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Lewis Acid Triggered Regioselective Magnesiation and Zincation of Uracils, Uridines, and Cytidines

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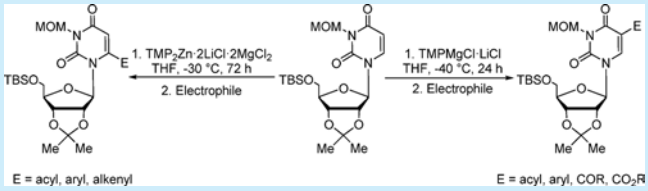
Supporting Information

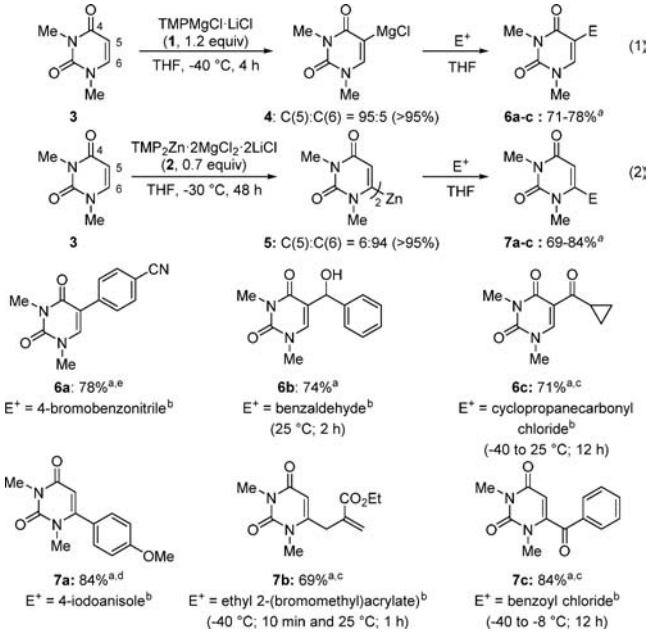
ABSTRACT: The Lewis acid $MgCl_2$ allows control of the metalation regioselectivity of uracils and uridines. In the absence of the Lewis acid, metalation of uracil and uridine derivatives with TMPMgCl·LiCl occurs at the position C(5). In the presence of $MgCl_2$, zincation using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ occurs at the position C(6). This metalation method provides easy access to functionalized uracils and uridines. Using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ also allows to functionalize cytidine derivatives at the position C(6).



The selective functionalization of uridines is an important synthetic goal because of the biological relevance of many substituted uridines.[1] They are known to display antibiotic, antifungal, anticancer, and antiviral activity. Many antiviral agents are based on modified nucleosides including modifications of both the sugar moiety and the heterocyclic system.[2] Therefore, the direct lithiation of various uridines has been studied, and the use of dilithiated uridine intermediates has allowed a selective functionalization by tuning the nature of the substituent at the C′(5)-hydroxyl function.[3a,b,f] Alternatively, the use of halogenated uracils and uridines allows cross-coupling reactions[4] or the preparation of metalated intermediates via a direct zinc insertion or via a halogen−metal exchange.[5] A direct Pd-catalyzed C−H arylation of uracils in the presence or absence of CuI allows functionalization of the positions C(5) and C(6).[6] Although lithium bases[7] are powerful bases for the direct lithiation of various heterocycles, magnesium or zinc bases are of special interest since they tolerate various functional groups as well as sensitive heterocyclic scaffolds.[8] Recently, we have reported a selection of mild magnesium and zinc TMP-(2,2,6,6-tetramethylpiperidyl) bases such as TMPMgCl·LiCl (**1**)[9] and $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**2**)[10] which allow a regioselective functionalization of polyfunctionalized aromatics and heterocycles.[11] We have demonstrated that a regioselective switch can be achieved by the presence or absence of Lewis acids for a range of metalations.[12] Herein, we report that the bases **1** or **2** allow a highly regioselective metalation at the C(5) or C(6) position of uracils and uridines or at the C(5) position of cytidine. More importantly, we show that these metalated nucleoside derivatives can be quenched with a range of electrophiles.

Preliminary experiments show that TMPMgCl·LiCl (**1**, 1.2 equiv, THF, −40 °C, 4 h) reacts smoothly with *N,N*-dimethyluracil (**3**) to afford the C(5)-magnesiated uracil (**4**), whereas treatment of **3** with $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**2**, 0.7 equiv, THF, −30 °C, 48 h) affords the C(6)-zincated uracil (**5**) with good regioselectivity (C(5)/C(6) = 6:94, Scheme 1). Based on previous studies on the chromone system, we

Scheme 1. $MgCl_2$-Triggered Regioselective Magnesiation and Zincation of Uracil 3 Leading to Products of Type 6 and 7



[a]Isolated yields of regioisomerically pure product. [b]Electrophile used (1.2 equiv). [c]Obtained after transmetalation with CuCN·2LiCl (1.2 equiv, −40 °C, 30 min). [d]2 mol % of $Pd(dba)_2$, 4 mol % of tfp (25 °C, 2 h). [e]Obtained after transmetalation with $ZnCl_2$ (1.2 equiv, −40 °C, 30 min), 2 mol % of $Pd(OAc)_2$, and 4 mol % of XPhos (50 °C, 72 h).

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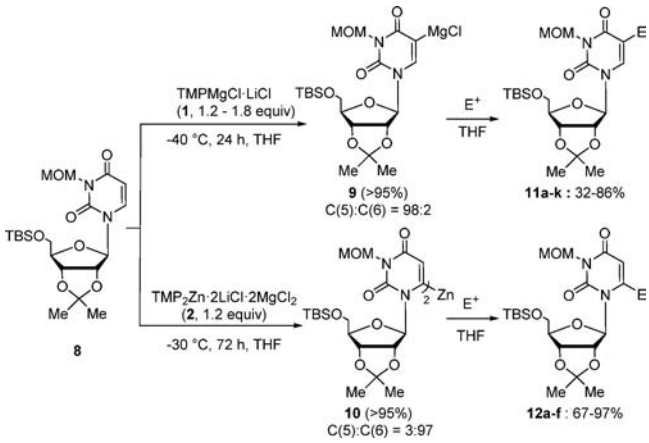
rationalized the observed regioselectivity by the presence of $MgCl_2$ (2.0 equiv) in the zinc TMP-base **2**.[12b] This Lewis acid complexes the C(4) carbonyl group and therefore directs the metalation to position C(6) (Scheme 1).[13] After the resulting metalated nucleosides **4** and **5** were quenched with various electrophiles such as aldehydes, aryl bromides, or iodides (Negishi cross-coupling),[14] allylic halides and acid chlorides (in the presence of CuCN·2LiCl),[15] functionalized uracils (**6a−c**) and (**7a−c**) were obtained in 69−84% yield.

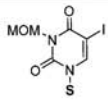
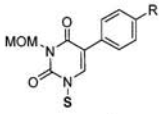
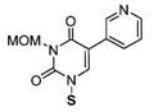
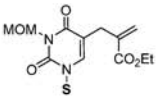
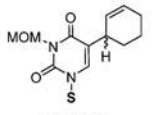
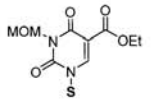
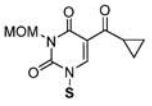
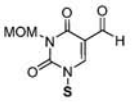
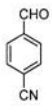
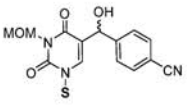
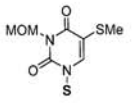
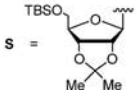
These reaction conditions were readily applied to protected uridine **8**.[16] Its treatment with TMPMgCl·LiCl (**1**, 1.2−1.8 equiv, THF, 40 °C, 24 h) affords the C(5)-magnesiated uridine **9** (C(5):C(6) = 98:2) in >95% yield as determined by ^{1}H NMR analysis of iodolyzed product **11a** (Scheme 2). The

Scheme 2. Reactions and Conditions for C(5) and C(6) Metalation of Uridine 8



presence of $MgCl_2$ inverses the regioselectivity, and the zincation of **8** with $TMP_2Zn·2LiCl·2MgCl_2$ (**2**, 1.2 equiv, THF, −30 °C, 72 h) produces the bis-zincated uridine (**10**) in >95% yield (C(5)/C(6) = 3:97, Scheme 2). With these optimized metalation conditions in hand, a number of C(5)- and C(6)-functionalized uridines were prepared. Reactions of the C(5)-magnesiated uridine **9** with various electrophiles (iodine, alkenyl-, aryl-, and heteroaryl iodides, allylic bromides, acid chlorides, morpholine-4-carbaldehyde, aldehydes, NC−CO_2Et, Me_2S_2) produced the expected regioisomerically pure C(5)-substituted uridines (**11a−k**) in 42−86% yield (entries 1−11, Table 1). Iodolysis of the magnesium reagent **9** provided C(5)-iodinated uridine (**11a**) in 70% yield (entry 1). Thus, after transmetalation of **9** to zinc, Pd-catalyzed Negishi cross-coupling (8 mol % $Pd(dba)_2$ (dba = *trans*,*trans*-dibenzylideneacetone) and 12 mol % of P(2-furyl)$_3$)[16] with 4-iodoanisole, ethyl 4-iodobenzoate, or 3-iodopyridine provided the products **11b−d** (66−81%, entries 2−4). Similarly, copper-mediated allylation with ethyl 2-(bromomethyl)acrylate or bromocyclohexene afforded the C(5)-functionalized uridine derivatives (**11e,f**) in 73−86% yield (entries 5 and 6). Upon treatment of **9** with ethyl cyanoformate, the functionalized ester (**11g**) was obtained in 44% yield (entry 7). The ketone (**11h**) was obtained in 71% yield when **9** was transmetalated to the corresponding copper derivative and acylated with cyclopropanecarbonyl chloride (entry 8). Aldehyde **11i** was obtained in 32% yield when **9** was formylated with morpholine-4-carbaldehyde (entry 9). Furthermore, **9** added readily to 4-cyanobenzaldehyde giving the corresponding alcohol **11j** (47%,

Table 1. Functionalization of Uridine 8 at C(5) Using $TMP_2Zn·LiCl·2MgCl_2$ (2) Leading to Products of Type 11

entry	electrophile/ reaction conditions	product: yield[a]
	I_2	
1	(1.8 equiv)/ 25 °C; 24 h	**11a:** 70%
		
2	R = OMe (1.5 equiv)/ 25 °C; 12 h	**11b:** 81%[b]
3	R = CO_2Et (1.2 equiv)/ 25 °C; 12 h	**11c:** 66%[b]
		
4	(1.2 equiv)/ 25 °C; 30 min	**11d:** 73%[b]
		
5	(1.2 equiv)/ -40 °C; 10 min and 25 °C; 1 h	**11e:** 86%[c]
		
6	(1.2 equiv)/ -40 °C; 10 min and 25 °C; 1 h	**11f:** 60%[c]
	NC-CO_2Et	
7	(1.2 equiv)/ -40 to -10 °C; 12 h	**11g:** 44%
		
8	(1.2 equiv)/ -40 to -10 °C; 12 h	**11h:** 71%[c]
		
9	(1.2 equiv)/ 25 °C; 12 h	**11i:** 32%
		
10	(1.2 equiv)/ -40 °C; 10 min and 25 °C; 1 h	**11j:** 47%
	MeSSMe	
11	(1.2 equiv)/ 25 °C; 1 h	**11k:** 42%
		

[a]Yield of isolated, analytically pure product. [b]Obtained after transmetalation with $ZnCl_2$ (1.2−1.5 equiv, −40 °C, 30 min), 8 mol % of $Pd(dba)_2$, and 12 mol % of P(2-furyl)$_3$. [c]Obtained after transmetalation with CuCN·2LiCl (1.2 equiv, −40 °C, 30 min).

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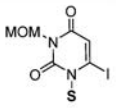
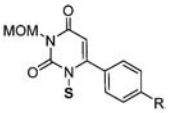
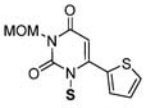
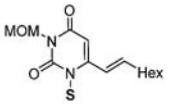
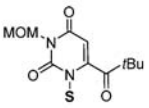
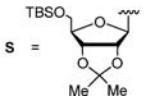
entry 10). The thioether (**11k**) was obtained in 42% yield when **9** was treated with MeSSMe (entry 11). We also examined the scope of the reaction of C(6) metalated uridine **10** with representative electrophiles (Table 2). Iodolysis of the zinc

Table 2. Functionalization of the Uridine 8 at C(6) Using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (2) Leading to Products of Type 12

entry	electrophile/reaction conditions	product: yield[a]
	I_2	
1	(2.0 equiv)/25 °C; 30 min	**12a:** 95%
		
2	R = Cl (1.5 equiv)/ 25 °C; 12 h	**12b:** 84%[b]
3	R = CN (1.2 equiv)/ 25 °C; 12 h	**12c:** 69%[b]
		
4	(1.2 equiv)/ 25 °C; 12 h	**12d:** 97%[b]
		
5	(2.1 equiv)/ 25 °C; 12 h	**12e:** 67%[c]
	t-BuCOCl	
6	(1.2 equiv)/ -40 to 0 °C; 12 h	**12f:** 97%[d]
		

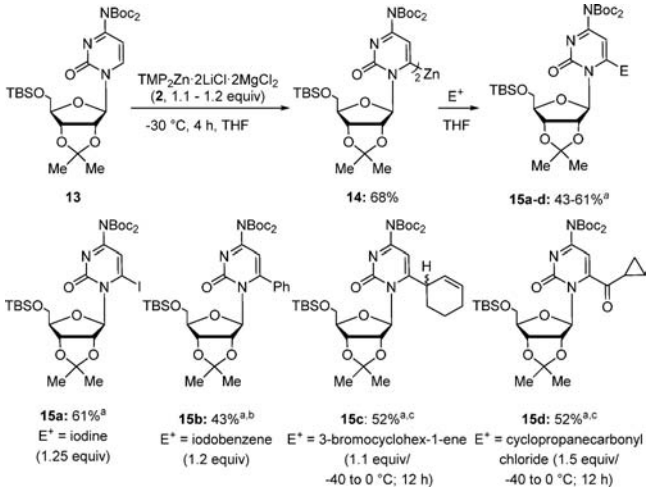
[a]Yield of isolated, analytically pure product. [b]Obtained using 8 mol % $Pd(dba)_2$ and 15 mol % P(2-furyl)$_3$. [c]Obtained using 4 mol % $Pd(PPh_3)_4$. [d]Obtained after transmetalation with CuCN·2LiCl (1.2 equiv, −40 °C, 30 min).

reagent **10** provided the C(6)-iodinated uridine (**12a**) in 95% yield (entry 1). Pd-catalyzed Negishi cross-coupling (8 mol % of $Pd(dba)_2$ and 15 mol % of P(2-furyl)$_3$)[17] with 4-chloroiodobenzene, 4-iodobenzonitrile, 2-iodothiophene, or (*E*)-1-iodooctene furnished the expected C(6)-arylated and alkenylated uracils **12b−e** (67−97%, entries 2−5). Similarly, copper-mediated acylation with pivaloyl chloride afforded the C(6) functionalized uridine **12f** (97%, entry 6).

The substitution of the cytidine scaffold is of biological interest, and its lithiation in C(6) is only briefly described in the literature.[18] The bis-Boc-protected cytidine **13**[19] was readily zincated using $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**2**, 1.1−1.2 equiv, THF, −30 °C, 4 h); it gave rise to the C(6)-metalated zinc reagent **14** in 68% yield. This bis-heteroarylzinc was iodolyzed, allylated, acylated, and cross-coupled leading to the expected products **15a−d** (43−61% yield, Scheme 3).[20]

The selective deprotection of the uridines **11a,h** and **12b,c** could be readily performed using concd HCl to afford the MOM-protected uridines **16a−d** in 72−82%.[20] A full

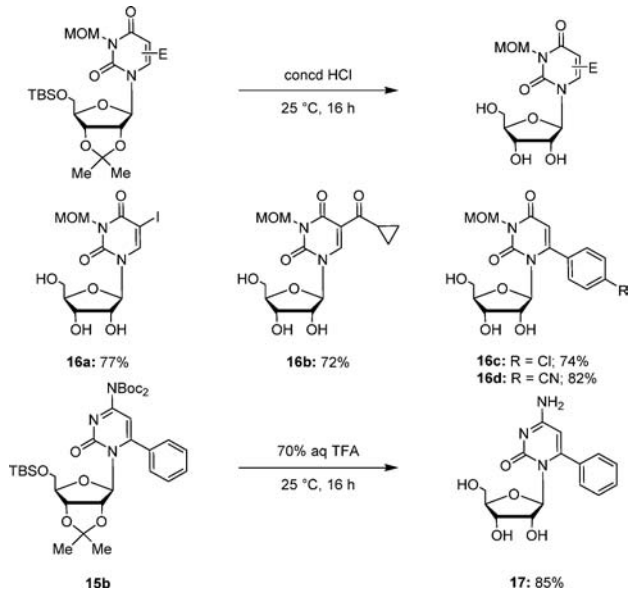
Scheme 3. Reactions and Conditions for the Preparation of C(6)-Substituted Cytidines 14a−d



[a]Yield of isolated, analytically pure product. [b]8 mol % $Pd(dba)_2$, 15 mol % tfp (25 °C, 2 h). [c]Obtained after transmetalation with CuCN·2LiCl (1.5 equiv, −40 °C, 30 min).

deprotection of the arylated cytidine **15b** with aqueous CF_3CO_2H resulted in the formation of the cytidine **17** in 85% yield (Scheme 4).

Scheme 4. Deprotection of Substituted Uridines and a Cytidine Leading to the Nucleosides 16a−d and 17



In summary, we have shown that the presence or absence of $MgCl_2$, which is acting as a Lewis acid, allows the efficient and regioselective preparation of metalated uracils, uridines, and cytidine derivatives. The resulting highly functionalized Mg− or Zn−organometallics thereafter react readily with a broad range of electrophiles leading to diversely functionalized uridines at position C(5) or C(6). Applications to the synthesis of biologically active uridines and cytidines are currently underway in our laboratories.

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■ ASSOCIATED CONTENT

Supporting Information

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Full experimental details and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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