 80%
3p: R = H: 95%

Scheme 2

Table 1 Preparation of Functionalized 2,6-Dimethoxypyrimidines via Direct Zinc Insertion

Entry	Zinc reagent Yield (%)[a]	Electrophile	Product Yield (%)[b]
1	 **2d**: 96		 **3h**: 89[c]
2	**2d**: 96		 **3i**: 86[d]
3	**2d**: 96		 **3j**: 83[d]
4	**2d**: 96		 **3k**: 45[d]
5	**2d**: 96		 **3l**: 96[e]
6	 **2e**: 98		 **3m**: 87[f]
7	 **2f**: 92		 **3n**: 81[f]

[a] Yield estimated after titration with I_2.
[b] Yield of analytically pure product.
[c] $Pd(Ph_3P)_4$ (5 mol%) was added.
[d] CuCN·2LiCl (0.5 equiv) was added.
[e] CuCN·2LiCl (1 equiv) was added.
[f] CuCN·2LiCl (5 mol%) was added.

resulted only in an insertion into the C–I bond at position 5 to give the zinc reagent **2e**. Treatment of **2e** with acid chlorides in the presence of CuCN·2LiCl (0.5 equiv) provided the products **3e** and **3f** in 83 and 81%, respectively. After a transmetalation using catalytic amount of CuCN·2LiCl (5 mol%) followed by the reaction with ethyl (2-bromomethyl)acrylate, the product **3m** was obtained in 87% yield (entry 6). A regioselective zinc insertion at position C5 into 4,5-dibromo-2,6-dimethoxypyrimidine (**1f**)[9] was also obtained under milder reaction conditions (12 h, 25 °C, **Procedure 6**). The corresponding zinc reagent **2f** reacted, by a Negishi cross-coupling,[15] with 4-iodobenzonitrile to give the polyfunctional 4-bromo-2,6-dimethoxypyrimidine (**3g**) in 86% yield. Furthermore, the zinc reagent **2f** was easily allylated in the presence of catalytic amount of CuCN·2LiCl (5 mol%) furnishing the expected product **3n** in 81% isolated yield (entry 7).

Starting from 4,5-diiodo-2,6-dimethoxypyrimidine (**1e**), two successive zinc insertion reactions were performed (Scheme 2). Thus, 5-substituted 4-iodo-2,6-dimethoxypy-

rimidine **3f** was subjected into the second insertion to give the corresponding zinc intermediate **2g**. A copper(I)-catalyzed allylation reactions provided the products **3o** and **3p** in 80 and 95% isolated yields, respectively (Scheme 2).

In summary, we have developed a synthetic method to selectively functionalize halogenated 2,6-dimethoxypyrimidines using a direct zinc insertion in the presence of LiCl. The zinc insertion proceeds within a practical temperature range (25–50 °C). Further extensions of this work concerning the large-scale preparation are currently underway in our laboratories.

All reactions were carried out under an argon atmosphere in dried glassware. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR and capillary GC analysis.

Zinc Reagent 2a; Procedure 1
Anhyd LiCl (169 mg, 4 mmol) was placed in an argon-flushed flask and dried for 30 min at 150 °C on high vacuum (1 mbar). After cooling to r.t. under argon, Zn powder (393 mg, 6 mmol) was added and the heterogeneous mixture of Zn and LiCl was dried again for 30 min at 150 °C on high vacuum (1 mbar). After cooling to r.t. under argon, the reaction flask was evacuated and refilled with argon three times. Anhyd THF (5 mL) was added and the zinc powder was activated by treatment first with $BrCH_2CH_2Br$ (25 μL, 5 mol%) and then with chlorotrimethylsilane (1 mol%). A solution of 5-iodo-2,6-dimethoxypyrimidine (**1a**, 532 mg, 2 mmol) in THF (2 mL) was added and the mixture was heated at 50 °C. The insertion reaction was complete after 1 h (checked by GC analysis of reaction aliquots, the conversion was higher than 98%). The organozinc reagent **2a** was titrated using iodine[13] showing ca. 0.95 M concentration of **2a** in THF. The solution of **2a** was decanted and carefully separated from the remaining zinc powder using a syringe and transferred to another dry argon-flushed flask.

Zinc Reagents 2b–e; Procedures 2–6
The zinc reagents were prepared from the corresponding iodides or bromide as described above and using the following conditions.

Zinc Reagent 2b; Procedure 2
Time and temperature of the insertion: 2 h at 50 °C.

Zinc Reagent 2c; Procedure 3
Time and temperature of the insertion: 1 h at 25 °C.

Zinc Reagent 2d; Procedure 4
Time and temperature of the insertion: 3 h at 50 °C.

Zinc Reagent 2e; Procedure 5
Time and temperature of the insertion: 3 h at 50 °C (in this case only 1.5 equiv of Zn and LiCl were used).

Zinc Reagent 2f; Procedure 6
Time and temperature of the insertion: 12 h at 25 °C (in this case only 1.5 equiv of Zn and LiCl were used).

All zinc reagents were used as solutions in THF.

1-(2,4-Dimethoxypyrimidin-5-yl)-2,2-dimethylpropan-1-one (3a)
The organozinc solution of **2a** in THF (0.9 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to the new dry and argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl in THF (1 M, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. Pivaloyl chloride (145 mg, 1.3 equiv, 1.2 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C. The mixture was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (20% EtOAc–pentane) to give **3a** (169 mg) in 84% yield as a colorless oil.

IR (neat): 1694 (m), 1586 (s), 1554 (s), 1468 (s), 1458 (s), 1382 (s), 1320 (m), 1265 (m), 1200 (s), 1173 (m), 1074 (m), 1011 (m), 944 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.13 (s, 1 H), 4.02 (s, 3 H), 4.00 (s, 3 H), 1.23 (s, 9 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 208.8, 167.8, 165.5, 156.5, 116.9, 55.3, 54.3, 45.5, 26.8 (3 C).

MS (EI, 70 eV): *m*/*z* (%) = 224 (M^+, 3), 167 (100), 124 (3), 72 (2), 59 (5).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{16}N_2O_3$ [M^+]: 224.1161; found: 224.1168.

4-(2,6-Dimethoxypyrimidin-4-yl)benzoic Acid Ethyl Ester (3b)
A flame-dried round-bottomed flask was charged with $Pd(dba)_2$ (27 mg, 5 mol%), P(*o*-furyl)$_3$ (22 mg, 10 mol%), and THF (0.9 mL). The mixture was stirred at 25 °C for 10 min and then transferred to the reaction flask which was charged with an organozinc solution of **2b**, prepared according to **Procedure 2** (0.9 mmol), and ethyl 4-iodobenzoate (304 mg, 1.2 equiv, 1.1 mmol). The mixture was refluxed for 4 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (40% Et_2O– pentane) to give **3b** (213 mg) in 82% yield as a white solid; mp 116.0–118.2 °C.

IR (neat): 1714 (m), 1597 (m), 1578 (m), 1559 (s), 1467 (m), 1350 (s), 1274 (s), 1217 (m), 1104 (s), 1013 (m), 825 (s), 771 (s), 703 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.16–8.06 (m, 4 H), 6.82 (s, 1 H), 4.41 (q, *J* = 7.5 Hz, 2 H), 4.09 (s, 3 H), 4.02 (s, 3 H), 1.41 (t, *J* = 7.1, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.7, 166.1, 165.6, 164.8, 140.7, 132.2, 129.9, 126.9, 98.0, 61.2, 54.9, 54.1, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 288 (M^+, 100), 258 (49), 243 (30), 143 (10), 99 (10).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{16}N_2O_4$ [M^+]: 288.1110; found: 288.1097.

4-(2-Ethoxycarbonylallyl)-2,6-dimethoxypyrimidine-5-carboxylic Acid Ethyl Ester (3c)
The resulting organozinc solution of **2c** from **Procedure 3** in THF (0.7 mmol) was transferred into a dry and argon-flushed flask and cooled to –20 °C. Ethyl (2-bromomethyl)acrylate (149 mg, 1.1 equiv, 0.77 mmol) was added at –20 °C, followed by a solution of CuCN·2LiCl in THF (cat., ca. 5 drops). The resulting mixture was stirred at 0 °C for 1 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (40% Et_2O–pentane) to give **3c** (214 mg) in 94% as a colorless oil.

IR (neat): 1715 (s), 1559 (s), 1483 (m), 1459 (m), 1375 (s), 1360 (s), 1256 (s), 1058 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 6.22–6.18 (m, 1 H) 5.48–5.44 (m, 1 H), 4.28 (dq, *J* = 1.3, 7.1 Hz, 2 H), 4.12 (dq, *J* = 1.5, 7.1 Hz, 2 H), 3.93 (d, *J* = 1.5 Hz, 3 H), 3.88 (d, *J* = 1.3 Hz, 3 H), 3.77–3.73 (m, 2 H), 1.28 (dt, *J* = 1.3, 7.0 Hz, 3 H), 1.17 (dt, *J* = 1.5, 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.5, 169.0, 166.8, 165.7, 164.7, 137.2, 127.0, 108.3, 61.7, 61.0, 55.2, 54.7, 38.0, 14.4, 14.3.

MS (EI, 70 eV): *m*/*z* (%) = 324 (M^+, 30), 295 (100), 279 (40), 251 (53), 223 (24), 205 (14).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{20}N_2O_6$ [M^+]: 324.1321; found: 324.1330.

4-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)benzoic Acid Ethyl Ester (3d)

A flame-dried round-bottomed flask was charged with $Pd(dba)_2$ (24 mg, 5 mol%), P(*o*-furyl)$_3$ (20 mg, 10 mol%), and THF (0.9 mL). The mixture was stirred at 25 °C for 10 min, and then transferred to the reaction flask containing an organozinc solution of **2d** (0.85 mmol, prepared according to **Procedure 4**) and ethyl 4-iodobenzoate (282 mg, 1.2 equiv, 1.02 mmol). The mixture was stirred at 25 °C for 2 h, then quenched with sat. aq NH_4Cl (25 mL), and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (30% Et_2O–pentane) to give **3d** (250 mg, 91%) as a white solid; mp 101.4–103.0 °C.

IR (neat): 1717 (s), 1587 (m), 1538 (s), 1461 (m), 1375 (s), 1271 (s), 1092 (s), 1022 (s), 937 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.06–8.00 (m, 2 H), 7.34–7.27 (m, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 3.98 (s, 3 H), 3.87 (s, 3 H), 1.33 (t, *J* = 7. 1 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.7, 166.5, 163.7, 159.7, 136.8, 130.7 (2 C), 130.5, 129.7 (2 C), 113.7, 61.3, 55.7, 55.3, 14.6.

MS (EI, 70 eV): *m*/*z* (%) = 322 (M^+, 100), 293 (15), 277 (63), 234 (14), 199 (8), 177 (7), 170 (8), 114 (9).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}ClN_2O_4$ [M^+]: 322.0720; found: 322.0697.

4-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)benzonitrile (3h)

A flame-dried round-bottomed flask was charged with $Pd(dba)_2$ (24 mg, 5 mol%), P(*o*-furyl)$_3$ (20 mg, 10 mol%), and THF (0.9 mL). The mixture was stirred at 25 °C for 10 min, and then transferred to the reaction flask containing an organozinc solution of **2d** (0.85 mmol, prepared according to the **Procedure 4**) and 4-iodobenzonitrile (234 mg, 1.2 equiv, 1.02 mmol). The mixture was stirred at 25 °C for 2 h, then quenched with sat. aq NH_4Cl (25 mL), and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3h** (208 mg, 89%) yield as a white solid; mp 144.9–146.4 °C.

IR (neat): 1589 (s), 1535 (m), 1488 (s), 1463 (s), 1394 (s), 1378 (s), 1304 (m), 1244 (m), 1194 (m), 1094 (m), 1019 (s), 993 (m), 938 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69–7.61 (m, 2 H), 7.40–7.33 (m, 2 H), 3.98 (s, 3 H), 3.88 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.5, 163.9, 159.7, 137.1, 132.2 (2 C), 131.6 (2 C), 118.8, 112.9, 112.3, 55.8, 55.4.

MS (EI, 70 eV): *m*/*z* (%) = 275 (M^+, 100), 260 (12), 245 (32), 240 (17), 210 (16), 182 (12), 175 (12), 140 (16), 114 (8), 102 (6).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}ClN_3O_2$ [M^+]: 275.0462; found: 275.0438.

(4-Chloro-2,6-dimethoxypyrimidin-5-yl)pentafluorophenylmethanone (3i)

The organozinc solution of **2d** in THF (1.1 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. Pentafluorobenzoyl chloride (323 mg, 1.3 equiv, 1.4 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C. The mixture was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (30% Et_2O–pentane) to give **3i** (349 mg, 86%) as a white solid; mp 120.3–122.9 °C.

IR (neat): 1693 (m), 1571 (s), 1521 (s), 1490 (s), 1464 (s), 1395 (m), 1367 (m), 1334 (m), 1309 (m), 1219 (s), 1192 (m), 1081 (s), 1030 (s), 976 (s), 937 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.00 (s, 3 H), 3.90 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 181.0, 169.8, 164.7, 159.9, 147.1, 145.4, 143.6, 142.0, 139.5, 136.1, 113.7, 56.2, 55.7.

MS (EI, 70 eV): *m*/*z* (%) = 368 (M^+, 100), 338 (32), 201 (68), 195 (47), 167 (25), 117 (11), 76 (26).

HRMS (EI): *m*/*z* calcd for $C_{13}H_6ClF_5N_2O_3$ [M^+]: 367.9987; found: 367.9965.

(4-Chloro-2,6-dimethoxypyrimidin-5-yl)(4-fluorophenyl)methanone (3j)

The organozinc solution of **2d** in THF (1.1 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. 4-Fluorobenzoyl chloride (222 mg, 1.3 equiv, 1.4 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C. The mixture was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (30% Et_2O–pentane) to give **3j** (271 mg, 83%) as a white solid; mp 102.2–104.7 °C.

IR (neat): 1667 (m), 1578 (s), 1536 (s), 1464 (m), 1379 (s), 1268 (s), 1157 (m), 1018 (s), 912 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.83–7.75 (m, 2 H), 7.13–7.03 (m, 2 H), 4.00 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 189.3, 169.6, 168.4, 165.0, 164.6, 158.4, 133, 132, 116.5, 116.2, 112.7, 56.0, 55.4.

MS (EI, 70 eV): *m*/*z* (%) = 296 (M^+, 84), 266 (10), 201 (100), 187 (10), 123 (60), 95 (31), 76 (14).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}ClFN_2O_3$ [M^+]: 296.0364; found: 296.0345.

(4-Chloro-2,6-dimethoxypyrimidin-5-yl)(2,6-dimethoxyphenyl)methanone (3k)

The organozinc solution of **2d** in THF (1.1 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. 2,6-Dimethoxybenzoyl chloride (281 mg, 1.3 equiv, 1.4 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C. The mixture was quenched with sat. aq NH_4Cl (10 mL), and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in

vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3k** (168 mg) in 45% yield as a white solid; mp 127.9–129.7 °C.

IR (neat): 1673 (m), 1580 (s), 1541 (s), 1472 (s), 1371 (m), 1257 (s), 1242 (s), 1108 (s), 1032 (s), 927 cm^{-1} (s).

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (t, *J* = 8.8 Hz, 1 H), 6.54 (d, *J* = 8.8 Hz, 2 H), 4.02 (s, 3 H), 3.92 (s, 3 H), 3.74 (s, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 189.5, 169.9, 163.6, 159.1 (2 C), 158.6, 132.7, 119.3, 116.4, 104.4 (2 C), 56.4 (2 C), 55.7, 55.2.

MS (EI, 70 eV): *m*/*z* (%) = 338 (M^+, 31), 303 (82), 202 (35), 165 (100).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{15}ClN_2O_5$ [M^+]: 338.0670; found: 338.0652:

3-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)cyclohex-2-enone (3l)

The resulting organozinc solution of **2d** in THF (0.80 mmol) was transferred into a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 1 equiv) was added and the mixture was stirred at –30 °C for 30 min. 3-Iodocyclohex-2-en-1-one (195 mg, 1.1 equiv, 0.88 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h, then slowly warmed to –10 °C for 15 h, and quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3l** (206 mg) in 96% as a white solid; mp 120.9–122.5 °C.

IR (neat): 1672 (s), 1581 (s), 1536 (s), 1461 (s), 1388 (s), 1344 (s), 1236 (m), 1190 (m), 1088 (s), 1028 (s), 940 cm^{-1} (m).

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.93 (s, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.48–2.39 (m, 4 H), 2.15–2.02 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 199.2, 168.8, 163.8, 158.3, 154.1, 131.8, 113.5, 55.7, 55.3, 37.6, 29.6, 23.1.

MS (EI, 70 eV): *m*/*z* (%) = 268 (M^+, 100), 240 (87), 225 (28), 197 (31), 177 (24), 77 (7).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{13}ClN_2O_3$ [M^+]: 268.0615; found: 268.0591.

Biphenyl-4-yl(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (3e)

The organozinc solution of **2e** in THF (0.9 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. Biphenyl-4-carbonyl chloride (260 mg, 1.3 equiv, 1.2 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C for 14 h. The mixture was quenched with sat. aq NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3e** (333 mg, 83%) as a white solid; mp 152.3–154.7 °C.

IR (neat): 1664 (m), 1600 (m), 1570 (s), 1526 (s), 1460 (m), 1384 (s), 1369 (s), 1311 (s), 1261 (s), 1200 (m), 1075 (s), 1008 (s), 916 cm^{-1} (s).

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.85 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 7.1 Hz, 2 H), 7.42–7.37 (m, 2 H), 7.36–7.31 (m, 1 H), 3.99 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 190.2, 165.0, 161.1, 144.6, 137.3, 131.9, 128.0 (2 C), 126.7 (2 C), 126.1, 125.2 (2 C), 125.0 (2 C), 124.3, 118.9, 53.3, 52.5.

MS (EI, 70 eV): *m*/*z* (%) = 446 (M^+, 100), 345 (15), 293 (37), 181 (49), 152 (31).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{15}IN_2O_3$ [M^+]: 446.0127; found: 446.0109.

(4-Fluorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (3f)

The organozinc solution of **2e** in THF (0.9 mmol) was decanted and carefully transferred from the rest of Zn powder using a syringe to a dry argon-flushed flask and cooled to –30 °C. A solution of CuCN·2LiCl (1 M in THF, 0.5 equiv) was added and the mixture was stirred at –30 °C for 30 min. 4-Fluorobenzoyl chloride (190 mg, 1.3 equiv, 1.2 mmol) was then added at –30 °C. The mixture was stirred at –30 °C for 1 h and then slowly warmed to 25 °C for 14 h. The mixture was quenched with sat. aq NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3f** (283 mg, 81%) as a white solid; mp 142.6–144.7 °C.

IR (neat): 1669 (m), 1595 (m), 1566 (s), 1525 (s), 1506 (m), 1475 (m), 1455 (m), 1381 (s), 1364 (s), 1312 (s), 1255 (s), 1245 (s), 1225 (s), 1158 (s), 1076 (s), 1015 (s), 920 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.83–7.77 (m, 2 H), 7.12–7.05 (m, 2 H), 3.98 (s, 3 H), 3.83 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 191.6, 167.9, 167.4, 165.3, 163.7, 132.6, 132.3, 126.9, 121.1, 116.5, 116.3, 55.9, 55.1.

MS (EI, 70 eV): *m*/*z* (%) = 388 (M^+, 55), 358 (5), 293 (30), 136 (37), 123 (100), 95 (81), 75 (28).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}FIN_2O_3$ [M^+]: 387.9720; found: 387.9734.

2-(4-Iodo-2,6-dimethoxypyrimidin-5-ylmethyl)acrylic Acid Ethyl Ester (3m)

The resulting organozinc solution of **2e** in THF (0.7 mmol) was transferred into a dry argon-flushed flask and cooled to –20 °C. Ethyl (2-bromomethyl)acrylate (149 mg, 1.1 equiv, 0.77 mmol) was added at –20 °C, followed by a solution of CuCN·2LiCl (cat., ca. 5 drops). The resulting mixture was stirred at 0 °C for 1.5 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (40% Et_2O–pentane) to give **3m** (230 mg, 87%) as a white solid; mp 49.7–51.5 °C.

IR (neat): 1705 (s), 1575 (s), 1534 (s), 1456 (s), 1375 (s), 1221 (s), 1129 (s), 1077 (s), 1015 (s), 944 cm^{-1} (m).

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.14–6.10 (m, 1 H), 5.07–5.03 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.57–3.54 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.0, 166.9, 162.8, 136.8, 135.5, 124.5, 117.4, 61.2, 55.5, 54.9, 33.9, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 321 [(^{81}Br) – M^+, 100], 304 (12), 291 (26), 240 (18), 210 (28), 182 (22), 168 (16), 140 (37).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}{}^{81}BrIN_3O_2$ [M^+]: 320.9936; found: 320.9911.

4-(4-Bromo-2,6-dimethoxypyrimidin-5-yl)benzonitrile (3g)

A flame-dried round-bottomed flask was charged with $Pd(dba)_2$ (24 mg, 5 mol%), P(*o*-furyl)$_3$ (20 mg, 10 mol%), and THF (0.9 mL). The mixture was stirred at 25 °C for 10 min and then transferred to

the reaction flask containing the organozinc solution **2f** (0.85 mmol, prepared according to the **Procedure 6**) and 4-iodobenzonitrile (234 mg, 1.2 equiv, 1.02 mmol). The mixture was refluxed for 2 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (40% Et_2O–pentane) to give **3g** (234 mg, 86%) as a white solid; mp 149.1–150.6 °C.

IR (neat): 2228 (w), 1587 (m), 1531 (m), 1460 (m), 1376 (s), 1324 (m), 1196 (m), 1094 (m), 1019 (m), 992 (m), 936 (m), 832 (m), 790 (m), 741 cm^{-1} (m).

^1H NMR ($CDCl_3$, 300 MHz): δ = 7.70 (d, *J* = 8.6 Hz, 2 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 4.04 (s, 1 H), 3.92 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.6, 163.4, 152.3, 138.4, 132.0, 131.3, 118.6, 115.6, 112.1, 104.7, 55.6, 55.1.

MS (EI, 70 eV): *m*/*z* (%) = 321 (M^+, 100), 304 (12), 289 (28), 240 (18), 225 (24), 210 (29), 189 (23), 168 (16), 140 (38).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{10}{}^{81}BrN_3$ [M^+]: 318.9936; found: 320.9911.

5-Allyl-4-bromo-2,6-dimethoxypyrimidine (3n)

The resulting organozinc solution of **2f** in THF (1 mmol) was transferred into a dry argon-flushed flask and cooled to –20 °C. Allyl bromide (144 mg, 1.2 equiv, 1.2 mmol) was added at –20 °C, followed by a solution of CuCN·2LiCl (cat., ca. 5 drops). The resulting mixture was stirred at 0 °C for 5 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (20% Et_2O–pentane) to give **3n** (210 mg, 81%) as a colorless oil.

IR (film): 3081 (w), 2957 (w), 1639 (w), 1586 (m), 1542 (s), 1459 (m), 1370 (s), 1223 (m), 1079 (m), 1026 cm^{-1} (s).

^1H NMR ($CDCl_3$, 400 MHz): δ = 5.87–5.77 (m, 1 H), 5.02 (2 dd, $^3J_{trans}$ = 13.2 Hz, J_{gem} and $^3J_{cis}$ = 1.7 Hz, 2 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.35 (dt, ^3J = 6.1 Hz, ^4J = 1.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 170.08, 162.61, 159.98, 133.39, 115.93, 110.71, 55.14, 54.82, 29.57.

MS (EI, 70 eV): 260.0 (98), 258.0 (100), 245.0 (23), 243.0 (22), 231.0 (41), 179.0 (25), 163.0 (14).

HRMS (EI): *m*/*z* calcd for $C_9H_{11}BrN_2O_2$: 258.0004; found: 258.0023.

Zinc Reagent 2g

Anhyd LiCl (203 mg, 4.8 mmol) was placed in an argon-flushed flask and dried 30 min at 150 °C on high vacuum (1 mbar). After cooling to r.t. under argon, Zn powder (471 mg, 7.2 mmol) was added, and the heterogeneous mixture of Zn and LiCl was dried again 30 min at 150 °C on high vacuum (1 mbar). After cooling to r.t. under argon, the reaction flask was evacuated and refilled with argon three times. Anhyd THF (5 mL) was added, and the Zn powder was activated by treating it first with $BrCH_2CH_2Br$ (30 μL, 5 mol%) followed by chlorotrimethylsilane (1 mol%). Then a solution of (4-fluorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (**3f**; 931 mg, 2.4 mmol) in THF (1 mL) was added and the mixture was stirred at 25 °C. The insertion reaction was complete after 1 h (checked by GC analysis of reaction aliquots, the conversion was higher than 98%). The organozinc reagent **2g** was titrated using I_2[13] showing ca. 0.96 M concentration of **2g** in THF. The solution of **2g** was carefully separated from the remaining Zn powder using a syringe and transferred to another dry argon-flushed flask.

2-[5-(4-Fluorobenzoyl)-2,6-dimethoxypyrimidin-4-ylmethyl]acrylic Acid Ethyl Ester (3o)

The resulting organozinc solution of **2g** in THF (0.7 mmol) was transferred into a dry argon-flushed flask and cooled to –20 °C. Allyl bromide (93 mg, 1.1 equiv, 0.77 mmol) was added at –20 °C, followed by a solution of CuCN·2LiCl (cat., ca. 5 drops). The resulting mixture was stirred at 0 °C for 1 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (50% Et_2O–pentane) to give **3o** (210 mg, 80%) as a colorless oil.

IR (neat): 1714 (m), 1665 (m), 1575 (s), 1557 (s), 1480 (m), 1458 (m), 1367 (s), 1262 (s), 1144 (s), 1082 (s), 916 (s), 852 cm^{-1} (m).

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.89–7.79 (m, 2 H), 7.17–7.07 (m, 2 H), 6.25–6.21 (m, 1 H), 5.58–5.54 (m, 1 H), 4.10 (q, *J* = 7.3 Hz, 2 H), 3.98 (s, 3 H), 3.86 (s, 3 H), 3.62–3.59 (m, 1 H), 1.20 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.8, 169.1, 168.3, 168.1, 166.6, 164.9, 164.7, 136.8.

MS (EI, 70 eV): *m*/*z* (%) = 374 (M^+, 87), 359 (31), 345 (26), 329 (23), 313 (15), 301 (81), 287 (18), 275 (71), 123 (100), 95 (35).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{19}FN_2O_5$ [M^+]: 374.1278; found: 374.1285.

(4-Allyl-2,6-dimethoxypyrimidin-5-yl)(4-fluorophenyl)methanone (3p)

The resulting organozinc solution of **2g** in THF (0.7 mmol) was transferred into a dry argon-flushed flask and cooled to –20 °C. Neat ethyl (2-bromomethyl)acrylate (149 mg, 1.1 equiv, 0.77 mmol) was added at –20 °C, followed by a solution of CuCN·2LiCl (cat., ca. 5 drops). The resulting mixture was stirred at 0 °C for 1 h and then quenched with sat. aq NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography (40% Et_2O–pentane) to give **3p** (201 mg, 95%) as a colorless oil.

IR (neat): 1666 (m), 1556 (s), 1480 (m), 1457 (m), 1367 (s), 1261 (s), 1237 (s), 1155 (m), 1078 (m), 1056 (m), 920 cm^{-1} (s).

^1H NMR ($CDCl_3$, 200 MHz): δ = 7.78–7.69 (m, 2 H), 7.09–6.99 (m, 2 H), 5.92–5.76 (m, 1 H), 4.94–4.83 (m, 2 H), 3.96 (d, *J* = 1.5 Hz, 3 H), 3.79 (d, *J* = 1.8 Hz, 3 H), 3.32–3.23 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 192.9, 169.1, 168.9, 168.0, 165.1, 164.6, 134.2, 133.6, 132.3, 132.1, 118.0, 116.2, 115.9, 113.0, 55.2, 54.4.

MS (EI, 70 eV): *m*/*z* (%) = 302 (M^+, 100), 287 (79), 273 (10), 247 (6), 207 (8), 191 (12), 123 (56), 95 (26).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{15}FN_2O_3$ [M^+]: 302.1067; found: 302.1076.

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