# 2- and 6-Purinylmagnesium Halides in Dichloromethane: Scope and New Insights into the Solvent Influence on the C-Mg Bond

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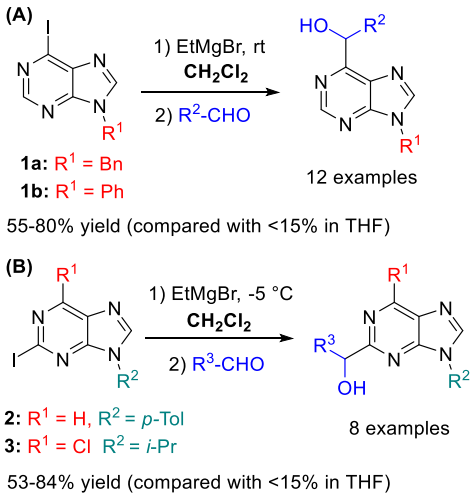
**Abstract:** The generation of positionally stable purin-2- and 6-yl magnesium halides is complicated by the often very rapid isomerization to give the 8-yl Grignards. By conducting the reaction in dichloromethane, we demonstrated that the anion isomerization can be stopped and these stable purin-2- and 6-yl Grignards react directly with a broad scope of aldehydes in good yields. Furthermore, purine functionalization with ketones has been achieved for the first time in the presence of $LaCl_3.2LiCl$. Density functional theory calculations offer a possible explanation of the special role played by solvent in this chemistry and show that in DCM the C-Mg bond has a covalent nature, whereas in THF it is predominantly ionic and much more basic in nature.

## Introduction

Purine is one of the most common heterocycles found in life essential systems such as DNA and RNA, enzyme cofactors (NAD/NADH), and neurotransmitters.[1] This fused imidazo[4,5-*d*]pyrimidine ring system is also an essential structural element in numerous compounds exhibiting a broad spectrum of biological activities ranging from antineoplastic,[2] antimycobacterial[3] and antiviral[4] to anti-inflammatory[5] and immunosuppressive properties[6]. As a consequence, pharmaceutical and agrochemicals industries are interested in preparing synthetic purines bearing one or more substitutions at their peripheral positions.[7] In particular, purines having carbon substituents in position 2,6 and/or 8 are of great interest due to the influence that such a variable functionalization may have in terms of the binding ability to selective biological targets or in tailoring metabolic stability. Among the synthetic approaches able to afford *C*-functionalized purines, the halogen-metal exchange methodology, which generates a purinyl-*C*-anion able to react with an electrophile, potentially represents a very versatile tool for achieving highly functionalized systems.[8]

However, purinyl anions often exhibit poor positional stability which leads to movement of the negative charge towards the more stable position 8,[9] resulting in a complicated mixture of final products. Leonard and, later, Dvořák reported the efficient formation of either 2 or 6 lithio- and magnesio-purinyl halides in ethereal solvents which could be successfully reacted with aldehydes. However, the reactions required very low temperatures between -78 °C and -130 °C in order to inhibit the isomerization process.[9,10] With the aim of achieving a more industrially friendly regioselective *C*-functionalization of the purine scaffold avoiding low temperatures, we recently developed an improved route for the formation of purin-6-yl[11] and purin-2-yl magnesium halides[12] utilizing halogen-metal exchange in dichloromethane. The generation of the Grignard reagent in a non-coordinating solvent such as dichloromethane led to enhanced positional stability of the negative charge allowing reactions to be performed at room temperature for the 6-iodopurines **1a-b** (path A, Scheme 1) and at -5 °C for the experimentally less stable 2-iododerivatives **3a-3b** (path B, Scheme 1). The ensuing C-anions reacted with aldehydes to afford the respective carbinols in good yields but reactions with ketones proceeded only in very low yields. Similar solvent-based effects upon positional C-anion stability were also seen with imidazoyl Grignards.[13]




**Scheme 1**. Previous work in our group

In the present publication we now report our results concerning the effect of using more highly substituted aldehydes and of varying the *N*-9 substituent upon anion stability. In addition, we

have extended the methodology to allow ketones to be used as electrophiles for the first time. Finally, we have conducted quantum mechanical calculations elucidating the role of the solvent in the purin-2- and 6-yl anion stability.

## Results and Discussion

### Expanding the scope of purin-6-yl Grignards

In our previous studies with purin-6-yl Grignards, we had used simple aryl and alkyl aldehydes without additional electrophilic centres.[11] Using purine **1b** as starting material, we have now extended the range of aldehydes to include aldehydes bearing ester or cyano functionality. The Grignard **1b** showed good chemoselectivity and the corresponding carbinols **4** and **5** were isolated in 74 and 76% yield respectively (Table 1, entries 1, 2). Quenching with paraformaldehyde yielded the corresponding primary alcohol **6** in 54 % yield (Table 1, entry, 3). The chemistry also worked well with heteroaromatic aldehydes yielding the desired products **7** and **8** in 63-76% yield (Table 1, Entries 4-5).
Next, the effect of varying the *N*-9 substituent upon purin-6-yl anion stability and reactivity was investigated (Table 1, entries 6-10). We had envisaged that more electronegative substituents might adversely affect the positional stability of the anion. However, the results depicted in Table 1 show that anion stability was excellent for purines containing both electron withdrawing (**1c-d,g**, Table 1, entries 6, 7, 10) and electron donating (**1e-f**, Table 1, entries 8, 9) groups on *N*-9. The desired 6-carbinols **9**-**13** were isolated in 64-75% yield and anion isomerization to position 8 was not observed.
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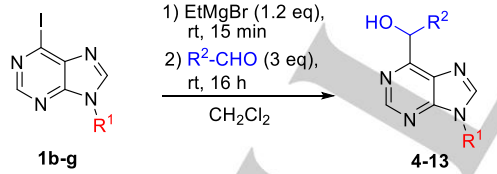
**Table 1.** Scope expansion of purin-6-yl magnesium halides reacting with aldehydes.



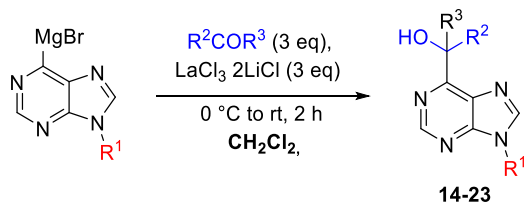

| Entry | $R^1$ | $R^2$-CHO | %Yield (product) |
|---|---|---|---|
| 1 | $C_6H_5$ (**1b**) | *p*-(COOMe)-$C_6H_4$- | 76 (**4**) |
| 2 | $C_6H_5$ (**1b**) | *p*-(CN)$C_6H_4$- | 74 (**5**) |
| 3 | $C_6H_5$ (**1b**) | -H | 54 (**6**) |
| 4 | $C_6H_5$ (**1b**) | 2-Furyl- | 76 (**7**) |
| 5 | $C_6H_5$ (**1b**) | 4-Me-2-thiophenyl- | 63 (**8**) |
| 6[a] | *p*-Cl-$C_6H_4$ (**1c**) | $C_6H_5$- | 68 (**9**) |
| 7[a] | *p*-$CF_3$-$C_6H_4$ (**1d**) | $C_6H_5$- | 75 (**10**) |
| 8[a] | *p*-MeO-$C_6H_4$ (**1e**) | $C_6H_5$- | 66 (**11**) |
| 9[a] | *i*-Pr (**1f**) | $C_6H_5$- | 68 (**12**) |
| 10[a] | $(CH_3)_2NSO_2$ (**1g**) | $C_6H_5$- | 64 (**13**) |

[a] Purine starting materials **1c-f** were synthesized as described in reference 10a. The $Me_2NSO_2$-iodide **1g** was prepared by sulfamoylation of 6-iodopurine **14** with $Me_2NSO_2Cl$, $Et_3N$ in MeCN at 0 °C for 4 h, then 16 h at rt (62%).

### Expanding the scope with ketones

Previous attempts to substitute aldehydes with less reactive electrophiles such as ketones, regardless of whether 6-or 2-iodopurines were used, resulted in complex mixtures of products where the respective carbinols were present only in small amounts (<20% yield for acetophenone). This unsatisfactory result was attributed to *i)* the poorer reactivity of ketones as electrophiles compared to aldehydes and *ii)* a competing reaction in which the purine anion reacted as a base leading to enolate formation. In support of this hypothesis, the aldol condensation product was isolated from several reactions involving acetophenone. It is interesting to note that such products were not observed with alkyl aldehydes, presumably due to their higher electrophilicity.[11,12]
In this context, the use of an additive such as $CeCl_3$ has been reported to suppress basicity and improve the yield of 1,2-addition products with ketones.[14] However, the use of dichloromethane, essential for avoiding the internal anion-isomerization process, limits the use of such salts due to their poor solubility in such apolar solvents. During our screening program, our attention was drawn to the use of the THF-soluble lanthanide complex $LaCl_3$•2LiCl which has been reported to substantially improve reaction yields between Grignard reagents and enolisable ketones in ethereal solvents.[16] Initial attempts to apply this methodology to our system were unsuccessful, but by modifying the experimental procedure by adding a premixed THF solution of the ketone and $LaCl_3$•2LiCl to a solution of the purin-6-yl Grignard reagent in dichloromethane at 0 °C, we were finally able to achieve good conversion for the reaction of purin-6-yl Grignards with ketones. As summarized in Table 2, the new protocol proved to be successful for a series of enolizable aromatic, non-aromatic and heterocyclic ketones affording carbinols **14-23** in 21-55% yield. Yields were not significantly affected by the different substituent on *N*-9 position (*N*-9-phenyl-6-iodo purine **1b,** entry 1,5; *N*-9-benzyl-6-iodopurine **1a**, entry 6-10, Table 2), and in all cases a complete regioselectivity was observed. Whilst the yields appear at first moderate, they are the first example of a direct formation of a 6-tertiary purinyl alcohol through direct addition to ketone substrates.

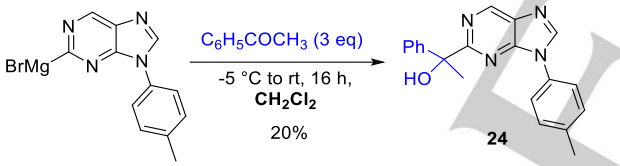
**Table 2.** Scope of the reaction of purin-6-yl magnesium halides with ketones in presence of $LaCl_3$•2LiCl.



| Entry | $R^1$ (starting purine) | $R^2COR^3$ | % Yield (product) |
|---|---|---|---|
| 1 | $C_6H_5$ **(1b)** | $C_6H_5COCH_3$ | 55 (**14**) |
| 2 | $C_6H_5$ **(1b)** | (*i*-Pr)$COCH_3$ | 43 (**15**) |
| 3 | $C_6H_5$ **(1b)** | (*c*-Pr)$COCH_3$ | 35 (**16**) |
| 4 | $C_6H_5$ **(1b)** | $C_6H_5CO$(*i*-Pr) | 44 (**17**) |
| 5 | $C_6H_5$ **(1b)** | (2-Furyl)$COCH_3$ | 21 (**18**) |
| 6 | Bn **(1a)** | $C_6H_5COCH_3$ | 55 (**19**) |
| 7 | Bn **(1a)** | (*i*-Pr)$COCH_3$ | 47 (**20**) |
| 8 | Bn **(1a)** | (*c*-Pr)$COCH_3$ | 29 (**21**) |
| 9 | Bn **(1a)** | $C_6H_5CO$(*i*-Pr) | 40 (**22**) |
| 10 | Bn **(1a)** | (2-Furyl)$COCH_3$ | 29 (**23**) |

[a] THF solution of $LaCl_3$.2LiCl 0.6 M (commercially available).

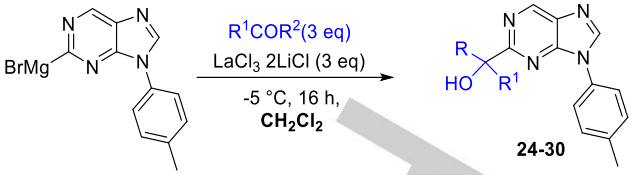
We next sought to apply the above procedure to the less stable purin-2-yl Grignard **2**,[12] and were disappointed to find that the reaction with acetophenone afforded a mixture of decomposed compounds in which the desired product **24** was present only in trace amounts. Our previous work had shown that the purin-2-yl system required lower temperatures than the purin-6-yl series and that THF was especially deleterious to the reaction.[12] Indeed, a reaction performed under our previously described conditions in $CH_2Cl_2$ at -5°C without any lanthanide salt (or THF) provided the desired carbinol **24** in 20% yield (Scheme 2).




**Scheme 2.** purin-2-yl magnesium halide addition to acetophenone without any additive in dichloromethane.

We therefore sought to reduce the amount of THF in the reaction mixture by increasing the concentration of the $LaCl_3$.2LiCl solution from 0.6 to 1.0 M. Under these conditions the lanthanum salt effectively promoted the addition of the halide **2** to acetophenone in dichloromethane at -5°C, increasing the yield of alcohol **24** to 53%, which is more than double the yield obtained without any additive (Table 3, entry 1). Subsequently we were able to expand the scope of this reaction to include a variety of different ketones, which gave products **24-30** in 22-64% yield (Table 3). Only in the case of *o*-nitro-benzophenone did the reaction fail, which is interesting since the reaction with *p*-nitro-benzophenone yielded the corresponding carbinol **25** in 49% yield. Worth to note is that when the $CH_2Cl_2$ was completely replaced with THF, then essentially no carbinol product could be isolated.

**Table 3.** Scope of the reaction of purin-2-yl magnesium halides with ketones in presence of $LaCl_3$.2LiCl[a]




| Entry | $R^1$ | $R^2$ | % Yield (Product) |
|---|---|---|---|
| 1 | $C_6H_5$- | $CH_3$ | 53 (**24**) |
| 2 | *p*-$NO_2$-$C_6H_4$ | $CH_3$ | 49 (**25**) |
| 3 | *p*-OMe-$C_6H_4$ | $CH_3$ | 35 (**26**) |
| 4 | *p*-$CF_3$-$C_6H_4$ | $CH_3$ | 64 (**27**) |
| 5 | (*i*-Pr) | $CH_3$ | 39 (**28**) |
| 7 | 3,4-($CH_2O_2$)-$C_6H_3$ | $CH_3$ | 22 (**29**) |
| 8 | $C_6H_5$- | $C_6H_5$- | 25 (**30**) |

[a] The commercial available 0.6 M THF solution of $LaCl_3$.2LiCl was concentrated up to 1 M.

The structure of carbinol **24** was unambiguously confirmed by an X-Ray crystallographic analysis, which absolutely excludes the possibility of anion isomerization prior to quenching with the acetophenone (Figure 1).

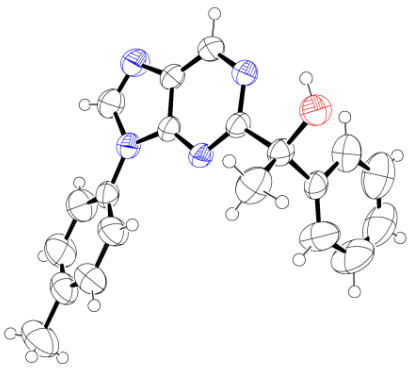


**Figure 1.** X-Ray analysis of compound **24**.[17] Blue sphere: nitrogen atoms; red sphere: oxygen atom; white sphere: carbon atoms.

**Insight into solvent influence on anion stability**

Density Functional Theory (DFT) calculations was conducted in order to investigate anion isomerization and the effect dichloromethane versus THF[18] as reaction solvent. Focusing on the less stable purin-2-yl magnesium halides, we initially compared the acidity of the H atom at positions C2 vs C8 through the indirect study of the stability of the corresponding C-

Mg complexes. These calculations confirm that metal complexes **I-C8** are more stable by a large amount (9 to 18 kcal/mol, Figure 2) compared to the corresponding **I-C2** compounds in both solvents, THF and dichloromethane (monomeric and dimeric structures were analyzed). The naked anion in position C8 is also lower in energy than in C2, confirming the higher acidity of the H atom at C8.

It is important to note that these results show that the C8-Mg complex is thermodynamically preferred if an equilibrium between all possible isomeric compounds exists, but it does not tell us anything about the isomerization process, which could indeed be kinetically disfavored.

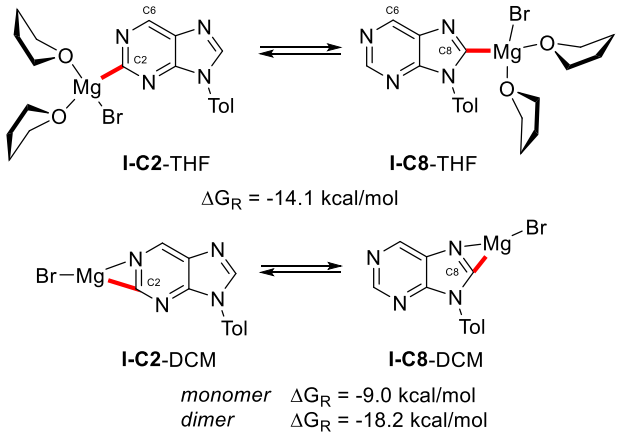
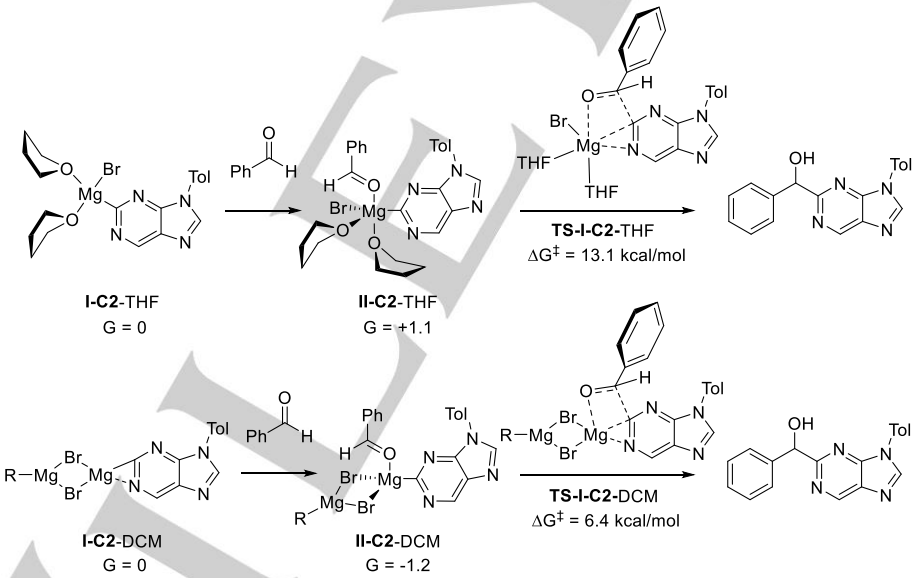



**Figure 2.** Isomerization of the C-Mg bond between C2 and C8 positions. THF: tetrahydrofuran; DCM: dichloromethane.

A second interesting question is about the nature of the C-Mg bond in the different solvent conditions. In dichloromethane, the C-Mg distance in the initial C2-position is 2.05 Å, regardless of the monomeric or dimeric nature of the complex. An interaction between the Mg center and the N1 nitrogen is noted in the computed structure (Scheme 3).




**Scheme 3**. DFT calculations of the benzaldehyde coordination to Mg center in *N*-9-(*p*-toluoyl)purin-2-yl and addition transition state.

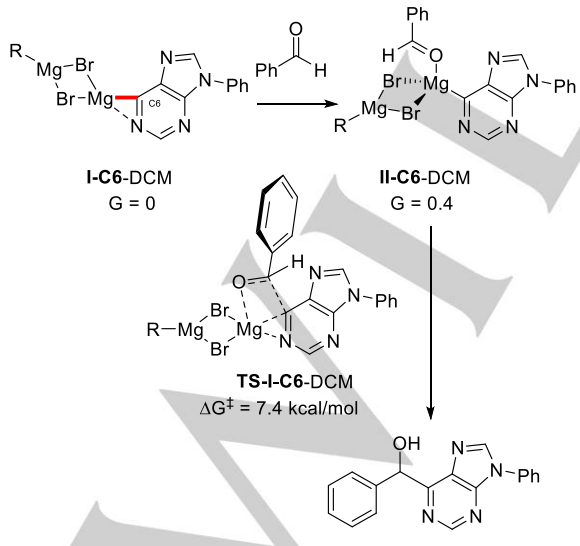
The intermediate **II-C2-DCM** may also explain the negative influence of the nitro group in ortho position of the ketone reagent (discussion on Table 3 results): contrary to a *p*-nitro group, an *o*-nitro substitution could actually disturb the Br-Mg stabilizing interactions represented in **TS-I-C2**, leading to a higher energy transition state.

In contrast, the THF molecules are able to coordinate the Mg through the ether oxygen resulting in a major stabilization of the metallic atom, and a longer C-Mg distance of 2.14 Å. This effect is crucial and ensures a greater degree of charge separation, a more ionic character of the C-Mg bond, and a higher basicity. Thus, the use of $CH_2Cl_2$ leads to a more covalent bond that is less prone to isomerization, while the opposite occurs in THF, partially explaining the easier isomerization from **I-C2**-THF to **I-C8**-THF. The NPA analysis of the structures also points in the same direction, the C2 carbon atom in **I-C2-**THF (C-Mg) being

more negative (-0.173 e) than in **I-C2-**DCM (-0.146 e) and even more significantly, C2 in **I-C2-**THF presents a higher nucleophilicity, showing Fukui indexes of 0.291 (THF) and 0.211 (DCM).

Our initial hypothesis implied that the reactivity of **I-C2** with benzaldehyde in THF would be low enough to allow a good degree of isomerization to **I-C8**, while in $CH_2Cl_2$, the reaction with benzaldehyde should be fast enough to outcompete the isomerization, ensuring the complete formation of the C-2 final isomer. In principle, this idea seems difficult to harmonize with the higher basicity encountered in THF, since it could be assumed that an enhanced basicity of the Mg-complex in THF would also mean a greater nucleophilicity. To shed light on this issue, the corresponding transition states for the C-C bond formation in both solvents were computed. Interestingly, the coordination of benzaldehyde to complex **I-C2**-THF is endothermic, forming an uphill in energy, pentacoordinated **II-C2**-THF intermediate (+1.1 kcal/mol, Scheme 3). The endothermicity arises from the weakening of the THF-Mg interactions in the presence of benzaldehyde. The following transition state (**TS-I-C2-**THF) presents an activation energy of 13.1 kcal/mol. In contrast, the coordination of the aldehyde to the dimer complex **I-C2**-DCM is stabilizing (-1.2 kcal/mol), positively affected by the new Mg-O interaction in **II-C2**-DCM. More interestingly, the transition state **TS-I-C2**-DCM presents a much lower activation barrier, of only 6.4 kcal/mol. This confirms our hypothesis that nucleophilic addition is much faster in dichloromethane than in THF, while the isomerization follows the opposite trend, explaining the formation of the C-2 isomer in dichloromethane and the C2 to C8 isomerization and formation of the C8 isomer in THF.

The reactivity at position C6 in dichloromethane was also analyzed and compared with position C2. Similar geometrical and energetic parameters were found, as can be seen in Scheme 4. The C-Mg distance in **I-C6-DCM** is 2.05 Å. The introduction of benzaldehyde does not significantly alter the energy of the system (0.4 kcal/mol) and the activation barrier is also low (7.4 kcal/mol) and affordable in the reaction conditions.




**Scheme 4.** DFT calculations of the benzaldehyde coordination to Mg center *N*-9-phenylpurin-6-yl and addition transition state. The resulting carbinol is described in reference 11a.

## Conclusion

In summary, in this work we have extended the scope of our halogen-metal exchange protocol for purin-2- and 6-yl Grignards in dichloromethane. In particular, we demonstrated that the stability of the anion is not affected by the electronic properties of the *N*-9-substituent of the purine ring, indeed both electron donating and electron withdrawing groups afforded the respective carbinols **9-13** in excellent yields. Furthermore, we also confirmed that our conditions tolerate aldehydes bearing reactive functionalities like nitrile or ester in reaction with the 6-purinyl-magnesium halide **1b** (Table 1, entries 1-5). Significantly, herein we present the first reported example of positionally stable 2- (Table 3) and 6- (Table 2) purinyl magnesium halides which react with enolizable ketones in dichloromethane when $LaCl_3$.2LiCl is added to the reaction mixture. The corresponding carbinols were obtaining in 21-64% yield, which compares favorably to the very low yields observed when no additives were present, or with the even lower yields obtained when dichloromethane was replaced by THF. The influence of the solvent on the anion stability has been studied using DFT calculations, which indicated a more covalent nature of the C-Mg bond in dichloromethane than in THF. In the latter, the C-Mg bond is more ionic and basic, and these are properties which lead to the instability and anion isomerization seen in this solvent. In conclusion, our results substantially broaden the available synthetic tools for accessing to carbon-substituted purines, a very important class of compounds for the agrochemical and pharmaceutical industry.

## Experimental Section

**General Methods:** All reactions were performed in hot-gun-dried round-bottom flasks and the reactions were conducted under nitrogen or argon atmosphere. Anhydrous solvents were stored under nitrogen or argon atmosphere. Reactions were monitored through thin layer chromatography (TLC) performed using silica gel coated aluminium plates and they were visualized by exposure toultraviolet light. Purification of the products was performed via flash column chromatography using silica gel (ICN SiliTech, 32-63 or Sigma-Aldrich 60 Å, particle size 40-64 μm) as stationary phase. Organic solvents were evaporated on a rotary evaporator at 35−40°C. NMR spectra were recorded on a Varian Gemini 300 ($^1$H: 300.07 MHz; $^{13}$C: 75.46 MHz), a Bruker AMX3 400 ($^1$H: 400.13 MHz; $^{13}$C: 100.62 MHz), a Bruker Avance 400 ($^1$H: 400.13 MHz; $^{13}$C: 100.56 MHz), or a Bruker DRX 500 Avance ($^1$H: 500.13 MHz; $^{13}$C: 125.77 MHz) spectrometer at 298 K. Assignment of the NMR signals is based on $^{13}$C{$^1$H}, $^{13}$C APT, COSY, HMQC and $^{13}$C HMBC spectra. Chemical shifts of the signals are reported in ppm relative to tetramethylsilane as external standard and calibrated against the solvent residual peaks ($CDCl_3$, δ = 7.26 ppm for $^1$H-NMR, δ = 77.16 ppm for $^{13}$C-NMR). The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet, hept = heptet, m = multiplet, br s = broad signal. High Resolution Mass Spectrometry (HRMS) analysis were measured on ZAB-SEQ (VG Analytical).

**Preparation and characterization data of new 6-iodopurines 1c-g (Table 1, entries 6-10):** the purine starting materials **1c-f** were synthesized as described in yields of 50 to 75% over the three steps.[11a] The $Me_2NSO_2$-iodide **1g** was prepared by sulfamoylation of 6-iodopurine[14] with $Me_2NSO_2Cl$, $Et_3N$ in MeCN at 0 °C for 4 h, then 16 h at rt. (62% yield)

**9-(4-chlorophenyl)-6-iodo-9*H*-purine (1c):** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.70 (s, 1H), 8.39 (s, 1H), 7.70-7.67 (m, 2H), 7.60-7.56 (m, 2H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 152.9, 147.8, 143.1, 139.2, 135.1, 132.7, 130.5, 124.9, 123.2 ppm. HRMS (ESI+): m/z calculated for $C_{11}H_6Cl_1I_1N_4$: 355.9404. Found: $C_{11}H_7Cl_1I_1N_4$: 356.9404 [M+H].

**9-(4-trifluoromethyl)-6-iodo-9*H*-purine (1d):** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.46 (s, 1H), 7.95-7.92 (m, 2H), 7.90-7.87 (m, 2H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.0, 147.7, 142.8, 139.4, 137.1, 131.1 (q, *J* = 33.2 Hz), 127.6, 123.6, 123.4 ppm. HRMS (ESI+): m/z calculated for $C_{12}H_6F_3I_1N_4$: 389.9668. Found: $C_{12}H_7F_3I_1N_4$: 390.9666 [M+H].

**9-(4-methoxy)-6-iodo-9*H*-purine (1e):** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.67 (m, 1H), 8.33 (s, 1H), 7.58-7.55 (m, 2H), 7.11-7.08 (m, 2H), 3.89 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 160.1, 152.7, 148.1, 143.9, 139.0, 126.9, 125.5, 122.9, 115.4, 55.85 ppm. HRMS (ESI+): m/z calculated for $C_{12}H_9I_1N_4O_1$: 351.9899. Found: $C_{12}H_{10}I_1N_4O_1$: 352.9899 [M+H].

**9-(*i*Pr)-6-iodo-9*H*-purine (1f):** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.19 (s, 1H), (hept, *J* = Hz 1H), 1.66-1.64 (d, *J* = 6.8 Hz, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 151.8, 147.8, 142.4, 139.0, 122.2, 48.3, 22.6 ppm. HRMS (ESI+): m/z calculated for $C_8H_9I_1N_4$: 287.9950. Found: $C_8H_{10}I_1N_4$: 288.9950 [M+H].

**6-iodo-*N*,*N*-dimethyl-9*H*-purine-9-sulfonamide (1g):** $^1$H NMR (400 MHz, $CDCl_3$): δ 8,71 (s, 1H), 8.43 (s, 1H), 3.12 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 153.6, 146.9, 143.5, 138.7, 123.3, 38.7 ppm. HRMS (ESI+): m/z calculated for $C_7H_8I_1N_5O_2S_1$: 352.9522. Found: $C_7H_9I_1N_5O_2S_1$: 353.9522 [M+H].

**General procedure (A) for the reaction between 6-iodopurines 1b-g with aldehydes (Table 1):** The purine **1b-g** (1 mmol) was charged in a flask that was flushed with argon for 5 min. Dry DCM (10 mL) was added and the mixture was stirred at room temperature until the purine was completely dissolved. EtMgBr (3 M $Et_2O$ solution, 1.2 mmol, 0.4 mL) was added dropwise and the mixture was stirred at room temperature for 15 minutes, then the corresponding aldehyde (3 mmol) was added at room temperature in one portion. The reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with sat. aq. $NH_4Cl$ (5 mL), diluted with sat. aq. $NaHCO_3$, extracted with DCM (2 x 25 mL), dried over magnesium sulphate, filtered and concentrated in vacuo to an orange/yellow oil. The crude mixture was purified by column chromatography (AcOEt/hexane, 0:1 to 1:0) to provide the corresponding products as white solids.

**Methyl 4-(hydroxy(9-phenyl-9*H*-purin-6-yl)methyl)benzoate (4): 4** was prepared according to general procedure A starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and methyl 4-formylbenzoate (colorless solid, 273 mg, 76% yield). $^1$H-NMR (500 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.34 (s, 1H), 8.03-7.99 (m, 2H), 7.78-7.74 (m, 2H), 7.70-7.66 (m, 2H), 7.63-7.57 (m, 2H), 7.53-7.47 (m, 1H), 6.51 (d, *J* = 6.0 Hz, 1H), 5.37 (d, *J* = 6.0 Hz, 1H), 3.88 (s, 3H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 166.9, 160.4, 152.7, 146.9, 134.2, 131.9, 130.2, 139.0, 129.9, 129.0, 127.0, 123.7, 77.3, 52.2. HRMS (ESI+): m/z calculated for $C_{20}H_{16}N_4O_3$ = 360.1301; found = 361.1299 $[M+H]^+$, 343.1197 $[M+H]^+$ - $H_2O$.

**4-(hydroxy(9-phenyl-9*H*-purin-6-yl)methyl)benzonitrile (5): 5** was prepared according to general procedure A starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 4-formylbenzonitrile (colorless solid, 242 mg, 74% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.36 (s, 1H), 7.86-7.82 (m, 2H), 7.71-7.67 (m, 2H), 7.65-7.57 (m, 4H), 7.54-7.48 (m, 1H), 6.49 (d, *J* = 6.0 Hz, 1H), 5.42 (d, *J* = 6.0 Hz, 1H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 159.7, 152.4, 151.6, 147.1, 144.1, 134.1, 132.5, 131.0, 130.2, 129.1, 127.7, 123.8, 118.9, 111.9, 72.0. HRMS (ESI+): m/z calculated for $C_{19}H_{13}N_5O$ = 327.1198; found = 328.1197 $[M+H]^+$, 310.1100 $[M+H]^+$ - $H_2O$.

**(9-phenyl-9*H*-purin-6-yl)methanol (6): 6** was prepared according to general procedure A starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and paraformaldehyde (white solid, 122 mg, 54% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.36 (s, 1H), 7.75-7.70 (m, 2H), 7.64-7.57 (m, 2H), 7.54-7.45 (m, 1H), 5.28 (s, 2H), 3.92 (br s, 1H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 159.9, 152.8, 150.8, 143.5, 134.3, 131.2, 130.2, 128.9, 123.7, 61.5. HRMS (ESI+): m/z calculated for $C_{12}H_{10}N_4O$ = 226.0933; found = 227.0931 $[M+H]^+$.

**Furan-2-yl(9-phenyl-9*H*-purin-6-yl)methanol (7): 7** was prepared according to general procedure A starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and furfural (colorless solid, 222 mg, 76% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.35 (s, 1H), 7.73-7.68 (m, 2H), 7.63-7.56 (m, 2H), 7.52-7.46 (m, 1H), 7.37-7.34 (m, 1H), 6.45-6.41 (m, 2H), 6.35 (m, 1H), 5.20 (br s, 1H) ppm. $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 158.5, 153.7, 152.6, 151.4, 144.0, 143.1, 134.2, 131.2, 130.2, 128.9, 123.7, 110.6, 108.4, 66.8 ppm. HRMS (ESI+): m/z calculated for $C_{16}H_{12}N_4O_2$ = 292.1039; found = 293.1032 $[M+H]^+$, 275.0938 $[M+H]^+$ - $H_2O$.

**(5-methylthiophen-2-yl)(9-phenyl-9*H*-purin-6-yl)methanol (8): 8** was prepared according to general procedure A starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 5-methylthiophene-2-carbaldehyde (colorless solid, 203 mg, 63% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.35 (s, 1H), 7.71-7.65 (m, 2H), 7.60-7.53 (m, 2H), 7.49-7.43 (m, 1H), 6.98-6.95 (m, 1H), 6.61-6.54 (m, 2H), 5.23 (br s, 1H), 2.38 (s, 3H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 160.3, 152.6, 151.4, 143.8, 142.9, 140.4, 137.9, 134.1, 130.7, 130.0, 128.7, 125.6, 125.0, 123.6, 66.9, 15.4. HRMS (ESI+): m/z calculated for $C_{17}H_{14}N_4OS$ = 322.0967; found = 323.0977 $[M+H]^+$, 305.0844 $[M+H]^+$ - $H_2O$.

**(9-(4-chlorophenyl)-9H-purin-6-yl)(phenyl)methanol (9): 9** was prepared according to general procedure A starting from 6-iodo-9-(4-chlorophenyl)-9*H*-purine (**1c**) and benzaldehyde (colorless solid, 230 mg, 68% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 8.30 (s, 1H), 7.67-7.62 (m, 4H), 7.59-7.54 (m, 2H), 7.37-7.32 (m, 2H), 7.29-7.24 (m, 1H), 6.45 (s, 1H), 5.23 (br s, 1H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 160.9, 151.9, 151.1, 144.6, 140.6, 135.3, 132.2, 131.0, 130.6, 130.5, 128.9, 128.7, 128.5, 127.1, 125.0, 72.1. HRMS (ESI+): m/z calculated for $C_{18}H_{13}ClN_4O$ = 336.0856; found = 337.0853 $[M+H]^+$.

**(9-(4-trifluoromethylphenyl)-9*H*-purin-6-yl)(phenyl)methanol (10): 10** was prepared according to general procedure A starting from 6-iodo-9-(4-trifluoromethylphenyl)-9*H*-purine (**1d**) and benzaldehyde (colorless solid, 279 mg, 75% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.38 (s, 1H), 7.92-7.85 (m, 4H), 7.67-7.63 (m, 2H), 7.37-7.30 (m, 2H), 7.28-7.22 (m, 1H), 6.46 (d, *J* = 6.7 Hz, 1H), 5.26 (d, *J* = 7.1 Hz, 1H). $^{13}$C{$^1$H}-NMR (150 MHz, $CDCl_3$): δ 161.7, 152.9, 151.3, 143.0, 141.8, 137.2, 131.1, 130.7 (q, *J* = 33 Hz), 128.7, 128.2, 127.5-127.4 (q, *J* = 4 Hz), 126.9, 123.6 (q, *J* = 272 Hz), 123.5, 72.7. HRMS (ESI+): m/z calculated for $C_{19}H_{13}F_3N_4O$ = 370.1120; found = 371.1124 $[M+H]^+$.

**(9-(4-methoxyphenyl)-9*H*-purin-6-yl)(phenyl)methanol (11): 11** was prepared according to general procedure A starting from 6-iodo-9-(4-methoxyphenyl)-9*H*-purine (**1e**) and benzaldehyde (colorless solid, 219 mg, 66% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.25 (s, 1H), 7.68-7.64 (m, 2H), 7.56-7.51 (m, 2H), 7.37-7.32 (m, 2H), 7.29-7.24 (m, 1H), 7.11-7.07 (m, 2H), 6.44 (s, 1H), 5.30 (br s, 1H), 3.88 (s, 3H). $^{13}$C{$^1$H}-NMR (125 MHz, $CDCl_3$): δ 160.7, 160.2, 152.0, 151.3, 145.0, 141.2, 131.0, 130.5, 129.0, 128.8, 128.3, 127.4, 127.1, 126.6, 125.5, 72.3, 55.8. HRMS (ESI+): m/z calculated for $C_{19}H_{16}N_4O_2$ = 332.1352; found = 333.1352 $[M+H]^+$.

**(9-(4-*iso*propylphenyl)-9*H*-purin-6-yl)(phenyl)methanol** (**12**): **12** was prepared according to general procedure A starting from 6-iodo-9-(4-*iso*propylphenyl)-9*H*-purine (**1f**) and benzaldehyde (colorless solid, 183 mg, 68% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.10 (s, 1H), 7.64-7.61 (m, 2H), 7.32-7.28 (m, 2H), 7.23-7.20 (m, 1H), 6.38 (s, 1H),

5.36 (s, 1H), 4.90 (hept, *J* = 6.8 Hz, 1H), 1.62 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 160.5, 151.6, 151.3, 142.5, 142.1, 130.8, 128.6, 128.0, 126.9, 72.8, 47.7, 22.6. HRMS (ESI+): m/z calculated for $C_{15}H_{16}N_4O$ = 268.1402; found = 269.1400 $[M+H]^+$.

**4-(6-(hydroxy(phenyl)methyl)-9*H*-purin-9-yl)-*N*,*N*-dimethylbenzenesulfonamide** (**13**): **13** was prepared according to general procedure A starting from 4-(6-iodo-9*H*-purin-9-yl)-*N*,*N*-dimethylbenzenesulfonamide (**1g**) and benzaldehyde (colorless solid, 213 mg, 64% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.36 (s, 1H), 7.62-7.59 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.24 (m, 1H), 6.39 (s, 1H), 5.01 (br s, 1H), 3.11 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ 161.9, 153.3, 150.5, 143.7, 141.4, 130.6, 128.8, 128.3, 126.9, 72.6, 38.7. HRMS (ESI+): m/z calculated for $C_{14}H_{15}N_4O_3S$ = 333.0974; found = 334.0974 $[M+H]^+$.

**General procedure for the reaction between 6-iodopurines 1a,b with ketones (B) (Table 2):** The ketone (3 mmol) was dissolved in a 0.6 M solution of lanthanum(III) chloride *bis*(lithium chloride) complex in THF (5 mL, 3 mmol). The resulting solution was stirred for 1 hour at room temperature under an argon atmosphere. In a separate flask, dry dichloromethane (9 mL) was added to the iodopurine **1a,b** (1 mmol, **1a**: 335.15 mg, **1b**: 321.1 mg) under an inert atmosphere of dry argon and the mixture was stirred at room temperature until the purine was completely dissolved. A 3 M solution of ethylmagnesium bromide in diethyl ether (0.4 mL, 1.2 mmol) was then added dropwise over 2 minutes. The mixture was stirred for 10 minutes at room temperature before cooling to 0 °C. The ketone-lanthanum solution was then added dropwise over 10 minutes to the purinyl magnesium halide solution at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and then allowed to warm up to room temperature and stirred for 2 more hours. The reaction mixture was quenched with sat. aq. $NH_4Cl$ (5 mL), diluted with $H_2O$ (50 mL) and DCM (40 mL). The organic layer was separated, and the aqueous layer extracted with DCM (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified via silica flash column chromatography giving pure compounds **14-23**.

**1-Phenyl-1-(9-phenyl-9*H*-purin-6-yl)ethan-1-ol (14): 14** was prepared according to general procedure B starting from 6-iodo9-phenyl-9*H*-purine (**1b**) and acetophenone (colorless oil, 174 mg, 55% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.31 (s, 1H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.23 (s, 1H), 2.28 (s, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 164.6, 152.1, 151.9, 146.4, 143.0, 134.3, 130.7, 130.2, 128.9, 128.3, 127.3, 125.8, 123.9, 76.4, 28.2 ppm. HRMS (ESI+): m/z calculated for $C_{19}H_{17}N_4O$ = 317.1402; found = 317.1411 $[M+H]^+$.

**3-Methyl-2-(9-phenyl-9*H*-purin-6-yl)butan-2-ol (15): 15** was prepared according to general procedure B starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 3-methylbutan-2-one (colorless solid, m.p.: 105.5 °C, 122 mg, 43% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.33 (s, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 5.29 (s, 1H), 2.65 (hept, *J* = 6.8 Hz, 1H), 1.78 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.66 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 166.5, 151.7, 151.4, 142.7, 134.4, 130.6, 130.2, 128.8, 123.9, 76.6, 37.2, 26.0, 17.5, 16.7 ppm. HRMS (ESI+): m/z calculated for $C_{16}H_{19}N_4O$ = 283.1559; found = 283.1557 $[M+H]^+$.

**1-Cyclopropyl-1-(9-phenyl-9*H*-purin-6-yl)ethan-1-ol (16): 16** was prepared according to general procedure B starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 1-cyclopropylethan-1-one (colorless solid, m.p.: 100.5 °C, 98 mg, 35% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.35 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.62-7.59 (m, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 5.18 (s, 1H), 1.90 (s, 3H), 1.77-1.73 (m, 1H), 0.77-0.73 (m, 1H), 0.50-0.46 (m, 1H), 0.42-0.38 (m, 1H), 0.22-0.10 (m, 1H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 166.1, 151.8, 151.5, 142.8, 134.4, 130.5, 130.2, 128.8, 123.8, 72.0, 27.7, 21.5, 0.9, 0.3 ppm. HRMS (ESI+): m/z calculated for $C_{16}H_{17}N_4O$ = 281.1402; found = 281.1409 $[M+H]^+$.

**2-Methyl-1-phenyl-1-(9-benzyl-9*H*-purin-6-yl)propan-1-ol (17): 17** was prepared according to general procedure B starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 2-methyl-1-phenylpropan-1-one (colorless solid, m.p.: 135.0 °C, 153 mg, 44% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.35 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.20 (s, 1H), 3.73 (hept, *J* = 6.7 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 Hz, $CDCl_3$): δ 164.5, 151.9, 151.8, 145.4, 142.9, 134.3, 130.6, 130.1, 128.9, 128.1, 127.0, 126.4, 123.9, 81.4, 35.5, 17.5, 16.6 ppm. HRMS (ESI+): m/z calculated for $C_{21}H_{21}N_4O$ = 345.1715; found = 345.1700 $[M+H]^+$.

**1-(Furan-2-yl)-1-(9-phenyl-9*H*-purin-6-yl)ethanol (18): 18** was prepared according to general procedure B starting from 6-iodo-9-phenyl-9*H*-purine (**1b**) and 1-(furan-2-yl)ethan-1-one (colorless solid, m.p.: 119.0 °C, 65 mg, 21% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.33 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.9 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.34 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.16 (s, 1H), 2.24 (s, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 162.0, 157.5, 152.0, 151.9, 143.4, 142.5, 134.3, 130.8, 130.2, 128.9, 123.9, 110.5, 106.6, 72.2, 26.1 ppm. HRMS (ESI+): m/z calculated for $C_{17}H_{15}N_4O_2$ = 307.1195; found = 307.1205 $[M+H]^+$.

**1-Phenyl-1-(9-benzyl-9*H*-purin-6-yl) ethan-1-ol (19): 19** was prepared according to general procedure B starting from 9-benzyl-6-iodo-9*H*-purine (**1a**) and acetophenone (colorless solid, 183 mg, 55% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.01 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 2H), 7.40-7.33 (m, 3H), 7.33-7.27 (m, 4H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.23 (br s, 1H), 5.41 (s, 2H), 2.23 (s, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 164.1, 152.2, 151.6, 146.5, 143.8, 134.9, 130.1, 129.3, 128.9, 128.3, 128.2, 127.2, 125.8, 76.3, 47.6, 28.3 ppm. HRMS (ESI+): m/z calculated for $C_{20}H_{19}N_4O$ = 331.1559; found = 331.1547 $[M+H]^+$.

**2-(9-Benzyl-9*H*-purin-6-yl)-3-methylbutan-2-ol (20): 20** was prepared according to general procedure B starting from 9-benzyl-6-iodo-9*H*-purine (**1a**) and 3-methylbutan-2-one (colorless oil, 140 mg, 47% yield). $^1$H-NMR (600 Hz, $CDCl_3$): δ 8.93 (s, 1H), 8.02 (s, 1H), 7.39-7.33 (m, 5H), 5.52-5.40 (m, 2H), 5.30 (s, 1H), 2.58 (hept, *J* = 6.8 Hz, 1H), 1.73 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.61 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 Hz, $CDCl_3$): δ 165.9, 151.7, 151.2, 143.4, 135.1, 130.0, 129.4, 128.9, 128.2, 76.5, 47.6, 37.2, 25.9, 17.4, 16.7 ppm. HRMS (ESI+): m/z calculated for $C_{17}H_{21}N_4O$ = 297.1715; found = 297.1702 $[M+H]^+$.

**1-(9-Benzyl-9H-purin-6-yl)-1-cyclopropylethan-1-ol (21): 21** was prepared according to general procedure B starting from 9-benzyl-6-iodo-9*H*-purine (**1a**) and 1-cyclopropylethan-1-one (colorless solid, m.p.: 88.0 °C, 84 mg, 29% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.04 (s, 1H), 7.40-7.34 (m, 5H), 5.49-543 (m, 2H), 5.19 (s, 1H), 1.85 (s, 3H), 1.71-1.67 (m, 1H), 0.74-0.70 (m, 1H), 0.48-0.43 (m, 1H), 0.40-0.35 (m, 1H), 0.16-0.10 (m, 1H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 165.5, 151.8, 151.3, 143.6, 135.1, 129.9, 129.3, 128.9, 128.2, 72.0, 47.6, 27.7, 21.5, 0.9, 0.3 ppm. HRMS (ESI+): m/z calculated for $C_{17}H_{19}N_4O$ = 295.1559; found = 295.1555 $[M+H]^+$.

**2-Methyl-1-phenyl-1-(9-phenyl-9H-purin-6-yl)propan-1-ol (22): 22** was prepared according to general procedure B starting from 9-benzyl-6-iodo-9*H*-purine (**1a**) and 2-methyl-1-phenylpropan-1-one (colorless oil, 145 mg, 40% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.04 (s, 1H), 7.97 (d, *J* = 7.4 Hz, 2H), 7.39-7.31 (m, 5H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 6.20 (s, 1H), 5.44-5.37 (m, 2H), 3.66 (hept, *J* = 6.7 Hz, 1H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H) ppm. $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$): δ 163.9, 152.0, 151.4, 145.5, 143.6, 134.9, 130.1, 129.3, 128.9, 128.2, 128.1, 126.8, 126.4, 81.3, 47.6, 35.6, 17.4, 16.6 ppm. HRMS (ESI+): m/z calculated for $C_{22}H_{23}N_4O$ = 359.1872; found = 359.1862 $[M+H]^+$.

**1-(9-Benzyl-9*H*-purin-6-yl)-1-(furan-2-yl)-ethanol (23): 23** was prepared according to general procedure B starting from 9-benzyl-6-iodo-9*H*-purine (**1a**) and 1-(furan-2-yl)ethan-1-one (colorless oil, 94 mg, 29% yield). $^1$H-NMR (600 MHz, $CDCl_3$): δ 8.99 (s, 1H), 8.03 (s, 1H), 7.40-7.32 (m, 5H), 7.28 (s, 1H), 6.40 (d, *J* = 3.3 Hz, 1H), 6.31-6.29 (m, 1H), 6.17 (s, 1H), 5.47-5.40 (m, 2H), 2.19 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (150 MHz, $CDCl_3$): δ 161.5, 157.5, 152.2, 151.6, 144.2, 142.5, 134.9, 130.2, 129.3, 128.9, 128.2, 110.4, 106.5, 72.2, 47.7, 26.1 ppm. HRMS (ESI+): m/z calculated for $C_{18}H_{17}N_4O_2$ = 321.1352; found = 321.1364 $[M+H]^+$.

**General procedure for the reaction between 2-iodopurine 3a with ketones (C) (Table 3):** A Lanthanum(III) chloride *bis*(lithium chloride) solution in THF (0.6 M, 0.750 mmol, 1.25 mL) was poured into a hot-gun dried Schlenk and it was concentrated to 1 M concentration. The corresponding ketone (0.750 mmol) was added and the solution was stirred for 1 h at room temperature under nitrogen atmosphere. Purine **3a** (80 mg, 0.250 mmol) was dissolved in dry DCM (2.5 mL) in a hot-gun dried flask under nitrogen atmosphere. EtMgBr ($Et_2O$ solution, 3 M, 0.300 mmol, 0.1 mL) was slowly added to the purine solution at -5 °C. The mixture was stirred at rt for 10 minutes and then cooled again to -5 °C. The $LaCl_3$/ketone solution was added dropwise. The temperature was maintained at -5 °C for 30 minutes, then the reaction was stirred at rt for 16 hours. After 16 hours the reaction was quenched with sat. aq. $NH_4Cl$ (2 mL). 10 mL of $H_2O$ were added, and the crude was extracted with DCM (4 x 10 mL). The organic layer was washed with brine, dried over sodium sulphate, and concentrated in vacuo. The crude was purified via flash column chromatography on silica gel affording the pure compounds **24-30.**

**1-Phenyl-1-(9-(4-methylphenyl)-9*H*-purin-2-yl)ethan-1-ol (24): 24** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and acetophenone (brown solid, m.p.: 168.0 °C, 43 mg, 53% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.34 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 5.52 (s, 1H), 2.49 (s, 3H), 2.09 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 168.1, 151.2, 148.7, 147.1, 144.7, 138.7, 133.1, 131.8, 130.6, 128.1, 127.0, 125.7, 123.2, 76.7, 29.4, 21.3 ppm. HRMS (ESI+): m/z calculated for $C_{20}H_{19}N_4O$ = 331.1553; found = 331.1558 $[M+H]^+$, 313.1439 $[M+H]^+$ - $H_2O$.

**1-(4-Nitrophenyl)-1-(9-(4-methylphenyl)-9*H*-purin-2-yl)-ethan-1-ol (25): 25** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and 4-nitroacetophenone (yellow solid, m.p. 176.5 °C, 45 mg, 49% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.37 (s, 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 5.68 (s, 1H), 2.50 (s, 3H), 2.06 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 166.6, 154.2, 148.8, 148.1, 147.1, 145.3, 139.1, 133.5, 131.6, 130.7, 127.0, 123.4, 123.3, 76.6, 29.9, 21.3 ppm. HRMS (ESI+): m/z calculated for $C_{20}H_{18}N_5O_3$ = 376.1410; found = 376. 1420 $[M+H^+]$; 358.1284 $[M+H]^+$ - $H_2O$.

**1-(4-Methoxyphenyl)-1-(9-(4-methylphenyl)-9H-purin-2-yl)ethan-1-ol (26): 26** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and 4-methoxyacetophenone (yellow solid, m.p.: 108.5 °C, 32 mg, 35% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.32 (s, 1H), 7.61-7.57 (m, 4H), 7.39 (d, *J* = 8.1 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.47 (s, 1H), 3.74 (s, 3H), 2.47 (s, 3H), 2.04 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 168.3, 158.6, 151.2, 148.7, 144.6, 139.4, 138.7, 133.0, 131.8, 130.6, 126.9, 123.2, 113.4, 76.4, 55.3, 29.5, 21.3 ppm. HRMS (ESI+): m/z calculated for $C_{21}H_{21}N_4O_2$ = 361.1665; found = 361.1685 $[M+H^+]$, 343.1470 $[M+H]^+$ - $H_2O$.

**1-(4-Trifluoromethylphenyl)-1-(9-(4-methylphenyl)-9H-purin-2-yl)ethan-1-ol (27): 27** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and 4-trifluoromethylacetophenone (brown solid, m.p.: 84 °C, 63 mg, 64% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.37 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 3H), 5.63 (s, 1H), 2.50 (s, 3H), 2.08 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 167.2, 151.4, 151.0, 148.7, 145.0, 144.5, 138.9, 133.3, 131.7, 130.6, 129.2 (q, *J* = 32.1 Hz), 126.2, 125.0 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 270.4 Hz), 123.3, 76.5, 29.7, 21.3 ppm. HRMS (ESI+): m/z calculated for $C_{21}H_{18}F_3N_4O$ = 399.1433; found = 399. 1440 $[M+H^+]$; 381.1277 $[M+H]^+$ - $H_2O$.

**3-Methyl-2-(9-(4-methylphenyl)-9H-purin-2-yl)butan-2-ol (28): 28** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and 3-methylbutan-2-one (yellow solid, m.p.: 154.5 °C, 29 mg, 39% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.34 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.75 (s, 1H), 2.45 (s, 3H), 2.27 (hept, *J* = 6.8 Hz, 1H), 1.58 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.8 Hz, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 169.4, 151.2, 148.3, 144.4, 138.6, 132.9, 131.9, 130.6, 123.2, 77.5, 38.1, 26.2, 21.3, 17.5, 16.9 ppm. HRMS (ESI+): m/z calculated for $C_{17}H_{21}N_4O$ = 297.1715; found = 297.1711 $[M+H^+]$, 279.1628 $[M+H]^+$ - $H_2O$.

**1-(Benzo[d][1,3]dioxol-5-yl)-1-(9-(4-methylphenyl)-9H-purin-2-yl)ethan-1-ol (29): 29** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-one (brown solid, m.p.: 81 °C, 20 mg, 22% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 8.34 (s, 1H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 5.88 (s, 2H), 5.45 (s, 1H), 2.48 (s, 3H), 2.01 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 168.1, 148.8, 147.5, 146.5, 144.7, 141.4, 138.8, 133.1, 131.8, 130.7, 123.3, 118.9, 107.8, 106.9, 101.1, 76.6, 29.6, 21.3 ppm. HRMS (ESI+): m/z calculated for $C_{21}H_{19}N_4O_3$ = 375.1457; found = 375. 1446 $[M+H^+]$; 357.1387 $[M+H]^+$ - $H_2O$.

**Diphenyl(9-(4-methylphenyl)-9H-purin-2-yl)methanol (30): 30** was prepared according general procedure C starting from 9-(4-methylphenyl)-6-iodo-9*H*-purine (**3a**) and benzophenone (colorless solid, m.p.: 176 °C, 24 mg, 25% yield). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.29 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 4H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.24-7.13 (m, 6H), 6.02 (s, 1H), 2.37 (s, 3H) ppm. $^{13}$C{$^1$H}-NMR (100 MHz, $CDCl_3$): δ 166.6, 151.0, 148.5, 146.0, 144.9, 138.7, 133.2, 131.8, 130.6, 128.1, 127.8, 127.4, 123.0, 81.4, 21.3 ppm. Melting point (°C): 175-177. HRMS (ESI+): m/z calculated for $C_{25}H_{21}N_4O$ = 393.1715; found = 393.1710 $[M+H^+]$, 375.1633 $[M+H]^+$ - $H_2O$.

**Computational details:** All structures were initially optimized using density functional theory (DFT) with B3LYP[19] and the 6-31G(d,p) basis set and SDD[20] for Mg and Br as implemented in Gaussian 16.[21] Final energy refinements were done at the wB97XD[22]/def2tzvpp[23] level of theory. Solvent effects were taken into account with the IEF-PCM model, at the same levels of theory, using dichloromethane or tetrahydrofuran as solvents,[24] as in the experimental conditions. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies, and the intrinsic reaction coordinates (IRC)[25] were followed to verify the energy profiles connecting the key transition structures to the correct associated local minima. The calculation of the atomic charges and nucleophilicity indexes was carried out through Natural Bond Orbital analysis.[26] In the Supporting information document are reported the energy Table and coordinates of all structures discussed in the main manuscript.

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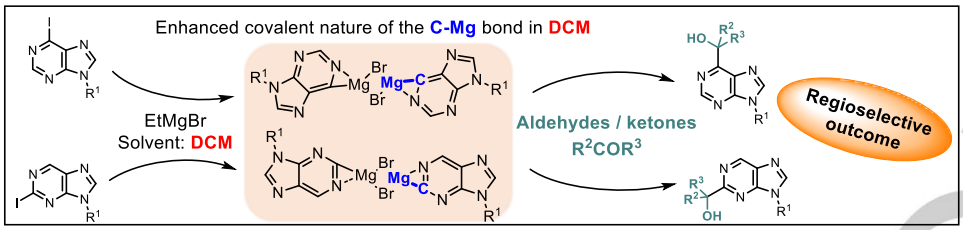


Highly functionalized purine systems were obtained using aldehydes and, for the first time, ketones through a recently developed iodo-Mg exchange methodology that works in DCM. DFT calculations suggested that the observed major stability of the C-Mg bond generated in DCM at higher temperature compared to the one in THF might derived from a more covalent nature of the C-Mg bond in such non-coordinating solvent.

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