

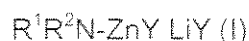
Preparation and use of zinc amides

Directed metalation of aromatic and heterocyclic compounds is an important method for the functionalization of these scaffolds. Lithium bases have been extensively used for performing the *ortho*-metalation of various unsaturated systems ((a) Snieckus, V. *Chem. Rev.* **1990**, 90, 879. (b) Clayden, J.; Stimson, C. C.; Keenan M. *Chem. Comm.* **2006**, 1393. (c) Schlosser M. *Angew. Chem. Int. Ed.* **2005**, 44, 376. (d) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, 3431. (e) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, 57, 4489. (f) Mongin F.; Quéguiner, G. *Tetrahedron* **2001**, 57, 4059. (g) Levoux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, 105, 827. (h) Kauch, M.; Hoppe, D. *Synthesis* **2006**, 1578. (i) Clegg, W.; Dale, S. H.; Hevia, E.; Honeyman, G. W.; Mulvey R. E. *Angew. Chem. Int. Ed.* **2006**, 45, 2371. (j) Hodgson, D. M.; Miles, S. M. *Angew. Chem. Int. Ed.* **2006**, 45, 93. (k) Yus, M.; Foubelo, F. *Handbook of Functionalized Organometallics*, Knochel, P. Ed., Wiley-VCH: Weinheim, Germany **2005**; Vol. 1, page 7). The use of magnesium bases, pioneered by Eaton, ((a) Eaton, P. E.; Martin, R. M. *J. Org. Chem.* **1988**, 53, 2728. (b) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, 111, 8016. (c) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc.* **1993**, 115, 11370. (d) Zhang, M.-X.; Eaton, P. E. *Angew. Chem. Int. Ed.* **2002**, 41, 2169) has recently found a renewed interest ((a) Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Sherrington, D. C. *Angew. Chem. Int. Ed.* **2005**, 44, 68. (b) Andrikopolous, P. C.; Armstrong, D. R.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Mulvey, R. E.; O'Hara, C. T.; Talmard, C. *Angew. Chem. Int. Ed.* **2005**, 44, 3459. (c) Kondo, Y.; Akihiro, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2331. (d) Shilai, M.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 442. (e) Bayh, O.; Awad, H.; Mongin, F.; Hoarau, C.; Bischoff, L.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *J. Org. Chem.* **2005**, 70, 5190. (f) Eaton, P. E.; Zhang, M.-X.; Komiya, N.; Yang, C.-G.; Steele, I.; Gilardi, R. *Synlett* **2003**, 9, 1275). Recently, lithium magnesiates ((a) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2000**, 39, 2481. (b) Farkas, J.; Stoudt, S. J.; Hannawalt, E. M.; Pajeski, A. D.; Richey, H. G. *Organometallics* **2004**, 23, 423. (c) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F.; Blanco, F.; Abarca, B.; Ballesteros, R. *Tetrahedron Lett.* **2004**, 45, 6697; (a) Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem. Int. Ed.* **2008**, 47, 8079. (b) Mulvey, R. E. *Organometallics* **2006**, 25, 1060. (c) Mulvey, R. E. *Chem. Comm.* **2001**, 1049. (d) Westerhausen, M. *Dalton Trans.* **2006**, 4755. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.*, **2007**, 46, 3802) have found useful synthetic applications. Mixed Mg/Li-bases of type R₂NMgCl·LiCl such as 2,2,6,6-tetramethylpiperidide magnesium chloride – lithium chloride

(TMPMgCl·LiCl; Turbo-Hauser base) proved to be especially effective metalating agent, compatible with functional groups such as an ester, a nitrile or an aryl ketone ((a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (d) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237. (e) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681. (f) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503). However, more sensitive functionalities such as an aldehyde or a nitro group are not tolerated. Also sensitive heterocycles may undergo fragmentation ((a) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006. (b) Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1974**, *95*, 3408. (c) Knaus, G. N.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189. (d) Miller, R. A.; Smith, M. R.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074. (e) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber. Rec.* **1997**, *130*, 1213). Therefore a range of zinc amides have been reported which provide after metalation organozinc reagents compatible with most functionalities. In pioneer work, lithium di-*tert*-butyl-(2,2,6,6-tetra-methylpiperidino)zincate (Li^t-Bu₂TMPZn) was reported by Kondo to be an excellent base for the zincation of various aromatics ((a) Micetich, R. G. *Can. J. Chem.* **1970**, *48*, 2006. (b) Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1974**, *95*, 3408. (c) Knaus, G. N.; Meyers, A. I. *J. Org. Chem.* **1974**, *39*, 1189. (d) Miller, R. A.; Smith, M. R.; Marcune, B. *J. Org. Chem.* **2005**, *70*, 9074. (e) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber. Rec.* **1997**, *130*, 1213). Unfortunately, the use of highly reactive zincates or related ate-bases ((a) Uchiyama, M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748. (b) Clegg, W.; Dale, S. H.; Drummond, A. M.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2006**, *128*, 7434. (c) Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *J. Am. Chem. Soc.* **2005**, *127*, 13106. (d) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 3775. (e) Clegg, W.; Dale, S. H.; Harrington, R. W.; Hevia, E.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2006**, *45*, 2374. (f) Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatly, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921) is not compatible with sensitive functions such as an aldehyde or a nitro group. Recently, we have reported the preparation of a highly chemoselective base TMP₂Zn·2MgCl₂·2LiCl for the directed zincation of sensitive aromatics and heteroaromatics ((a) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685. (b) Mosrin, M.; Knochel P. *Chem. Eur. J.* **2009**, DOI: 10.1002/chem.200801831). However, some electron-poor functionalized arenes and heteroarenes still give with this reagent, unsatisfactory results in terms of yields and reaction selectivity. Moreover, several activated aromatics or

heteroaromatics like nitro derivatives or pyridazines require metalations below -50 °C, which is not convenient for the reaction upscaling ((a) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, 46, 7685. (b) Mosrin, M.; Knochel P. *Chem. Eur. J.* **2009**, DOI: 10.1002/chem.200801831; Wunderlich, S. H.; Knochel, P. *Chem. Comm.* **2008**, 47, 6387).

A reagent of the general formula



wherein

R^1 , R^2 are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silyl derivatives thereof; and R^1 and R^2 together can be part of a cyclic or polymeric structure; and wherein at least one of R^1 and R^2 is other than H;
Y is selected from the group consisting of F; Cl; Br; I; CN; SCN; NCO; $HalO_n$, wherein $n = 3$ or 4 and Hal is selected from Cl, Br and I; NO_3 ; BF_4 ; PF_6 ; H; a carboxylate of the general formula R^XCO_2 ; an alcoholate of the general formula OR^X ; a thiolate of the general formula SR^X ; $R^XP(O)O_2$; or $SCOR^X$; or $SCSR^X$; O_nSR^X , wherein $n = 2$ or 3; or NO_n , wherein $n = 2$ or 3; and a derivative thereof; wherein R^X is a substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or derivatives thereof, or H;
or as adduct with a solvent.

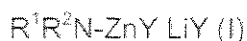
R^1 , R^2 are cyclic and substituted by R^3 , and R^4 that are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silyl derivatives thereof; and R^1 and R^2 together, or R^3 and R^4 together can be part of a cyclic or polymeric structure; and wherein at least one of R^1 and R^2 and at least one of R^3 and R^4 is other than H.

Preferable the reagent $R^1R^2N-ZnY LiY$ (I) is 2,2,6,6-Tetramethylpiperide Zinc Chloride Lithium Chloride or the solution of the reagent in a solvent. The solvent is polar and aprotic. Preferable is the solvent selected from cyclic, linear or branched mono or polyethers, thioethers, amines, phosphines, and derivatives thereof containing one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofuran (THF), 2-methyltetrahydrofuran, dibutyl ether, diethyl ether, tert-butylmethyl ether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropyl amine, dimethylsulfide, dibutylsulfide; cyclic amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogens are replaced by a halogen, preferably dichloromethane, 1,2-

dichloroethane, CCl_4 ; urea derivatives, preferably N,N'-dimethylpropyleneurea (DMPU); aromatic, heteroaromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorus triamide (HMPA), CS_2 ; or combinations thereof.

The inventive process for the preparation of a mixed Zn/Li amide comprises the reaction in a solvent a primary or secondary amine with a lithium alkyl.

Preferable comprises the process for the preparation of a reagent having the general formula



wherein

R^1 , R^2 are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silicon derivatives thereof; and R^1 and R^2 together can be part of a cyclic or polymeric structure; and wherein at least one of R^1 and R^2 is other than H;

Y is selected from the group consisting of F; Cl; Br; I; CN; SCN; NCO; HalO_n , wherein $n = 3$ or 4 and Hal is selected from Cl, Br and I; NO_3 ; BF_4 ; PF_6 ; H; a carboxylate of the general formula R^xCO_2 ; an alcoholate of the general formula OR^x ; a thiolate of the general formula SR^x ; $\text{R}^x\text{P}(\text{O})\text{O}_2$; or SCOR^x ; or SCSR^x ; O_nSR^x , wherein $n = 2$ or 3; or NO_n , wherein $n = 2$ or 3; and a derivative thereof;

wherein R^x is a substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or derivatives thereof, or H;

and the reaction is carried out in a solvent of $\text{R}^1\text{R}^2\text{N-H}$ with R^xLi in the presence of ZnY_2 and X is defined as Y above.

X and Y are independently or both Cl, Br or I, and preferably Cl. The lithium organyl reagent is sec-butyl-Li and the solvent is selected from cyclic, linear or branched mono or polyethers, thioethers, amines, phosphines, and derivatives thereof containing one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofuran (THF), 2-methyltetrahydrofuran, dibutyl ether, diethyl ether, tert-butylmethylether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropylamine, dimethylsulfide, dibutylsulfide; cyclic amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogens are replaced by a halogen, preferably dichloromethane, 1,2-dichloroethane, CCl_4 ; urea derivatives, preferably N,N'-dimethylpropyleneurea (DMPU);

aromatic, hetero aromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorus triamide (HMPA), CS₂; or combinations thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications and other references mentioned herein are incorporated by reference in their entirety.

As used herein, the terms "alkyl", "alkenyl" and "alkynyl" refer to linear, cyclic and branched, substituted and unsubstituted C₁-C₂₀ compounds. Preferred ranges for these compounds are C₁-C₁₀, preferably C₁-C₅ (lower alkyl) and C₂-C₁₀ and preferably C₂-C₅, respectively, for alkenyl and alkynyl. The term "cycloalkyl" generally refers to linear and branched, substituted and unsubstituted C₃-C₂₀ cycloalkanes. Here, preferred ranges are C₃-C₁₅, more preferably C₃-C₈.

Whenever any of the residues R¹, R², R³ and/or R⁴ are substituted by a substituent, the substituent may be selected by a person skilled in the art from any known substituent. A person skilled in the art will select a possible substituent according to his knowledge and will be able to select a substituent which will not interfere with other substituents present in the molecule and which will not interfere or disturb possible reactions, especially the reactions described within this application. Possible substituents include without limitation

- halogenes, preferably fluorine, chlorine, bromine and iodine;
- aliphatic, alicyclic, aromatic or heteroaromatic hydrocarbons, especially alkanes, alkylenes, arylenes, alkylidenes, arylidenes, heteroarylenes and heteroarylidenes; carbonxylic acids including the salts thereof;
- carboxylic acid halides;
- aliphatic, alicyclic, aromatic or heteroaromatic carboxylic acid esters;
- aldehydes;
- aliphatic, alicyclic, aromatic or heteroaromatic ketones;
- alcohols and alcoholates, including a hydroxyl group;
- phenoles and phenolates;
- aliphatic, alicyclic, aromatic or heteroaromatic ethers;
- aliphatic, alicyclic, aromatic or heteroaromatic peroxides;
- hydroperoxides;
- aliphatic, alicyclic, aromatic or heteroaromatic amides or amidines;
- nitriles;
- aliphatic, alicyclic, aromatic or heteroaromatic amines;
- aliphatic, alicyclic, aromatic or heteroaromatic imines;

- aliphatic, alicyclic, aromatic or heteroaromatic sulfides including a thiol group;
- sulfonic acids including the salts thereof;
- thioles and thiolates;
- phosphonic acids including the salts thereof;
- phosphinic acids including the salts thereof;
- phosphorous acids including the salts thereof; phosphinous acids including the salts thereof.

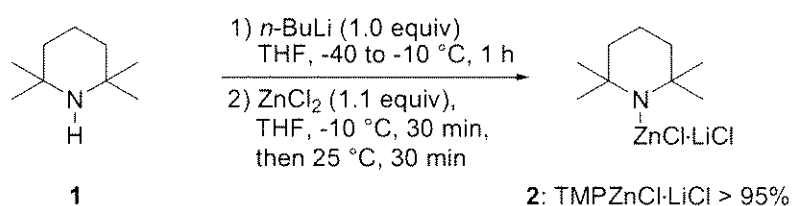
The substituents may be bound to the residues R^1 , R^2 , R^3 and/or R^4 via a carbon atom, an oxygen atom, a nitrogen atom, a sulfur atom, or a phosphorus atom. The hetero atoms in any structure containing hetero atoms, as e.g. heteroarylenes or heteroaromatics, may preferably be N, O, S and P.

When R^1 and R^2 , or R^3 and R^4 can be part of a cyclic structure, it is to be understood that R^1 and R^2 together, or R^3 and R^4 together, are a divalent saturated or unsaturated, linear or branched alkyl, alkenyl or alkynyl which forms in connection with the nitrogen atom of the amide a cyclic secondary amide. An example of such a cyclic amide is the amide of TMPH. Further, the residues R^1 and R^2 , and/or R^3 and R^4 can be part of a polymeric structure. The nitrogen atom of the amide is connected to a polymeric backbone which may even contain more than one nitrogen atom for the formation of an amide according to the invention.

The term "aryl" as used herein refers to substituted or unsubstituted C_4 - C_{24} aryl. By "heteroaryl", a substituted or unsubstituted C_3 - C_{24} aryl, containing one or more heteroatoms as B, O, N, S, Se, P, is meant. Preferred ranges for both are C_4 - C_{15} , more preferably C_4 - C_{10} , and includes aryls and fused aryls with or without heteroatoms. A preferred ring size comprises 5 or 6 ring atoms.

For example, we have explored the preparation of more selective zinc base which would allow chemoselective metalations at 25 °C for the directed zincation of sensitive aryl and heteroaryl substrates. The treatment of 2,2,6,6-tetramethylpiperidine (**1**; TMP-H) with *n*-BuLi (1.0 equiv, -40 to -10 °C, 1 h) followed by the addition of $ZnCl_2$ (1.1 equiv, -10 °C, 30 min) provides a ca. 1.3 M solution of $TMPZnCl \cdot LiCl$ (**2**), stable at room temperature (Scheme 1). In contrast to $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$, this complex base showed a very good chemoselectivity for the zincation at 25 °C of various sensitive aromatics and heterocycles.

Scheme 1: Preparation of 2,2,6,6-Tetramethylpiperidide Zinc Chloride Lithium Chloride ($TMPZnCl \cdot LiCl$) (**2**)



The inventive reagent could be used in a reaction with an electrophile preferably for the deprotonation of any substrate which can form stabilized or unstabilized carbaniones.

Examples for the use of the reagent according to the invention are given in the following tables.

Table 1: Products Obtained by Regio- and Chemoselective Zincation of Diazines of Type **3**, **6** and **9** with TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Quenching with Electrophiles

entry	substrate of type 3, 6 and 9	electrophile	product	yield, % ^a
1		I ₂		84
2	3	4-fluorobenzoyl chloride		96 ^b
3	3			83 ^c
4		I ₂		83
5	6	furoyl chloride		71 ^b
6	6	allyl bromide		89 ^d
7		I ₂		90
8	9			87 ^c
9	9			72 ^d

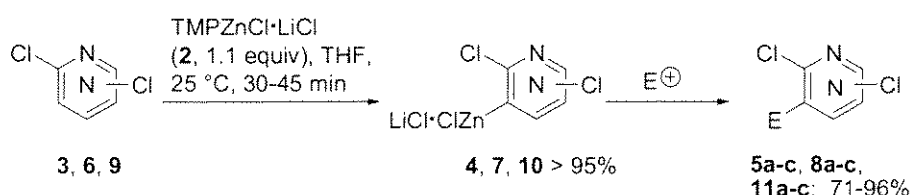
^a Isolated, analytically pure product;

^b Transmetalation performed with 1.1 equiv of CuCN·2LiCl;

^c Obtained by palladium-catalyzed cross-coupling using Pd(dba)₂ (3 mol %) and (o-furyl)₃P (6 mol %);

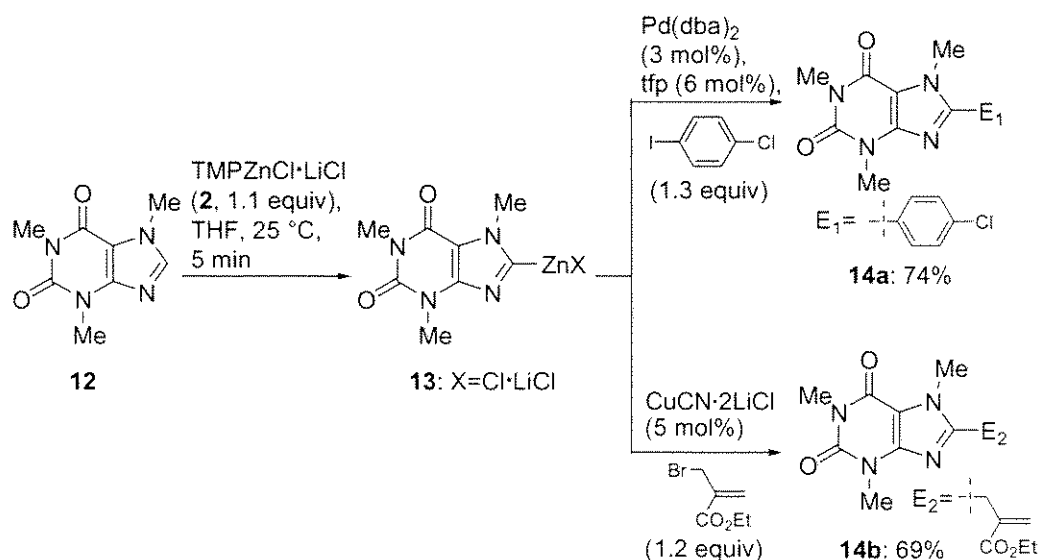
^d Transmetalation performed with 5 mol % of CuCN·2LiCl.

Scheme 2: Zincation of 3,6-Dichloropyridazine (**3**), 4,6-Dichloropyrimidine (**6**) and 2,6-Dichloropyrazine (**9**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



Several sensitive heteroarenes such as pyridazines, (Wunderlich, S. H.; Knochel, P. *Chem. Comm.* **2008**, 47, 6387) pyrimidines ((a) Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1990**, 37, 2149. (b) Radinov, R.; Chanev, C.; Haimova, M. *J. Org. Chem.* **1991**, 56, 4793 and pyrazines (Turck A.; Trohay, D.; Mojovic, L.; Plé, N.; Quéguiner, G. *J. Organomet. Chem.* **1991**, 412, 301)) are cleanly zincated at 25 °C using the new base TMPZnCl·LiCl (**2**; Scheme 2 and Table 1). Thus, the treatment of 3,6-dichloropyridazine (**3**) with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 30 min) leads to the zincated species (**4**), which can be trapped with I₂, 4-fluorobenzoyl chloride (after transmetalation with CuCN·2LiCl) (Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390) or undergo a Negishi (Negishi, E.; *Acc. Chem. Res.* **1982**, 15, 340) cross-coupling leading to the expected products **5a-c** in 83-96% yields (entries 1-3 of Table 1). Zincations of other sensitive heteroaromatics can be readily achieved by the addition of TMPZnCl·LiCl (**2**). Thus, 4,6-dichloropyrimidine (**6**) is converted within 45 min at 25 °C to the 5-zincated species. Trapping with I₂ is furnishing the iodopyrimidine **8a** in 83% yield (entry 4). Reaction with furoyl chloride (after transmetalation with CuCN·2LiCl) (Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390) provides the 5-ketopyrimidine **8b** in 71% (entry 5). An allylation (after addition of CuCN·2LiCl) leads to the allyled derivative **8c** in 89% (entry 6). Similarly, 2,6-dichloropyrazine (**9**) is zincated quantitatively with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 30 min) and reacted with iodine or undergoes a Negishi (Negishi, E.; *Acc. Chem. Res.* **1982**, 15, 340) cross-coupling or an allylation with ethyl 2-(bromomethyl)acrylate (Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, 66, 220) (after addition of CuCN·2LiCl) affording the expected products **11a-c** in 72-90% yields (entries 7-9).

Scheme 3: Zincation of Caffeine (**12**) using TMPZnCl·LiCl (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles

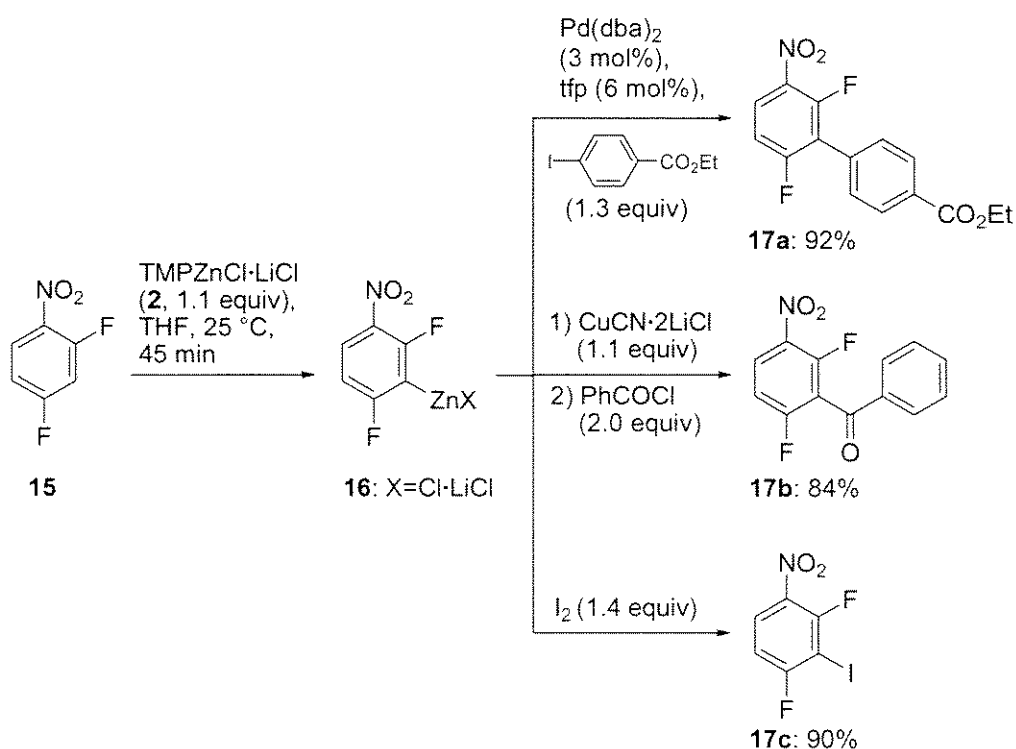


Other sensitive heterocycles such as purines ((a) Boudet, N; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2007**, *10*, 1715. (b) Tobrman, T.; Dvořák, D. *Org. Lett.* **2006**, *8*, 1291) can be metalated as well under mild conditions (Scheme 3). Thus, caffeine (**12**) (Do, H-Q; Kashif-Khan R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185) undergoes a smooth zincation using TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 5 min) furnishing the zinc species **13**. Negishi (Negishi, E.; *Acc. Chem. Res.* **1982**, *15*, 340) cross-coupling or trapping with ethyl 2-(bromomethyl)acrylate (Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220) (after addition of CuCN·2LiCl) lead to the purine derivative **14a** and **14b** in 74 and 69% yields respectively.

A unique advantage of the zinc base **2** is that very sensitive functional groups such as a nitro group can be tolerated at 25 °C (I. Sapountzis, P. Knochel, *Angew. Chem. Int. Ed.* **2002**, *41*, 1610). Thus, 2,4-difluoronitrobenzene (**15**) was converted to the corresponding zinc reagent **16** by treatment with TMPZnCl·LiCl (**2**; 1.1 equiv, 25 °C, 45 min). A Negishi (Negishi, E.; *Acc. Chem. Res.* **1982**, *15*, 340) cross-coupling can be readily performed to furnish the aryl derivative **17a** in 92% yield (Scheme 4). Trapping with benzoyl chloride (after transmetalation with CuCN·2LiCl) (Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390) provides the ketone **17b** in 84% yield. After trapping with I₂, the iodobenzene derivative **17c** was obtained in 90% yield.

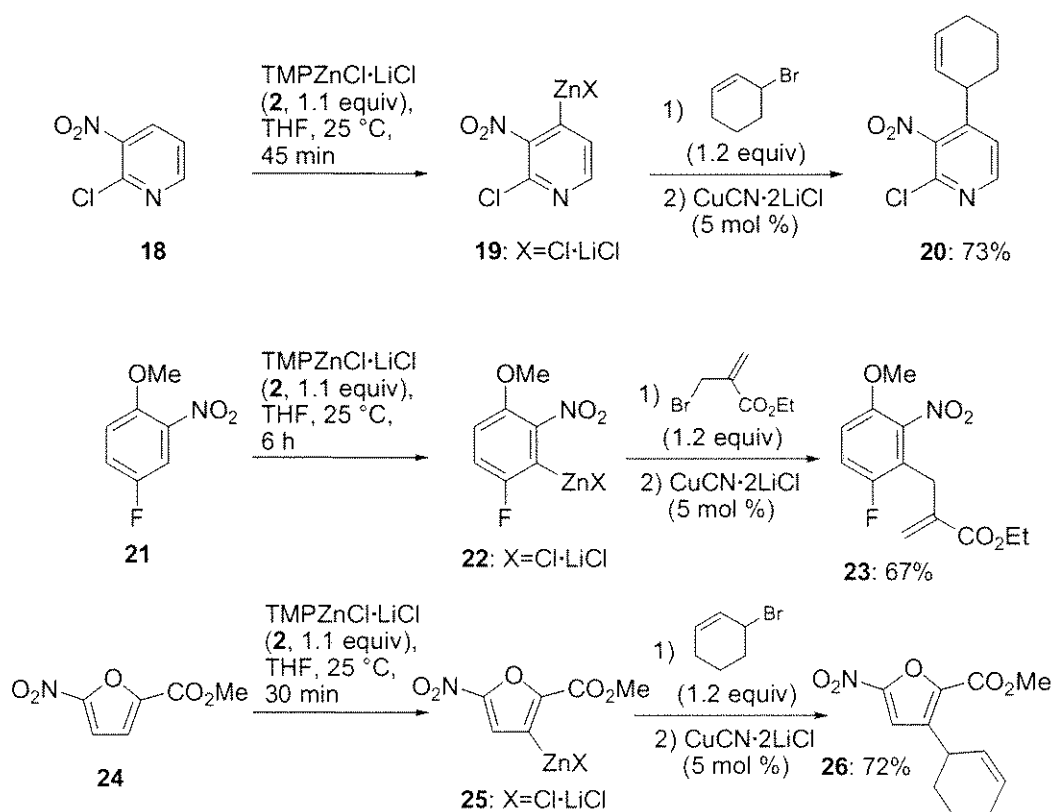
Scheme 4. Zincation of 2,4-Difluoronitrobenzene (**15**) using TMPZnCl·LiCl (**2**; 1.1 equiv;

25 °C) and Trapping with Electrophiles



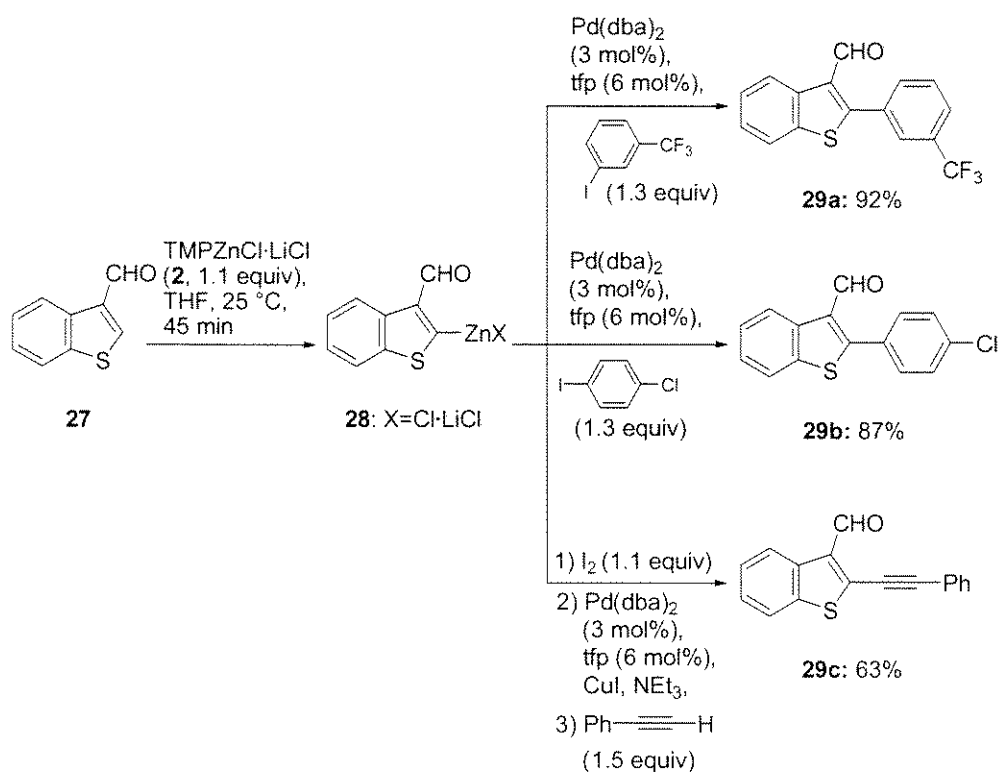
Other sensitive electron-poor arenes and heteroarenes are metalated as well using **2**. Thus, 2-chloro-3-nitropyridine (**18**) undergoes smooth metalation with $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**; 1.1 equiv, 25 °C, 45 min) furnishing the zinc species **19**. Trapping using 3-bromocyclohexene (after addition of $\text{CuCN}\cdot 2\text{LiCl}$) provides the pyridine **20** in 73% yield. Similarly, 4-fluoro-1-methoxy-2-nitrobenzene (**21**) was converted within 6 h at 25 °C to the corresponding zinc reagent **22**. Quenching with ethyl 2-(bromomethyl)acrylate (Villieras, J.; Rambaud, M. *Org. Synth.* **1988**, 66, 220) (after addition of $\text{CuCN}\cdot 2\text{LiCl}$) leads to the allyled derivative **23** in 67% yield. Zincation of methyl 5-nitrofuran-2-carboxylate (**24**) can also be readily carried out using **2** (1.1 equiv) and furnishes the zinc species **25** in 30 min at 25 °C. Allylation with 3-bromocyclohexene (after addition of $\text{CuCN}\cdot 2\text{LiCl}$) gives the furan **26** in 72% yield.

Scheme 5: Zincation of 2-Chloro-3-nitropyridine (**18**), 4-Fluoro-1-methoxy-2-nitrobenzene (**21**) and Methyl 5-nitrofuran-2-carboxylate (**24**) using $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**; 1.1 equiv, 25 °C) and Trapping with Electrophiles



An aldehyde is also well tolerated ((a) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, 43, 1017. (b) Gong, L.-Z.; Knochel, P. *Synlett* **2005**), 267 Thus, benzo[*b*]thiophene-3-carbaldehyde (**27**) can be converted to the zinc species **28** at 25 °C using $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**; 1.1 equiv) within 30 min. The formation of a subsequent carbon-carbon bond is also easily carried out by a Negishi (Negishi, E.; *Acc. Chem. Res.* **1982**, 15, 340) cross-coupling and a Sonogashira ((a) Benderitter, P.; de Araujo, J. X. Jr.; Schmitt, M.; Bourguignon, J. J. *Tetrahedron* **2007**, 63, 12465. (b) Kim, J. T.; Gevorgyan, V. *Org. Lett.* **2002**, 4, 4697. (c) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 50, 4467. (d) Sonogashira, K. *Comprehensive Organic Synthesis* Pergamon Press: New York, 1991, Vol. 3, reaction giving the aryl heterocycles **29a-c** in 63-92% yield.

Scheme 6: Zincation of Benzo[*b*]thiophene-3-carbaldehyde (**27**) using $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**; 1.1 equiv; 25 °C) and Trapping with Electrophiles



2) Experimental Procedures and Analytical Data

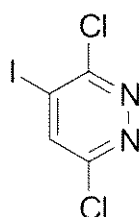
Typical Procedure 1: Preparation of the reagent $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**):

A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly 2,2,6,6-tetramethylpiperidine (10.22 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to -40 °C and *n*-BuLi (2.4 M in hexane, 25 mL, 60 mmol) was dropwise added. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. ZnCl_2 (1.0 M in THF, 66 mL, 66 mmol) was dropwise added and the resulting solution was stirred for 30 min at -10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared $\text{TMPZnCl}\cdot\text{LiCl}$ (**2**) solution was titrated prior to use at 25 °C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.3 M in THF was obtained.

Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with $\text{TMPZnCl}\cdot\text{LiCl}$ (TP 2):

A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirring bar and a septum was charged with the zinc base (**2**; 1.1 equiv). After setting the desired temperature (Table 1), a solution of the corresponding arene (1.0 mmol) in dry THF (2 mL) was dropwise added and stirred at the same temperature. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I₂ in dry THF.

Synthesis of 3,6-dichloro-4-iodopyridazine (5a):



3,6-Dichloropyridazine (**3**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. I₂ (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with a sat. aq. Na₂S₂O₃ solution (10 mL) and with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **5a** (231 mg, 84%) as a colourless solid.

m.p.: 145.1 – 146.6 °C.

¹H-NMR (300 MHz, CDCl₃) δ: 8.06 (s, 1 H).

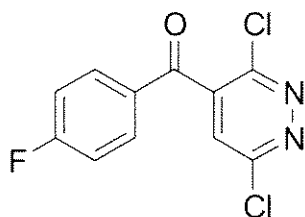
¹³C-NMR (75 MHz, CDCl₃) δ: 159.7, 153.9, 139.7, 105.4.

MS (70 eV, EI) *m/z* (%): 274 (95) [M⁺], 127 (23), 123 (10), 121 (10), 119 (100), 86 (15), 84 (43), 49 (8).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3092, 3020, 1796, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 588, 564.

HRMS (EI) for C₄HCl₂IN₂ (273.8561): 273.8538.

Synthesis of (3,6-dichloropyridazin-4-yl)(4-fluorophenyl)methanone (5b):



3,6-Dichloropyridazine (**3**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. After cooling down to –20 °C, CuCN·2LiCl (1.0 M in THF, 1.1 mmol, 1.1 equiv) was added and the resulting mixture was stirred for 30 min at this temperature. 4-Fluorobenzoyl chloride (317 mg, 2.0 mmol) was then slowly added and the resulting mixture was allowed to warm up slowly to 10 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:1) furnished compound **5b** (259 mg, 96%) as a white solid.

m.p.: 71.1 – 72.6 °C.

¹H-NMR (400 MHz, CDCl₃) δ: 7.79-7.83 (m, 2 H), 7.51 (s, 1 H), 7.19-7.24 (m, 2 H).

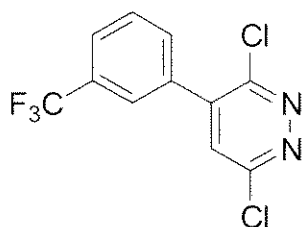
¹³C-NMR (100 MHz, CDCl₃) δ: 187.4, 167.0 (d, *J* (C-F) = 259.9 Hz), 156.3, 151.5, 139.6, 132.8 (d, *J* (C-F) = 9.9 Hz), 130.4 (d, *J* (C-F) = 3.1 Hz), 127.7, 116.8 (d, *J* (C-F) = 22.6 Hz).

MS (70 eV, EI) *m/z* (%): 270 (11) [M⁺], 123 (100), 95 (19).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3067, 2927, 2358, 1917, 1673, 1590, 1504, 1414, 1344, 1319, 1256, 1237, 1178, 1157, 1140, 1103, 1041, 1009, 967, 955, 909, 849, 841, 818, 795, 760, 753, 683, 659, 650, 645, 638, 633, 625, 620, 614, 606, 602.

HRMS (EI) for C₁₁H₅Cl₂FN₂O (269.9763): 269.9762.

Synthesis of 3,6-dichloro-4-(3-(trifluoromethyl)phenyl)pyridazine (**5c**):



3,6-Dichloropyridazine (**3**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was

then stirred at this temperature for 30 min according to **TP 2**. Pd(dba)₂ (17 mg, 3 mol%) and P(o-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzomethyltrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **5c** (243 mg, 83%) as a colourless solid.

m.p.: 93.0 – 94.9 °C.

¹H-NMR (400 MHz, CDCl₃) δ: 7.66-7.81 (m, 4 H), 7.53 (s, 1 H).

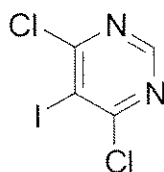
¹³C-NMR (100 MHz, CDCl₃) δ: 156.1, 154.4, 143.3, 141.2, 133.9, 131.5 (q, *J* (C-F) = 33.0 Hz), 129.6 (2), 128.3, 127.0 (q, *J* (C-F) = 3.8 Hz), 125.7 (q, *J* (C-F) = 3.8 Hz), 123.4 (q, *J* (C-F) = 272.5 Hz).

MS (70 eV, EI) *m/z* (%): 294 (60), 292 (100) [M⁺], 266 (17), 264 (25), 229 (28), 206 (16), 204 (49), 194 (21), 169 (13), 138 (10), 136 (24), 113 (25), 59 (18).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3048, 2359, 1743, 1614, 1558, 1485, 1435, 1361, 1323, 1309, 1281, 1241, 1226, 1214, 1167, 1144, 1109, 1097, 1078, 1060, 1042, 1001, 933, 917, 903, 884, 803, 782, 755, 709, 697, 660, 645, 639, 632, 625, 620, 614, 606, 601.

HRMS (EI) for C₁₁H₅Cl₂F₃N₂ (291.9782): 291.9785.

Synthesis of 4,6-dichloro-5-iodo-pyrimidine (**8a**):



4,6-Dichloropyrimidine **6** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. I₂ (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with a sat. aq. Na₂S₂O₃ solution (10 mL) and with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:4) furnished compound **8a** (227 mg, 83%) as a colourless solid.

m.p.: 134.9-136.5 °C.

¹H NMR (300 MHz, CDCl₃) δ: 8.65 (s, 1 H).

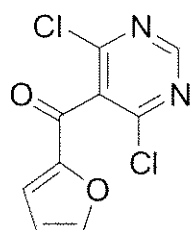
¹³C NMR (75 MHz, CDCl₃) δ: 166.6, 156.8, 98.9.

MS (70 eV, EI) *m/z* (%): 274 (100) [M⁺], 239 (27), 97 (12), 83 (12), 57 (21).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2923, 2855, 1900, 1499, 1386, 11341, 1296, 1214, 1080, 1014, 790, 763, 745.

HRMS (EI) for C₄HCl₂N₂ (273.8561): 273.8565.

Synthesis of (4,6-dichloropyrimidin-5-yl)(furan-2-yl)methanone (8b):



4,6-Dichloropyrimidine **6** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at -20 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, furan-2-carbonyl chloride (261 mg, 2.0 mmol) was dropwise added at -20 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (30 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane 1:1) furnished **8b** as a colourless solid (172 mg, 71%).

m.p.: 143.6 – 145.4 °C.

¹H NMR (400 MHz, CDCl₃) δ: 8.88 (s, 1 H), 7.70 (m, 1 H), 7.28 (m, 1 H), 6.66 (m, 1 H).

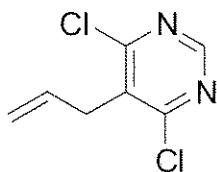
¹³C NMR (100 MHz, CDCl₃) δ: 175.6, 158.8, 158.4, 150.8, 149.0, 130.9, 121.5, 113.5.

MS (70 eV, EI) *m/z* (%): 242 (48) [M⁺], 167 (49), 95 (100), 58 (21), 43 (33).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3133, 2969, 2359, 2340, 1738, 1636, 1558, 1540, 1512, 1450, 1403, 1375, 1361, 1297, 1230, 1216, 1168, 1123, 1083, 1032, 956, 904, 888, 878, 815, 789, 781, 746, 738, 668, 626, 615, 609.

HRMS (EI) for C₉H₄Cl₂N₂O₂ (241.9650): 241.9653.

Synthesis of 5-allyl-4,6-dichloropyrimidine (8c):



4,6-Dichloropyrimidine **6** (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. CuCN·2LiCl (1 M in THF; 0.05 mL, 5 mol %) was then slowly added at -20 °C. Allyl bromide (242 mg, 2.0 mmol) was then slowly added at -60 °C. The resulting mixture was then allowed to warm up slowly to 0 °C for 4 h. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (5 × 30 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane 1:2) furnished **8c** as a colourless solid (215 mg, 89%).

¹H NMR (300 MHz, CDCl₃) δ: 8.64 (s, 1 H), 5.80–5.90 (m, 1 H), 5.09–5.18 (m, 2 H), 3.64 (dt, ³J = 6.4 Hz, ⁴J = 1.4 Hz, 2 H).

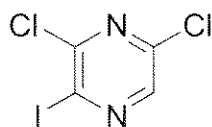
¹³C NMR (75 MHz, CDCl₃) δ: 162.0, 155.8, 130.9, 130.6, 118.2, 34.0.

MS (70 eV, EI) *m/z* (%): 188 (70) [M⁺], 125 (22), 117 (44), 90 (59), 64 (35), 49 (43), 41 (100).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 2360, 1739, 1639, 1539, 1513, 1435, 1406, 1375, 1348, 1313, 1290, 1200, 1162, 1129, 1090, 989, 929, 906, 839, 777, 687, 668, 627, 621, 616.

HRMS (EI) for C₇H₆Cl₂N₂ (187.9908): 187.9913.

Synthesis of 3,5-dichloro-2-iodopyrazine (11a):



2,6-Dichloropyrazine (**9**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. I₂ (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with a sat. aq. Na₂S₂O₃ solution (10 mL) and with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-

chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **11a** (251 mg, 90%) as a colourless solid.

m.p.: 101.3 – 103.0 °C.

¹H-NMR (300 MHz, CDCl₃) δ: 8.30 (s, 1 H).

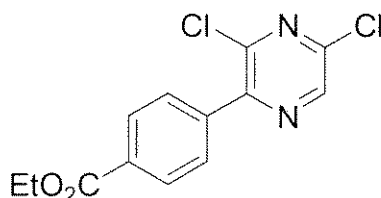
¹³C-NMR (75 MHz, CDCl₃) δ: 153.1, 146.9, 142.4, 115.7.

MS (70 eV, EI) *m/z* (%): 274 (100) [M⁺], 147 (75), 127 (18), 86 (32), 57 (21), 44 (94).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 2633, 2281, 1784, 1738, 1510, 1491, 1379, 1353, 1323, 1274, 1230, 1217, 1205, 1175, 1162, 1143, 1018, 893, 843, 655, 634, 618, 611, 604.

HRMS (EI) for C₄HCl₂N₂ (273.8561): 273.8555.

Synthesis of ethyl 4-(3,5-dichloropyrazin-2-yl)benzoate (**11b**):



2,6-Dichloropyrazine (**9**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. Pd(dba)₂ (17 mg, 3 mol%) and P(*o*-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of ethyl 4-iodobenzoate (359 mg, 1.3 mmol), were then transferred *via* cannula to the reaction mixture. The reaction mixture was stirred at 25 °C for 1.5 h. with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **11b** (251 mg, 87%) as a colourless solid.

m.p.: 88.5 – 90.0 °C.

¹H-NMR (300 MHz, CDCl₃) δ: 8.59 (s, 1 H), 8.14 (d, *J* = 8.6 Hz, 2 H), 7.84 (d, *J* = 8.6 Hz, 2 H), 4.40 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

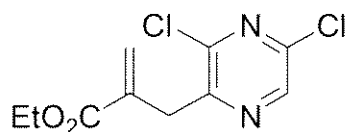
¹³C-NMR (75 MHz, CDCl₃) δ: 165.8, 150.1, 145.9, 142.0, 139.0, 131.6, 129.4 (2), 61.2, 14.3.

MS (70 eV, EI) *m/z* (%): 296 (32) [M⁺], 270 (24), 268 (38), 251 (100), 223 (26).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3086, 3005, 2985, 2359, 1966, 1708, 1611, 1569, 1537, 1507, 1482, 1466, 1446, 1423, 1408, 1366, 1310, 1283, 1263, 1190, 1175, 1140, 1131, 1114, 1098, 1028, 1021, 1009, 915, 858, 843, 786, 758, 719, 698, 657, 634, 621, 616, 610, 602.

HRMS (EI) for C₁₃H₁₀Cl₂N₂O₂ (296.0119): 296.0119.

Synthesis of ethyl 2-((3,5-dichloropyrazin-2-yl)methyl)acrylate (11c**):**



2,6-Dichloropyrazine (**9**) (149 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. After cooling down to -50 °C, ethyl 2-(bromomethyl)acrylate (230 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added and the resulting mixture was allowed to warm up slowly to -20 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:3) furnished compound **11c** (187 mg, 72%) as a colourless oil.

¹H-NMR (300 MHz, CDCl₃) δ: 8.38 (s, 1 H), 6.34 (s, 1 H), 5.56 (s, 1 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.92 (s, 2 H), 1.21 (t, *J* = 7.1 Hz, 3 H).

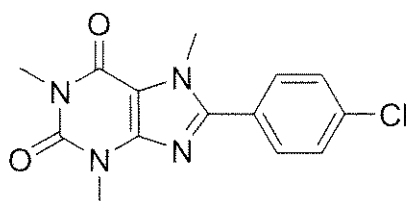
¹³C-NMR (75 MHz, CDCl₃) δ: 166.0, 151.5, 146.8, 145.0, 141.5, 136.0, 127.6, 60.9, 36.7, 14.0.

MS (70 eV, EI) *m/z* (%): 261 (100) [M⁺-H], 163 (10).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 2359, 1738, 1503, 1385, 1342, 1294, 1226, 1215, 1084, 1013, 987, 954, 795, 764, 749, 667, 621, 615, 608, 603.

HRMS (ESI) for C₁₀H₁₀Cl₂N₂O₂ (260.0119 (M⁺-H)): 261.0196.

Synthesis of 8-(4-chlorophenyl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (14a**):**



TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) was added to a solution of 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (**12**) (194 mg, 1.0 mmol) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for max. 5 min. Pd(dba)₂ (17 mg, 3 mol%) and P(*o*-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-

iodobenzene (310 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 $\times$ 50 mL) and dried over anhydrous Na_2SO_4 . After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH_2Cl_2 /ether, 1:1) furnished compound **14a** (226 mg, 74%) as a colourless solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 7.62 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H), 4.03 (s, 3 H), 3.59 (s, 3 H), 3.39 (s, 3 H).

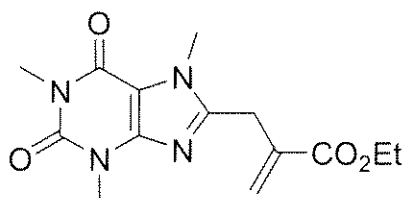
$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ : 155.4, 151.5, 150.7, 148.1, 136.7, 130.4, 129.2, 126.7, 108.6, 33.9, 29.8, 28.0.

MS (70 eV, EI) m/z (%): 304 (100) [M^+], 82 (23), 67 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2969, 1738, 1694, 1646, 1605, 1569, 1538, 1473, 1454, 1430, 1408, 1374, 1288, 1229, 1216, 1180, 1108, 1090, 1074, 1030, 1008, 977, 835, 803, 759, 749, 739, 730, 708, 685, 671, 650, 645, 639, 632, 625, 620, 614, 606, 601.

HRMS (ESI) for $\text{C}_{14}\text{H}_{13}\text{ClN}_4\text{O}_2$ (304.0727): 304.0722.

Synthesis of ethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)methyl)acrylate (14b**):**



TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) was added to a solution of 1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (**12**) (194 mg, 1.0 mmol) in THF (2 mL) at 25 °C and the reaction mixture was then stirred at this temperature for max. 5 min. After cooling down to -50 °C, ethyl 2-(bromomethyl)acrylate (230 mg, 1.2 mmol) and $\text{CuCN}\cdot 2\text{LiCl}$ (1.0 M solution in THF, 5 drops) were added and the resulting mixture was allowed to warm up slowly overnight. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 $\times$ 50 mL) and dried over anhydrous Na_2SO_4 . After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH_2Cl_2 /ether, 1:1) furnished compound **14b** (211 mg, 69%) as a colourless solid.

$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 6.28 (s, 1 H), 5.49 (s, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.70 (s, 2 H), 3.45 (s, 3 H), 3.29 (s, 3 H), 1.21 (t, J = 7.1 Hz, 3 H).

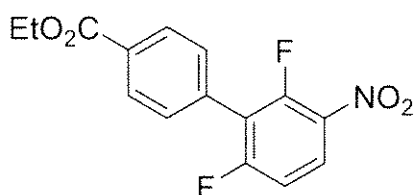
¹³C-NMR (75 MHz, CDCl₃) δ : 165.7, 155.1, 151.4, 150.8, 147.7, 135.0, 127.3, 107.4, 61.1, 31.8, 29.6, 29.3, 27.7, 14.0.

MS (70 eV, EI) m/z (%): 306 (78) [M⁺], 260 (28), 232 (100), 219 (11), 67 (13).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2998, 2956, 2358, 1719, 1697, 1658, 1548, 1497, 1448, 1426, 1402, 1362, 1340, 1293, 1253, 1215, 1162, 1112, 1033, 978, 960, 939, 894, 858, 831, 812, 759, 743, 718, 693, 663, 641, 630, 602.

HRMS (ESI) for C₁₄H₁₈N₄O₄ (306.1328): 306.1320.

Synthesis of ethyl 2',6'-difluoro-3'-nitrophenyl-4-carboxylate (17a):



2,4-Difluoro-1-nitrobenzene **15** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. Pd(dba)₂ (17 mg, 3 mol%) and P(*o*-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), followed by the addition of ethyl 4-iodobenzoate (359 g, 1.3 mmol), were then transferred *via* cannula at -20°C. The resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **17a** (281 mg, 92%) as a colourless solid.

m.p.: 85.0 – 86.7 °C.

¹H NMR (300 MHz, CDCl₃) δ : 8.09-8.18 (m, 1 H), 8.15 (d, J = 8.8 Hz, 2 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.11-7.18 (m, 1 H), 4.40 (q, J = 7.0 Hz, 3 H), 1.40 (d, J = 7.0 Hz, 2 H).

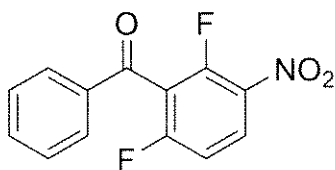
¹³C NMR (75 MHz, CDCl₃) δ : 165.8, 162.5 (dd, J = 6.0 Hz, J = 260.1 Hz), 153.7 (dd, J = 6.0 Hz, J = 260.1 Hz), 131.2 (dd, J = 0.5 Hz, J = 3.9 Hz), 130.2 (dd, J = 1.8 Hz, J = 2.0 Hz), 129.7, 126.6 (dd, J = 1.8 Hz, J = 21.4 Hz), 120.2 (dd, J = 28.1 Hz, J = 1.8 Hz), 112.1 (dd, J = 4.3 Hz, J = 24.7 Hz), 61.3, 14.3.

MS (70 eV, EI) m/z (%): 307 (23) [M⁺], 279 (48), 262 (100), 216 (43), 188 (34), 44 (12).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3101, 2969, 2359, 1712, 1621, 1589, 1567, 1535, 1510, 1472, 1404, 1368, 1341, 1304, 1286, 1269, 1215, 1185, 1170, 1148, 1127, 1103, 1070, 1020, 1011, 948, 879, 857, 824, 778, 756, 714, 702, 667, 636, 620, 607, 602.

HRMS (EI) for C₁₅H₁₁F₂NO₄ (307.0656): 307.0651.

Synthesis of (2,6-difluoro-3-nitrophenyl)(phenyl)methanone (17b):



2,4-Difluoro-1-nitrobenzene **15** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at -40 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at -40 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **17b** (221 mg, 84%) as a colourless solid.

m.p.: 75.8 – 77.2 °C.

¹H NMR (300 MHz, CDCl₃) δ : 7.14-8.31 (m, 7 H).

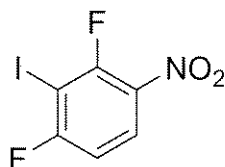
¹³C NMR (75 MHz, CDCl₃) δ : 186.2, 162.2 (dd, *J* = 4.2 Hz, *J* = 262.4 Hz), 153.7 (dd, *J* = 9.0 Hz, *J* = 269.9 Hz), 135.7, 135.1, 133.8, 130.2, 129.6, 129.1, 128.7 (dd, *J* = 2.1 Hz, *J* = 10.9 Hz), 128.5, 119.3 (dd, *J* = 21.9 Hz, *J* = 2.1 Hz).

MS (70 eV, EI) *m/z* (%): 263 (52) [M⁺], 105 (100), 33 (77).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3100, 1912, 1738, 1675, 1619, 1594, 1530, 1496, 1469, 1450, 1351, 1320, 1311, 1280, 1266, 1217, 1180, 1159, 1128, 1100, 1073, 1034, 1027, 1000, 970, 934, 862, 834, 828, 797, 774, 759, 731, 705, 692, 683, 668, 645, 638, 630, 626, 620, 614, 606, 601.

HRMS (EI) for C₁₃H₇F₂NO₃ (263.0394): 263.0393.

Synthesis of 1,3-difluoro-2-iodo-4-nitrobenzene (17c):



2,4-Difluoro-1-nitrobenzene **15** (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 45 min according to **TP 2**. I₂ (381 mg, 1.5 mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with a sat. aq. Na₂S₂O₃ solution (10 mL) and with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:1) furnished compound **17c** (256 mg, 90%) as a colourless solid.

m.p.: 46.1 – 47.5 °C.

¹H NMR (300 MHz, CDCl₃) δ: 8.12-8.17 (m, 1 H), 7.04-7.08 (m, 1 H).

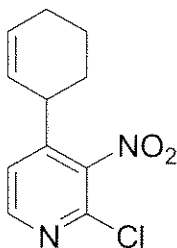
¹³C NMR (75 MHz, CDCl₃) δ: 165.6 (dd, *J* = 5.0 Hz, *J* = 252.6 Hz), 156.4 (dd, *J* = 6.9 Hz, *J* = 264.1 Hz), 127.7 (dd, *J* = 2.3 Hz, *J* = 10.3 Hz), 111.6 (dd, *J* = 4.2 Hz, *J* = 26.1 Hz), 74.3 (dd, *J* = 29.2 Hz, *J* = 1.9 Hz).

MS (70 eV, EI) *m/z* (%): 285 (100) [M⁺], 258 (17), 239 (19), 227 (17), 167 (25), 149 (66), 112 (58), 71 (11), 57 (12), 44 (12).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3098, 2926, 2855, 2359, 1916, 1739, 1602, 1584, 1529, 1463, 1425, 1336, 1301, 1277, 1218, 1147, 1105, 1011, 860, 827, 751, 698, 669, 621, 616.

HRMS (EI) for C₆H₂F₂INO₂ (284.9098): 284.9094.

Synthesis of 2-chloro-4-cyclohex-2-enyl-3-nitro-pyridine (**20**):



2-Chloro-3-nitropyridine (**18**) (159 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was

then stirred at this temperature for 30 min according to **TP 2**. After cooling down to -50 °C, 3-bromo-cyclohexene (192 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 0.05 mL, 0.05 mmol) were added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:1) furnished 2-chloro-4-cyclohex-2-enyl-3-nitro-pyridine (**20**) (173 mg, 73%) as a colourless solid.

m.p.: 54.5 – 55.4 °C.

¹H-NMR (300 MHz, CDCl₃) δ: 8.44 (d, ³J = 5.1 Hz, 1 H), 7.32 (d, ³J = 5.1 Hz, 1 H), 6.07 (ddd, ³J = 10.0 Hz, ³J = 6.1 Hz, ⁴J = 3.7 Hz, 1 H), 5.54 (dd, ³J = 10.0, ⁴J = 1.9 Hz, 1 H), 3.46 (m, 1 H), 2.09 (m, 3 H), 1.76 (m, 1 H), 1.64 (m, 1 H), 1.51 (m, 1 H).

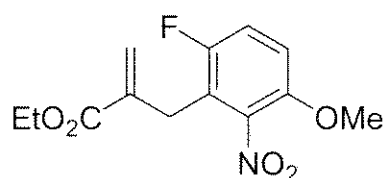
¹³C-NMR (75 MHz, CDCl₃) δ: 150.2, 150.0, 146.5, 141.8, 131.9, 125.9, 123.3, 37.4, 31.3, 24.7, 20.8.

MS (70 eV, EI) *m/z* (%): 237 (3) [M⁺-H], 223 (31), 221 (100), 203 (48), 193 (48), 185 (20), 181 (45), 167 (32), 165 (31), 157 (21), 129 (29), 128 (31), 115 (21), 77 (35), 51 (22), 41 (34).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2939, 1589, 1539, 1446, 1361, 1347, 1231, 1137, 1041, 973, 918, 890, 855, 845, 757, 723, 691, 616.

HRMS (EI) for C₁₁H₁₁ClN₂O₂ (237.0431 [M⁺-H]): 237.0424 [M⁺-H].

Synthesis of ethyl 2-(6-fluoro-3-methoxy-2-nitrobenzyl)acrylate (**23**):



4-Fluoro-1-methoxy-2-nitrobenzene (**21**) (171 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 6 h according to **TP 2**. After cooling down to -50 °C, ethyl 2-(bromomethyl)acrylate (230 mg, 1.2 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added at -40 °C and the resulting mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:3) furnished compound **23** (189 mg, 67%) as a colourless oil.

¹H-NMR (300 MHz, CDCl₃) δ : 7.15 (m, 1 H), 8.89-8.93 (m, 1 H), 6.24 (s, 1 H), 5.31 (s, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.63 (bs, 2 H), 1.27 (t, J = 7.1 Hz, 3 H).

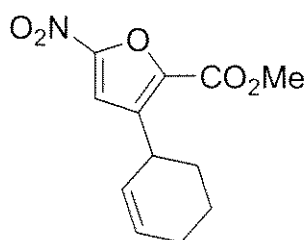
¹³C-NMR (75 MHz, CDCl₃) δ : 165.9, 154.3 (d, J = 243.6 Hz), 147.1 (d, J = 2.8 Hz), 136.2 (d, J = 0.8 Hz), 126.3 (d, J = 0.8 Hz), 120.0 (d, J = 21.9 Hz), 117.6, 117.3, 111.7 (d, J = 8.3 Hz), 61.1, 56.7, 26.9 (d, J = 2.9 Hz), 14.1.

MS (70 eV, EI) m/z (%): 283 (1) [M⁺], 237 (100), 209 (88), 192 (58), 166 (20), 149 (21), 133 (16), 121 (13), 99 (11).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 2359, 1738, 1503, 1385, 1342, 1294, 1226, 1215, 1084, 1013, 987, 954, 795, 764, 749, 667, 621, 615, 608, 603.

HRMS (ESI) for C₁₃H₁₄FNO₅ (283.0856): 283.0845.

Synthesis of methyl 3-(cyclohex-2-enyl)-5-nitrofuran-2-carboxylate (**26**):



Methyl 5-nitrofuran-2-carboxylate (**24**) (171 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. After cooling down to -50 °C, 3-bromocyclohexene (209 mg, 1.3 mmol) and CuCN·2LiCl (1.0 M solution in THF, 5 drops) were added and the resulting mixture was stirred for 1 h at this temperature. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **26** (179 mg, 72%) as a yellowish oil.

¹H-NMR (400 MHz, CDCl₃) δ : 7.20 (s, 1 H), 5.94 (m, 1 H), 5.56 (m, 1 H), 4.10 (m, 1 H), 3.92 (s, 3 H), 2.07 (m, 3 H), 1.50-1.69 (m, 3 H).

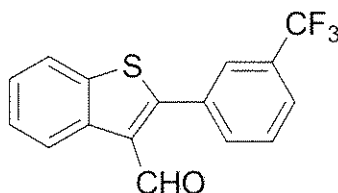
¹³C-NMR (100 MHz, CDCl₃) δ : 157.5, 142.6, 133.9, 130.4, 126.2, 120.1, 52.8, 32.2, 29.0, 24.6, 20.5.

MS (70 eV, EI) m/z (%): 252 (2) [M⁺], 234 (100), 217 (55), 146 (10).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2936, 2356, 1729.35, 1629, 1594, 1532, 1502, 1435, 1398, 1338, 1288, 1226, 1206, 1110, 1091, 985, 925, 880, 848, 819, 799, 763, 725, 668, 634, 622.

HRMS (EI) for C₁₂H₁₃NO₅ (251.0794): 251.0794.

Synthesis of 2-(3-(trifluoromethyl)phenyl)benzo[b]thiophene-3-carbaldehyde (29a):



Benzo[b]thiophene-3-carbaldehyde (**27**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. Pd(dba)₂ (17 mg, 3 mol%) and P(o-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzomethyltrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:3) furnished compound **29a** (281 mg, 92%) as a colourless solid.

m.p.: 102.8 – 104.2 °C.

¹H-NMR (400 MHz, CDCl₃) δ: 10.02 (s, 1 H), 8.79 (m, 1 H), 7.45-7.87 (m, 7 H).

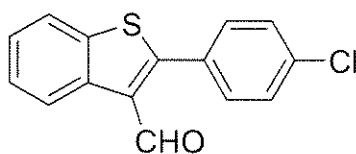
¹³C-NMR (100 MHz, CDCl₃) δ: 185.9, 158.0, 138.0, 136.8, 133.7, 132.4, 131.5 (q, *J* (C-F) = 33.0 Hz), 130.7, 129.5, 127.0 (q, *J* (C-F) = 3.8 Hz), 126.6 (q, *J* (C-F) = 3.8 Hz), 126.5, 126.2, 123.5 (q, *J* (C-F) = 272.5 Hz), 121.7.

MS (70 eV, EI) *m/z* (%): 306 (97) [M⁺], 305 (100), 278 (12), 257 (13), 237 (28), 233 (18), 208 (29), 160 (13), 44 (40).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3068, 2866, 2359, 1926, 1745, 1669, 1590, 1520, 1483, 1459, 1438, 1421, 1392, 1351, 1325, 1310, 1288, 1265, 1217, 1178, 1156, 1118, 1097, 1092, 1073, 1051, 1018, 1000, 994, 966, 947, 933, 907, 868, 863, 812, 773, 754, 733, 703, 679, 653, 641, 633, 620, 608, 603.

HRMS (EI) for C₁₆H₉F₃OS (306.0326): 306.0326.

Synthesis of 2-(4-chlorophenyl)benzo[b]thiophene-3-carbaldehyde (29b):



Benzo[b]thiophene-3-carbaldehyde (**27**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. Pd(dba)₂ (17 mg, 3 mol%) and P(o-furyl)₃ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (310 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was then quenched with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:3) furnished compound **29b** (236 mg, 87%) as a colourless solid.

m.p.: 99.7 – 101.4 °C.

¹H-NMR (300 MHz, CDCl₃) δ: 10.02 (s, 1 H), 8.76 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.42-7.54 (m, 6 H).

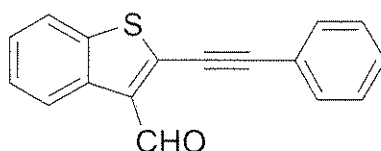
¹³C-NMR (75 MHz, CDCl₃) δ: 186.2, 158.9, 137.8, 136.9, 136.4, 131.6, 130.3, 130.0, 129.2, 126.4, 126.0, 125.2, 121.6.

MS (70 eV, EI) *m/z* (%): 272 (100) [M⁺], 237 (54), 208 (34), 165 (12), 118 (20), 104 (23).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3054, 2969, 2867, 2362, 1947, 1739, 1671, 1590, 1562, 1517, 1482, 1457, 1431, 1407, 1397, 1346, 1265, 1218, 1187, 1161, 1135, 1109, 1091, 1050, 1020, 1012, 971, 952, 938, 846, 830, 813, 748, 723, 716, 710, 698, 667, 638, 616, 610, 603.

HRMS (EI) for C₁₅H₉ClOS (272.0063): 272.0057.

Synthesis of 2-(phenylethynyl)benzo[b]thiophene-3-carbaldehyde (**29c**):



Benzo[b]thiophene-3-carbaldehyde (**27**) (162 mg, 1.0 mmol) in THF (2 mL) was added to a solution of TMPZnCl·LiCl (**2**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min according to **TP 2**. I₂ (381 mg, 1.5

mmol) dissolved in dry THF (2 mL) was then dropwise added and the resulting mixture was stirred for 0.5 h. To the solution of freshly generated in situ 2-iodobenzo[b]thiophene-3-carbaldehyde, NEt₃ (7 mL), CuI (8 mg, 4 mol%), Pd(dba)₂ (17 mg, 3 mol%) and P(o-furyl)₃ (14 mg, 6 mol%) in THF (2 mL) and phenylacetylene (254 mg, 1.5 mol, 1.5 equiv) were successively slowly added. The reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with a sat. aq. Na₂S₂O₃ solution (10 mL) and with a sat. aq. NH₄Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated *in vacuo*. Purification by flash-chromatography (CH₂Cl₂/*n*-pentane, 1:2) furnished compound **29c** (165 mg, 63%) as a yellowish solid.

m.p.: 104.9 – 106.5 °C.

¹H-NMR (400 MHz, CDCl₃) δ: 10.47 (s, 1 H), 8.69 (m, 1 H), 7.77 (m, 1 H), 7.60 (m, 2 H), 7.38-7.51 (m, 5 H).

¹³C-NMR (100 MHz, CDCl₃) δ: 185.6, 138.9, 138.5, 135.9, 135.2, 131.8, 129.8, 128.6, 126.8, 126.5, 124.9, 121.6, 121.3, 102.9, 80.0.

MS (70 eV, EI) *m/z* (%): 262 (100) [M⁺], 234 (38), 232 (13), 202 (11), 189 (13).

IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2969, 2832, 2359, 2340, 2203, 1739, 1661, 1587, 1569, 1507, 1481, 1458, 1442, 1427, 1361, 1316, 1293, 1250, 1229, 1216, 1177, 1162, 1141, 1119, 1070, 1059, 1043, 1015, 997, 953, 918, 868, 748, 737, 697, 687, 668, 630, 621, 616, 610.

HRMS (EI) for C₁₇H₁₀OS (262.0452): 262.0459.

Claims

1. A reagent of the general formula
 $R^1R^2N-ZnY LiY$ (I)
wherein
 R^1 , R^2 are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silyl derivatives thereof; and R^1 and R^2 together can be part of a cyclic or polymeric structure; and wherein at least one of R^1 and R^2 is other than H;
Y is selected from the group consisting of F; Cl; Br; I; CN; SCN; NCO; $HalO_n$, wherein $n = 3$ or 4 and Hal is selected from Cl, Br and I; NO_3 ; BF_4 ; PF_6 ; H; a carboxylate of the general formula R^xCO_2 ; an alcoholate of the general formula OR^x ; a thiolate of the general formula SR^x ; $R^xP(O)O_2$; or $SCOR^x$; or $SCSR^x$; O_nSR^x , wherein $n = 2$ or 3 ; or NO_n , wherein $n = 2$ or 3 ; and a derivative thereof; wherein R^x is a substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or derivatives thereof, or H; or as adduct with a solvent.
2. A reagent according to claim 1 wherein R^1 , R^2 are cyclic and substituted by R^3 , and R^4 that are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silyl derivatives thereof; and R^1 and R^2 together, or R^3 and R^4 together can be part of a cyclic or polymeric structure; and wherein at least one of R^1 and R^2 and at least one of R^3 and R^4 is other than H.
3. A reagent according to claim 1 or 2 wherein
 $R^1R^2N-ZnY LiY$ (I) is
2,2,6,6-Tetramethylpiperide Zinc Chloride Lithium Chloride.
4. Solution of the reagent according to claim 1 to 3 in a solvent.
5. Solution of the reagent according to claim 1 to 4 wherein the solvent is polar and aprotic.

6. Solution according to claim 5, wherein the solvent is selected from cyclic, linear or branched mono or polyethers, thioethers, amines, phosphines, and derivatives thereof containing one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofuran (THF), 2-methyltetrahydrofuran, dibutyl ether, diethyl ether, tert-butylmethyl ether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropyl amine, dimethylsulfide, dibutylsulfide; cyclic amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogens are replaced by a halogen, preferably dichloromethane, 1,2-dichloroethane, CCl₄; urea derivatives, preferably N,N'-dimethylpropyleneurea (DMPU); aromatic, heteroaromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorus triamide (HMPA), CS₂; or combinations thereof.

7. Process for the preparation of a mixed Zn/Li amide comprising reacting in a solvent a primary or secondary amine with a lithium alkyl.

8. Process for the preparation of a reagent having the general formula

$$R^1R^2N-ZnY LiY \text{ (I)}$$
 wherein
 R¹, R² are, independently, selected from H, substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or silicon derivatives thereof; and R¹ and R² together can be part of a cyclic or polymeric structure; and wherein at least one of R¹ and R² is other than H;
 Y is selected from the group consisting of F; Cl; Br; I; CN; SCN; NCO; HalO_n, wherein n = 3 or 4 and Hal is selected from Cl, Br and I; NO₃; BF₄; PF₆; H; a carboxylate of the general formula R^xCO₂; an alcoholate of the general formula OR^x; a thiolate of the general formula SR^x; R^xP(O)O₂; or SCOR^x; or SCSR^x; O_nSR^x, wherein n = 2 or 3; or NO_n, wherein n = 2 or 3; and a derivative thereof;
 wherein R^x is a substituted or unsubstituted aryl or heteroaryl containing one or more heteroatoms, linear, branched or cyclic, substituted or unsubstituted alkyl, alkenyl, alkynyl, or derivatives thereof, or H;
 comprising the reaction in a solvent of R¹R²N-H with R^xLi in the presence of ZnY₂ and X is defined as Y above.

9. Process according to claim 8, wherein X and Y are independently or both Cl, Br or I, and preferably Cl.
10. Process according to any of the claims 8 or 9, wherein the lithium organyl reagent is sec-butyl-Li.
11. Process according to any of the claims 8 to 10, wherein the solvent is selected from cyclic, linear or branched mono or polyethers, thioethers, amines, phosphines, and derivatives thereof containing one or more additional heteroatoms selected from O, N, S and P, preferably tetrahydrofuran (THF), 2-methyltetrahydrofuran, dibutyl ether, diethyl ether, tert-butylmethyl ether, dimethoxyethane, dioxanes, preferably 1,4-dioxane, triethylamine, ethyldiisopropylamine, dimethylsulfide, dibutylsulfide; cyclic amides, preferably N-methyl-2-pyrrolidone (NMP), N-ethyl-2-pyrrolidone (NEP), N-butyl-2-pyrrolidone (NBP); cyclic, linear or branched alkanes and/or alkenes wherein one or more hydrogens are replaced by a halogen, preferably dichloromethane, 1,2-dichloroethane, CCl₄; urea derivatives, preferably N,N'-dimethylpropyleneurea (DMPU); aromatic, hetero aromatic or aliphatic hydrocarbons, preferably benzene, toluene, xylene, pyridine, pentane, cyclohexane, hexane, heptane; hexamethylphosphorus triamide (HMPA), CS₂; or combinations thereof.
12. Use of the reagent according to claim 1 to 6 in a reaction with an electrophile.
13. Use of the reagent according to claim 1 to 6 for the deprotonation of any substrate which can form stabilized or unstabilized carbaniones.
14. Use of the reagent according to claim 1 to 6 for the formation of
 - 3,6-dichloro-4-iodopyridazine,
 - (3,6-dichloropyridazin-4-yl)(4-fluorophenyl)methanone,
 - 3,6-dichloro-4-(3-(trifluoromethyl)phenyl)pyridazine,
 - 4,6-dichloro-5-iodo-pyrimidine,
 - (4,6-dichloropyrimidin-5-yl)(furan-2-yl)methanone,
 - 5-allyl-4,6-dichloropyrimidine,
 - 3,5-dichloro-2-iodopyrazine,
 - ethyl 4-(3,5-dichloropyrazin-2-yl)benzoate,
 - ethyl 2-((3,5-dichloropyrazin-2-yl)methyl)acrylate,
 - 8-(4-chlorophenyl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione,

- ethyl 2-((1,3,7-trimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)methyl)acrylate,
- ethyl 2',6'-difluoro-3'-nitrobiphenyl-4-carboxylate,
- (2,6-difluoro-3-nitrophenyl)(phenyl)methanone,
- 1,3-difluoro-2-iodo-4-nitrobenzene,
- 2-chloro-4-cyclohex-2-enyl-3-nitro-pyridine,
- ethyl 2-(6-fluoro-3-methoxy-2-nitrobenzyl)acrylate,
- methyl 3-(cyclohex-2-enyl)-5-nitrofuran-2-carboxylate,
- 2-(3-(trifluoromethyl)phenyl)benzo[b]thiophene-3-carbaldehyde,
- 2-(4-chlorophenyl)benzo[b]thiophene-3-carbaldehyde or
- 2-(phenylethynyl)benzo[b]thiophene-3-carbaldehyde.