Top Heterocycl Chem (2013) 31: 21–64
DOI: 10.1007/7081_2012_94
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Published online: 8 November 2012

Lithiations and Grignard Reactions on Pyrimidine and Quinazoline

Andrej Kolarovič

Abstract Pyrimidine and quinazoline structural motifs are abundantly found in naturally occurring compounds, with uracil, thymine, and cytosine being the most prominent representatives. Furthermore, the pyrimidine core constitutes a subunit of many compounds rendering substantial medicinal or economic benefits. This review focuses on lithiations and Grignard reactions as tools for selective yet variable purposive derivatizations of pyrimidine and quinazoline, excluding stochiometric transmetalations. A brief introduction into the topic is followed by a detailed summary of what has been done in the field since 2005. The chemistry is discussed in several sections based on the structure of the substrates, which is expected to simplify orientation in the text. Deprotonative and halogen–metal exchange metalations, respectively, are reported separately for each major group of the substrates.

Keywords Deprotonation · Halogen–metal exchange · Pyrimidine functionalization · Pyrimidine nucleobases ·

Contents

A. Kolarovič (✉)
Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, Bratislava, Slovakia
e-mail: andrej.kolarovic@stuba.sk

Abbreviations

Ac	Acetyl
aq	Aqueous
Bn	Benzyl
BOM	Benzyloxymethyl
Bu	Butyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
concd	Concentrated
dba	Dibenzylideneacetone
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
E+	Electrophile
equiv	Equivalent(s)
h	Hour(s)
HMPA	Hexamethylphosphoric triamide
i-Pr	Isopropyl
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
LUMO	Lowest unoccupied molecular orbital
min	Minute(s)
MOM	Methoxymethyl
NIS	*N*-Iodosuccinimide
NMP	*N*-Methyl-2-pyrrolidinone
PMB	4-Methoxyphenyl
rt	Room temperature
s	Second(s)
satd	Saturated
s-Bu	*sec*-Butyl
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TDS	Dimethyl-(2,3-dimethylbut-2-yl)silyl (thexyl-dimethylsilyl)

THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine
TMP	2,2,6,6-Tetramethylpiperidyl
TMS	Trimethylsilyl
Tr	Triphenylmethyl

1 Introduction

Pyrimidines comprise an important class of heterocyclic compounds, with numerous applications in medicinal and agricultural chemistry [1]. A structural diversity in decoration of pyrimidines is highly desired, and carefully elaborated metalations of the pyrimidine core are expected to provide valuable synthetic shortcuts. Lithiations and magnesiations of pyrimidines can be either deprotonative or accessible by halogen–metal exchange. The synthesis of derivatized diazines via deprotonative metalation was reviewed several times, most recently by Quéguiner et al. [2] and Mongin and Chevallier [3].[1] Based on the values calculated in DMSO [5], the most acidic hydrogens are at C-5 in pyrimidine **1** and at C-4 in quinazoline **2**, respectively (Fig. 1).

However, coordination of a ring nitrogen to a metal usually favors deprotonations at adjacent positions. In general, the regioselective introduction of a metal requires the presence of directing metalation groups (DMGs; typically halo, methoxy, or methylthio). The electron-withdrawing properties of the two nitrogens are reflected in lower LUMO energy levels and make pyrimidines and quinazolines susceptible to nucleophilic additions. Thus alkyllithiums, being good nucleophiles, are in deprotonative lithiations usually avoided and non-nucleophilic alkylamides proved to be more reliable. LDA (p*K*a = 35.7) and LTMP (p*K*a = 37.3) are the most common choices. Importantly, due to relatively low basicity of alkylamides, the deprotonations of some pyrimidines are equilibria and as such are under thermodynamic control. Hence an excess of an amide may be required for satisfactory conversions. On the other hand, as halogen–lithium exchange reactions in arenes are known to be faster than deprotonations [6], alkyl lithiums are particularly suitable for dehalogenative lithiations at low temperatures. Over the last several years, mixed Mg/Li amides TMPMgCl·LiCl and $TMP_2MgCl·LiCl$ [7–10] have proved to be highly efficient both in deprotonative and in dehalogenative magnesiations and have become a valuable alternative to lithiations.

[1] A nice concise survey of pyrimidine lithiations can be found in the introduction part of a work published by Schlosser et al. [4].

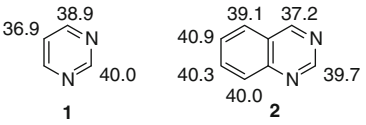
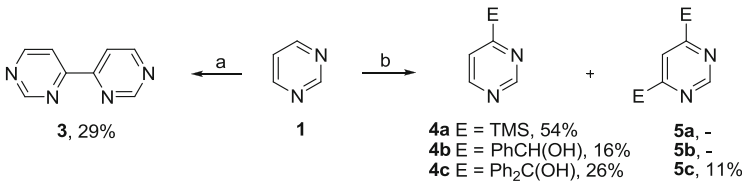


Fig. 1 Calculated p*K*a values for pyrimidine **1** and quinazoline **2**



Scheme 1 (**a**) (i) 1.3 equiv LTMP, THF, −75°C, 1 h; (ii) HCl, EtOH, THF, −75°C; (**b**) (i) 1.2 equiv LTMP, 1.3 equiv E+ (TMSCl, PhCHO or Ph_2CO), THF, −75°C, 2 h; (ii) HCl, EtOH, THF, −75°C [12]

This review covers literature on lithiations and magnesiations published mainly since 2005. Stoichiometric transmetalations of metallated pyrimidines are a subject of the next chapter within this book and herein are included merely in a context. Also, lateral metalations are outside the scope of this account and are not presented.[2]

2 Unsubstituted Pyrimidines and Pyrimidines with Uncommon Directing Metalation Groups

Lithiated pyrimidines lacking a DMG are reported to be unstable even at low temperatures (−75°C) and prone to a quick dimerization (Scheme 1, conditions a) [12, 13].[3]

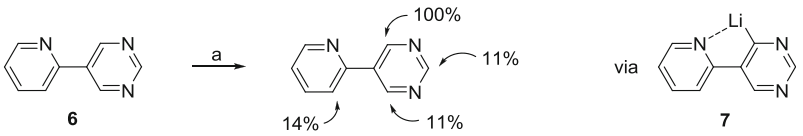
Significantly better results were achieved when trapping of lithiated species was performed in situ. LTMP proved to be compatible with some electrophiles and 4- and 4,6-disubstituted pyrimidines (**4a–c**, **5c**) were isolated in moderate to low yields.

Tacke et al. [15] studied co-condensation reactions of nitrogen-containing heterocycles with lithium atoms, in the presence of THF at −196°C. The reaction of pyrimidine **1** afforded the dimer **3** in 32% yield, supposedly through a radical intermediate.

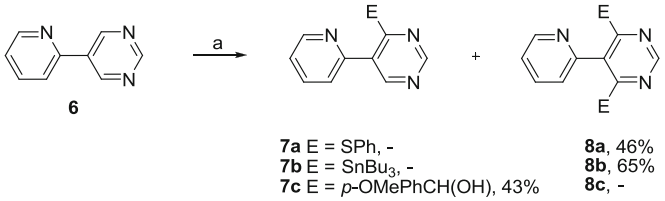
The role of pyridine as DMG in pyridin-2-yl substituted diazines was examined by Plé et al. [16]. The regioselectivity of lithiations with an excess of LTMP was

[2] An interesting example of a lateral lithiation is discussed in Sect. 6.1, Scheme 32 [11].

[3] A radical coupling of pyrimidines promoted by 3 equiv of sodium and followed by air oxidation was reported to provide 6,6′-disubstituted 4,4′-bipyrimidines in yields of 56–93% [14].



Scheme 2 (**a**) (i) 4 equiv LTMP, THF, −78°C, 15 min; (ii) 6 equiv DCl, EtOD, THF, −78°C, then warming to rt



Scheme 3 (**a**) (i) 4 equiv LTMP, THF, −78°C, 15 min; (ii) 4 equiv E+ (PhSSPh, Bu_3SnCl or *p*-OMePhCHO), THF, −100°C, 30 min; (iii) THF/EtOH/H_2O

determined by quenching with DCl/EtOD and following examination of ^{1}H-NMR spectra of the mixtures (Scheme 2).

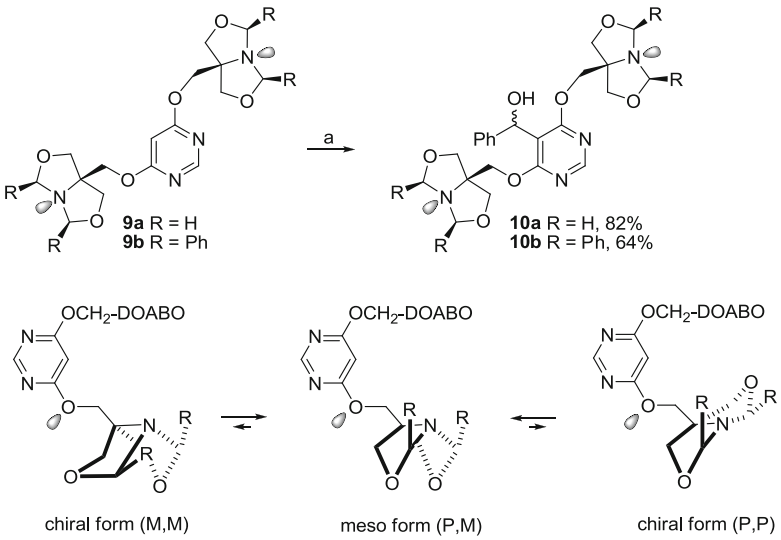
The *ortho*-position of the pyridine–pyrimidine linkage was completely deuterated via supposed intermediate **7**, along with minor deuterations at other sites. Nevertheless, two of the three other electrophiles exhibited a strong preference for repetitive substitutions at the *ortho*-position (Scheme 3).

Darabantu et al. [17] described lithiations of pyrimidines bearing two DMGs in positions 4 and 6. The system was rather complex, as each of the DMGs, that is α-(3,7-dioxa-r-1-azabicyklo[3.3.0]oct-*c*-5-ylmethoxy groups (DOABO-CH_2O), could exist in two chiral forms interconverting through a *meso* form (Scheme 4).

The CH_2O bridges were expected to coordinate the lithium atom and assist in hydrogen removal. The pyrimidine **9a** bearing (2H)DOABO units was unreactive at −78°C and the reaction temperature had to be raised to rt, which was rationalized by DOABO systems being locked in *meso* form. In case of pyrimidine **9b**, the (2Ph) DOABO conformers were still flipping at −78°C and a complete conversion was observed at this temperature. However, mechanistic details explaining the observed differences in reactivity remain unclear.

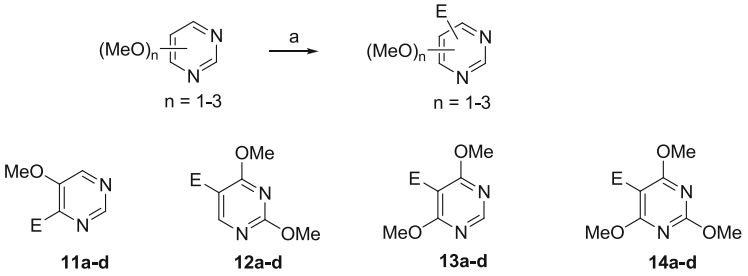
3 Alkoxy and Alkylthiopyrimidines

Lithiations of pyrimidines bearing methoxy group(s) have been known for a longer time and are well covered in several reviews [2, 3, 18]. Over the last several years research activity in this area has been relatively low. An example illustrating standard protocols is depicted in Table 1 [19].



Scheme 4 (**a**) (i) 4 equiv LTMP, THF, −78°C, 2 h; (ii) 4 equiv PhCHO, THF, −78°C to rt, 12 h; (iii) CH_2Cl_2/H_2O, rt

Table 1 Functionalization of methoxy pyrimidines by means of *ortho*-lithiation



(**a**) (i) 1.3 equiv LTMP, THF, −78°C, 15 min; (ii) 1.5 equiv E+ (TMSCl, MeI, PhCHO or PhCOCl), THF, −78°C to rt, overnight

E	Products (%)			
TMS	**11a** (47)	**12a** (68)	**13a** (76)	**14a** (99)
Me	**11b** (47)	**12b** (83)	**13b** (75)	**14b** (92)
PhCHOH	**11c** (49)	**12c** (98)	**13c** (97)	**14c** (95)
PhCO	**11d**[a]	**12d**[a]	**13d** (84)	**14d** (91)

[a]Formation of a complex mixture was observed

In general, lithiated alkoxy substituted pyrimidines exhibit a better thermal stability and are less susceptible to dimerizations. Acidity of *ortho* hydrogens is increased by the inductive electron-withdrawing properties of the substituents. Moreover, coordination of the DMG to a metal makes *ortho* metalation more likely

Scheme 5 (**a**) (i) 1.2 equiv *n*-BuLi, Et_2O, −30°C, 1.5 h; (ii) 1.0 equiv HCO_2Et, −70°C, 1 h

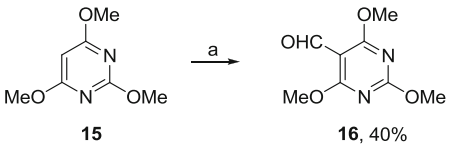
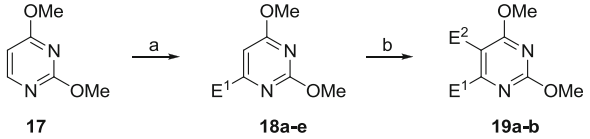
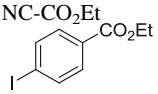
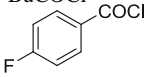
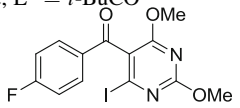


Table 2 A selective magnesiation utilized in derivatization of 2,4-dimethoxypyrimidine **17**



(**a**) (i) 1.1 equiv TMPMgCl·LiCl, THF, 25°C, 15 min; (ii) E+; (**b**) (i) 1.1 equiv TMPMgCl·LiCl, THF, 0°C (**18a**) or −40°C (**18b**), 1 h; (ii) E+

Entry	Substrate	E+	Product	Yield (%)
1	**17**	I_2	**18a**, E^1 = I	74
2	**17**	TMS-CN	**18b**, E^1 = TMS	70
3	**17**	NC-CO_2Et	**18c**, E^1 = CO_2Et	71
4	**17**		**18d**, E^1 = *p*-PhCO_2Et	75[a]
5	**17**	*t*-BuCOCl	**18e**, E^1 = *t*-BuCO	72[b]
6	**18a**, E^1 = I		 **19a**	84[b]
7	**18b**, E^1 = CO_2Et	PhCOCl	**19b**, E^1 = CO_2Et, E^2 = COPh	78[b]

[a]Transmetalation with 1.2 equiv $ZnCl_2$, followed by coupling catalyzed by 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$

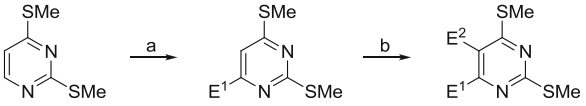
[b]1 equiv of CuCN·2LiCl was added [22]

due to the so-called "complex-induced proximity effect of the base" [20]. Methoxylated pyrimidines are less prone to nucleophilic additions, as illustrated by a recently reported lithiation of **15** with *n*-BuLi at −30°C (Scheme 5) [21].

A fresh blow to the field was brought by Knochel et al. [7]. They disclosed that 2,4-dimethoxypyrimidine **17** can be magnesiated by TMPMgCl·LiCl exclusively in position 6 (Table 2, **18**), thus establishing a complementary metalation procedure to lithiations by LTMP in position 5 (Table 1, **12a–d**).

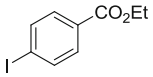
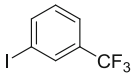
Magnesiated intermediate can be directly reacted with an electrophile (entries 1–3) or transmetallated for a subsequent coupling reaction (entries 4, 5). Repeated magnesiation enables a successive functionalization of positions 6 and 5, respectively (entries 6, 7). A tolerance of relatively high reaction temperatures is

Table 3 A synthesis of 6- and 5,6-substituted 2,4-bis(methylthio)pyrimidines via magnesiation



20 **21a-e** **22a-b**

(**a**) (i) 1.1 equiv $TMP_2Mg{\cdot}2LiCl$, THF, −20°C, 1 h; (ii) E+; (**b**) (i) 1.1 equiv $TMP_2Mg{\cdot}2LiCl$, THF, −5°C, 45 min; (ii) E+

Entry	Substrate	E+	Product	Yield (%)
1	**20**	I_2	**21a**, $E^1 = I$	76
2	**20**	$(BrCCl_2)_2$	**21b**, $E^1 = Br$	81
3	**20**	$FCCl_2CClF_2$	**21c**, $E^1 = Cl$	78
4	**20**		**21d**, $E^1 = p\text{-}PhCO_2Et$	71[a]
5	**20**		**21e**, $E^1 = m\text{-}PhCF_3$	80[a]
6	**21c**, $E^1 = Cl$	I_2	**22a**, $E^1 = Cl$, $E^2 = I$	61
7	**21c**, $E^1 = Cl$	PhCOCl	**22b**, $E^1 = Cl$, $E^2 = COPh$	65[b]
8	**21c**, $E^1 = Cl$	PhCHO	**22c**, $E^1 = Cl$, $E^2 = CH(OH)Ph$	66

[a]Transmetalation with 1.2 equiv $ZnCl_2$, followed by coupling catalyzed by 3 mol% $Pd(dba)_2$ and 6 mol% P(*o*-furyl)$_3$

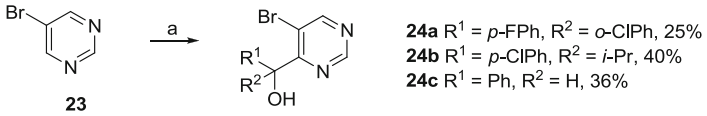
[b]1 equiv of CuCN·2LiCl was added [22]

remarkable. The same approach was successfully extended to analogous 2,4-bis (methylthio)pyrimidine **20** (Table 3). The reagent switch for $TMP_2Mg{\cdot}2LiCl$ was not commented on.

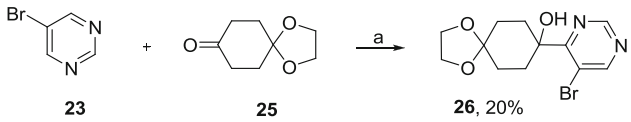
4 Halopyrimidines

4.1 Deprotonative Lithiations and Grignard Reactions

Similar to unsubstituted pyrimidines, monohalogenated pyrimidines upon deprotonation tend to dimerise [4, 12, 23]. However, when lithiations are performed in the presence of an electrophile, 4-substituted-5-bromopyrimidines **24a–c** are accessible in moderate yields (Scheme 6). A decrease in reaction temperatures to −65°C was reported to affect the reaction outcome just marginally (a yield improvement of 5% for **24c**).



Scheme 6 (**a**) (i) 1 equiv LDA, 1 equiv E+, Et_2O, −10°C to 0°C, 2 h; (ii) 7% aq HCl [23]



Scheme 7 (**a**) (i) **23**, LDA, THF, −78°C; (ii) **25**

Lately, a lithiation of 4-bromopyrimidine **23** and a quench with ketone **25** were performed in a stepwise manner with success; however, the target ketal **26** was isolated in only 20% yield (Scheme 7) [24].

In fluoro, chloro, and bromo 2,4-dihalopyrimidine series, similar trends in regioselectivity were observed. LDA turned out to be suitable for generation of the 5-lithio derivatives [25–27], while LTMP can preferentially deprotonate the position next to the nitrogen (Table 4, illustrative examples) [27, 28].

In general, the obtained yields were decreasing in the order of F ≈ Cl > Br, and the regioselectivity was closely related to the reaction conditions, particularly to the reaction temperature.

A significantly better outcome can be expected if lithiated 2,4-dihalopyrimidine species are stabilized by an additional electron-withdrawing group (e.g., CF_3). Schlosser et al. described syntheses of 2,4-dihalo-6-(trifluoromethyl)pyrimidine-5-carboxylic acids **31a–b** in excellent yields (Scheme 8) [4].

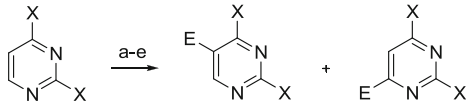
A deprotonative lithiation of 2,4-dichloropyrimidine **27b** with LDA was recently applied in a synthesis of a novel p38α inhibitor **34**, exhibiting potent activity in treatment of arthritic diseases (Scheme 9) [29].

In addition to 2,4-dihalopyrimidines, only few reports exist on lithiations of other dihalo and trihalopyrimidines. Radinov et al. selectively converted 4,6-dichloro and 2,4,6-trichloropyrimidines to 5-lithio species, being flanked by two activating halogen atoms [30, 31].

In the field of magnesiations, an introduction of mixed Mg/Li amides by Knochel et al. represented a remarkable breakthrough [8]. TMPMgCl·LiCl has very good solubility (ca. 1.2 M) and stability (over 6 months) in THF and improved kinetic activity in comparison with TMPMgX. Upon inverse addition to THF solution of TMPMgCl·LiCl and subsequent reaction with an electrophile, monohalopyrimidines **23** and **37** furnished functionalized derivatives **36** and **39a–b** in a completely regioselective fashion (Scheme 10).

A remarkable synthetic flexibility of magnesiations effectuated by TMPMgCl·LiCl was convincingly demonstrated on successive functionalizations of 2-bromopyrimidine **40** (Table 5) [9, 10].

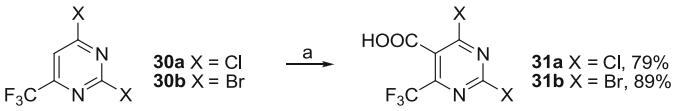
Table 4 Examples of 2,4-dihalopyrimidine lithiations



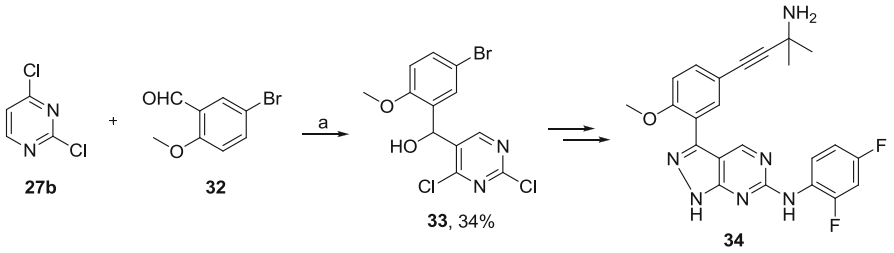
(**a**) (i) 2.3 equiv LDA, THF, −70°C, 30 min; (ii) E+, −70°C, 1 h; (iii) 35% aq HCl/EtOH/THF, −70°C; (**b**) (i) 2.3 equiv LDA, THF, −78°C, 1 h; (ii) E+, −78°C, 1 h; (iii) hydrolysis, −78°C; (**c**) (i) 1.4 equiv LTMP, 2.7 equiv HMPA, THF, −70°C, 1.5 h; (ii) E+, −70°C, 1 h; (iii) 35% aq HCl/EtOH/THF, −70°C; (**d**) (i) 3.2 equiv LDA, THF, −100°C, 30 min; (ii) E+, −100°C, 1.5 h; (iii) concd HCl/EtOH/THF, −100°C; (**e**) (i) 3.2 equiv LTMP, THF, −100°C, 30 min; (ii) E+, −100°C, 1.5 h; (iii) concd HCl/EtOH/THF, −100°C

Entry	Subst/Cond	E+	Product	Yield (%)
1	**27a**/a [26]	MeCHO	**28a**, X = F, E = MeCH(OH)	61
2	**27a**/a [26]	3,4,5-$(OMe)_3$PhCHO	**28b**, X = F, E = 3,4,5-$(OMe)_3$PhCH(OH)	47
3	**27b**/b [25]	DCl/CD_3OD	**28c**/**29c** = 94/6, X = Cl, E = D	58[a]
4	**27b**/b [25]	MeCHO	**28d**, X = Cl, E = MeCH(OH)	57
5	**27b**/b [25]	3,4,5-$(OMe)_3$PhCHO	**28e**/**29e** = 90/10, X = Cl, E = 3,4,5-$(OMe)_3$PhCH(OH)	58[a]
6	**27b**/c [28]	DCl/CD_3OD	**29f**, X = Cl, E = D	43
7	**27b**/c [28]	MeCHO	**29g**, X = Cl, E = MeCH(OH)	19
8	**27c**/d [27]	MeCHO	**28h**/**29h** = 80/20, X = Br, E = MeCH(OH)	25[a]
9	**27c**/e [27]	MeCHO	**29h**, X = Br, E = MeCH(OH)	21

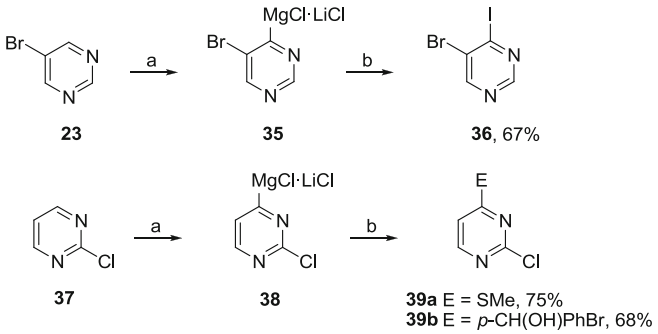
[a]Overall yield



Scheme 8 (**a**) (i) 1 equiv LDA, THF, −75°C, 45 min; (ii) solid CO_2; (iii) 2M HCl



Scheme 9 (**a**) (i) **27b**, LDA, THF, −78°C; (ii) **32**



Scheme 10 (**a**) 1.2 equiv TMPMgCl·LiCl, THF, −55 to −40°C, 2 h; (**b**) (i) E+ (I_2, $MeSO_2SMe$, *p*-BrPhCHO); (ii) aq NH_4Cl

All positions of the pyrimidine ring could be regioselectively metalated in a stepwise fashion, in a sequence of C-4, C-6, and C-5. The magnesiated intermediates were either directly trapped by suitable electrophiles or transmetalated to broaden the coupling options. The method was extended to concise syntheses of p38 kinase inhibitor **46** and sPLA2 inhibitor **50**, both having anti-inflammatory properties, starting from commercially available pyrimidine **44** (Scheme 11).[4]

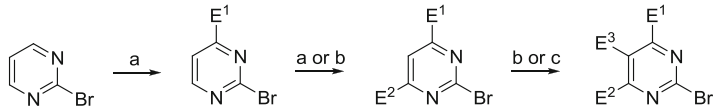
4.2 Lithiations and Grignard Reactions by Halogen–Metal Exchange

In cases when structural features of a pyrimidine substrate do not permit a region- and chemoselective deprotonative functionalization, a halogen–metal exchange is an alternative enabling a safe permutation at a desired position of the ring [6]. Availability of some starting halopyrimidines may nevertheless be cumbersome and if having an option, direct deprotonative metalations are usually preferred. A characteristic situation when halogen–metal permutation is the method of choice comprises lithiations at position C-5. Typically, lithiations are executed with *n*-BuLi at very low temperatures (−100°C) to suppress competitive alkylations, followed by a rapid quench with an electrophile (Table 6) [32–36].

The halogen–metal exchange can be extremely fast, as evident from reaction conditions reported for entries 4 and 5. However, depending on both the halogen itself and the flanking substituents, significant differences in reactivity between two halogen atoms can be observed and a highly chemo- and regioselective monometalation of dihalogenated pyrimidines is achievable (Table 7) [4, 37].

[4] Metalations of other alkylthiohalopyrimidines are discussed in Sect. 5.

Table 5 Repetitive functionalization of 2-bromopyrimidine **40** using TMPMgCl·LiCl



(**a**) (i) 1.1 equiv TMPMgCl·LiCl, THF, −60 to −55°C; (ii) E+; (**b**) (i) 1.1 equiv TMPMgCl·LiCl, THF, rt; (ii) E+; (**c**) (i) 1.1 equiv $TMP_2Mg·2LiCl$, THF, −10°C; (ii) E+

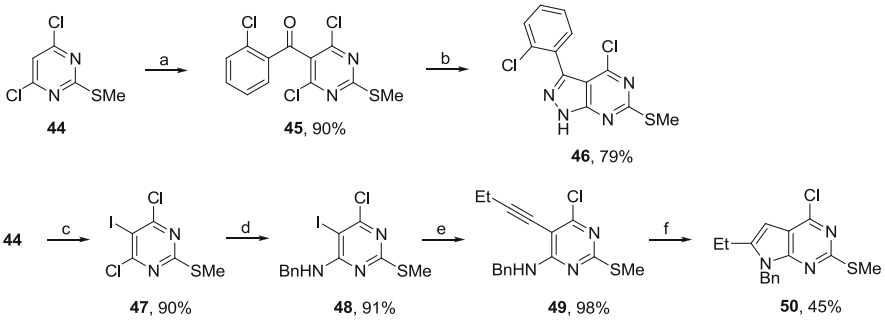
Entry	Subst/Cond	E+	Product	Yield (%)
1	**40**/a [9]	$MeSO_2SMe$	**41a**, E^1 = SMe	81
2	**40**/a [10]	$PhSO_2SPh$	**41b**, E^1 = SPh	77
3	**40**/a [9]	I_2	**41c**, E^1 = I	85[a]
4	**40**/a [9]	$BrCCl_2CCl_2Br$	**41d**, E^1 = Br	71
5	**40**/a [10]	$ClCF_2CCl_2F$	**41e**, E^1 = Cl	71
6	**40**/a [9]	TMSCN	**41f**, E^1 = TMS	68
7	**40**/a [10]	*p*-IPhCl	**41g**, E^1 = *p*-PhCl	67[b]
8	**40**/a [9]	*m*-$IPhCF_3$	**41h**, E^1 = *m*-$PhCF_3$	72[b]
9	**40**/a [9]	*p*-$IPhCO_2Et$	**41i**, E^1 = *p*-$PhCO_2Et$	81[b]
10	**40**/a [10]	2-iodothiophene	**41j**, E^1 = thiophen-2-yl	62[b]
11	**41c** [10]	hex-1-yne	**41k**, E^1 = hex-1-ynyl	56[c]
12	**41c** [9]	phenylacetylene	**41l**, E^1 = phenylethynyl	71[c]
13	**41a**/b [9]	$ClCF_2CCl_2F$	**42a**, E^1 = SMe, E^2 = Cl	76
14	**41a**/b [9]	$BrCCl_2CCl_2Br$	**42b**, E^1 = SMe, E^2 = Br	81
15	**41a**/b [9]	I_2	**42c**, E^1 = SMe, E^2 = Br	78
16	**41b**/a [10]	$ClCF_2CCl_2F$	**42d**, E^1 = SPh, E^2 = Cl	90
17	**41b**/a [10]	TsCN	**42e**, E^1 = SPh, E^2 = CN	67
18	**41b**/a [10]	$BrCCl_2CCl_2Br$	**42f**, E^1 = SPh, E^2 = Br	85
19	**41c**/a [9]	TMS-CN	**42g**, E^1 = I, E^2 = TMS	93
20	**41c**/a [10]	I_2	**42h**, E^1 = I, E^2 = I	82[a]
21	**41c**/a [10]	$BrCCl_2CCl_2Br$	**42i**, E^1 = I, E^2 = Br	67
22	**41c**/a [10]	TMS-CN	**42j**, E^1 = I, E^2 = TMS	89
23	**41h**/a[d] [9]	$ClCF_2CCl_2F$	**42k**, E^1 = *m*-$PhCF_3$, E^2 = Cl	91
24	**41h**/a[d] [9]	TMS-CN	**42l**, E^1 = *m*-$PhCF_3$, E^2 = TMS	72
25	**41h**/a[d] [9]	$MeSO_2SMe$	**42m**, E^1 = *m*-$PhCF_3$, E^2 = SMe	76
26	**41l**/a[e] [9]	$ClCF_2CCl_2F$	**42n**, E^1 = phenylethynyl, E^2 = Cl	84
27	**42a**/b [9]	PhCOCl	**43a**, E^1 = SMe, E^2 = Cl, E^3 = PhCO	81[f]
28	**42a**/b [9]	PhCHO	**43b**, E^1 = SMe, E^2 = Cl, E^3 = PhCH(OH)	75
29	**42a**/b [9]	$MeSO_2SMe$	**43c**, E^1 = SMe, E^2 = Cl, E^3 = SMe	92
30	**42d**/c [10]	*o*-ClPhCOCl	**43d**, E^1 = SPh, E^2 = Cl, E^3 = *o*-ClPhCO	77[f]
31	**42d**/c [10]	Allyl bromide	**43e**, E^1 = SPh, E^2 = Cl, E^3 = allyl	89 [a,f]

(continued)

Table 5 (continued)

Entry	Subst/Cond	E+	Product	Yield (%)
32	**42d**/c [10]	$MeSO_2SMe$	**43f**, E^1 = SPh, E^2 = Cl, E^3 = SMe	80
33	**42n**/b[g] [9]	I_2	**43g**, E^1 = phenylethynyl, E^2 = Cl, E^3 = I	71
34	**42n**/b[g] [9]	PhCOCl	**43h**, E^1 = phenylethynyl, E^2 = Cl, E^3 = PhCO	69[f]
35	**42n**/b[g] [9]	allyl bromide	**43i**, E^1 = phenylethynyl, E^2 = Cl, E^3 = allyl	67[f]

[a]The magnesiated pyrimidine derivative was transmetalated with 1.1 equiv $ZnCl_2$
[b]Transmetalation with $ZnCl_2$, followed by coupling catalyzed by $Pd(dba)_2/P(o\text{-furyl})_3$
[c]2-Bromo-4-iodopyrimidine **41c** was generated in situ and reacted with $Pd(dba)_2/P(o\text{-furyl})_3$, CuI, Et_3N, and alkyne
[d]Magnesiations at −40°C
[e]Magnesiations at −20°C
[f]Transmetalation with CuCN·2LiCl [22]
[g]Magnesiations at −5°C



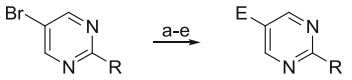
Scheme 11 (**a**) (i) 1.1 equiv TMPMgCl·LiCl, THF, rt, 20 min; (ii) 1.1 equiv CuCN·2LiCl, 2.0 equiv *o*-ClPhCOCl, rt, 1 h; (**b**) $NH_2NH_2{\cdot}H_2O$, THF, rt, 10 min; (**c**) (i) 1.1 equiv TMPMgCl·LiCl, THF, rt, 20 min; (ii) 1.5 equiv I_2, THF, rt, 20 min; (**d**) 1.7 equiv $BnNH_2$, THF, rt, 20 min; (**e**) (i) 3 mol% $Pd(dba)_2$, 6 mol% $P(o\text{-furyl})_3$, 4 mol% CuI, Et_3N; (ii) 2.0 equiv but-1-yne, 50°C, 1 h; (**f**) 2.0 equiv *t*-BuOK, NMP, rt, 1 h

5 Pyrimidines Bearing a Combination of Halo, Alkoxy, and Alkylthio Substituents

5.1 Deprotonative Lithiations and Grignard Reactions

Unsurprisingly, metalations of pyrimidines decorated with miscellaneous arrangements of halo, alkoxy, and alkylthio substituents are often found to exhibit features similar to those of halogenated or alkoxylated pyrimidines. Analogous with 2,4-dihalopyrimidines **27a–c** (Table 4), 4-halo-2-methylthiopyrimidines were

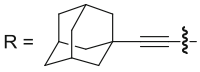
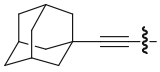
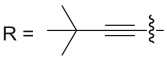
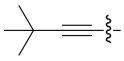
Table 6 Recent examples of dehalogenative lithiations on 5-bromopyrimidines **23** and **51a–c**, respectively



23 (R = H)
51a-c

52a-e

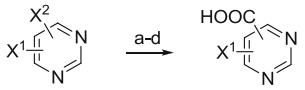
(**a**) (i) 1.4 equiv *n*-BuLi, THF/Et_2O 1:1, −100°C, 30 min; (ii) 1.4 equiv E+, −100 to 25°C, 16 h; (**b**) (i) 1.0 equiv *n*-BuLi, THF, −100°C, 20 min; (ii) 1.0 equiv E+, −100°C, 20 min; (iii) 2 M HCl/Et_2O, <−85°C; (**c**) (i) 2 equiv *n*-BuLi, 1 equiv TMEDA, THF, −110°C, 30 min; (ii) 1.0 equiv E+, −110°C, 20 min; (iii) HCl, dioxane, −110°C; (**d**) (i) 1.2 equiv *n*-BuLi, THF, −95°C, 30 s; (ii) excess of E+, −90°C, 20 min; (iii) aq NH_4Cl; (**e**) (i) 1.0 equiv *n*-BuLi, THF, −100°C, 2 min; (ii) 1.0 equiv E+, −100°C to rt

Entry	Subst/Cond	E+	Product	Yield (%)
1	**23**/a [32]	2-F-6-CF_3PhCHO	**52a**, R = H, E = 2-F-6-CF_3PhCH(OH)	65
2	**23**/b [33]	HCO_2Et	**52b**, R = H, E = CHO	52
3	**51a**/c [34]	HCO_2Et	**52c**, E = CHO	54
	R = 		R = 	
4	**51b**/d [35] R = *p*-CF_3OPh	DMF	**52d**, R = *p*-CF_3OPh, E = CHO	74
5	**51c**/e [36]	$(CH_3)_2CHCHO$	**52e**, E = $(CH_3)_2CHCH(OH)$	79
	R = 		R = 	

regioselectively lithiated with LDA at C-5, while bulkier and more basic LTMS provided mainly the corresponding C-6-regioisomers [25, 26, 38]. The preference for C-6 was even more pronounced when a highly hindered lithium *N*,*N*-*t*-butyl-(1-*i*-propylpentyl)amide was employed as a base [39]. However, in the presence of a methoxy group at C-4, *ortho*-lithiations at C-5 are favored even with LTMS (Scheme 12) [40, 41].

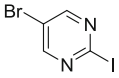
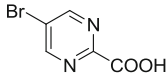
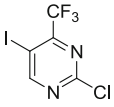
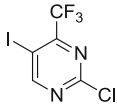
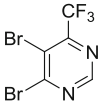
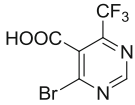
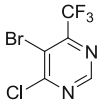
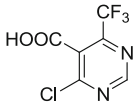
Remarkably, on the contrary to the other electrophiles, trapping of lithiated pyrimidine **55** with iodine at −70°C provided six-substituted derivative **57**. This has been attributed to a possible isomerization of 5-iodo derivative **56d**, promoted by either LTMP or lithiated intermediates ("halogen-dance" [42, 43]). Indeed, iodination at −100°C furnished 6-iodo pyrimidine **56d** in 42% yield, along with 18% of **57**.

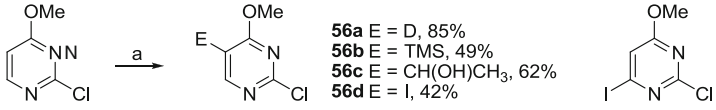
Table 7 Monometalations of dihalogenated pyrimidines **53a–d**



53a-d **54a-d**

(**a**) (i) 1.05 equiv *n*-BuLi, THF, −78°C, 1 h; (ii) CO_2 (s); (iii) AcOH; (**b**) (i) *n*-BuLi, THF, −75°C, 15 min; (ii) CO_2 (s); (iii) HCl; (**c**) (i) 1.0 equiv *i*-PrMgCl, THF/Et_2O, −10°C, 2 h; (ii) CO_2 (s); (iii) 2 M HCl; (**d**) (i) 1.0 equiv *n*-BuLi, hexanes/toluene, −75°C, 45 min; (ii) CO_2 (s); (iii) 2 M HCl

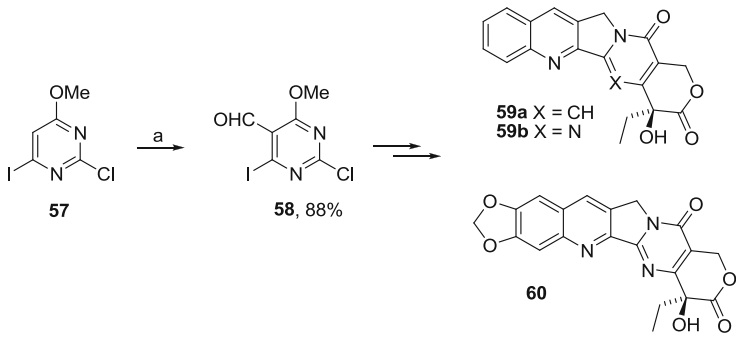
Entry	Substrate	Cond	Product
1	 **53a**	a [37]	 **54a**, 62%
2	 **53b**	b [4]	 **54b**, 29%
3	 **53c**	c [4]	 **54c**, 54%
4	 **53d**	d [4]	 **54d**, 73%



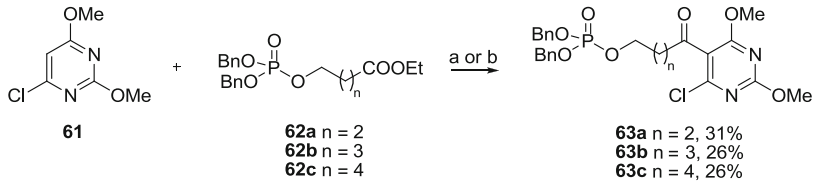
55 **57**, 85%

Scheme 12 (**a**) (i) 2.3 equiv LTMP, THF, −70°C, 1 h; (ii) E+ (DCl/CD_3OD, TMSCl, CH_3CHO or I_2), −70°C (−100°C for **56d**), 1–1.5 h; (iii) 35% HCl/EtOH/THF

The protocol describing preparation of pyrimidine **57** [41], as depicted in Scheme 12, was later exploited by Hecht et al. in synthesis of analogues of anticancer agent camptothecin **59a** (Scheme 13, X = CH), 14-azacamptothecin



Scheme 13 (**a**) (i) 2.5 equiv LTMP, THF, −70°C, 1 h; (ii) 13 equiv HCO_2Et, −70°C, 1 h; (iii) HCl/EtOH/THF



Scheme 14 (**a**) (i) 1.0 equiv *n*-BuLi, THF, −30°C, 1.5 h; (ii) 1.0 equiv **62a**, −78°C, 1 h; (iii) 35% HCl, THF; (**b**) (i) 1.0 equiv *n*-BuLi, THF, −78 to −70°C, 20 min; (ii) 1.0 equiv **62b** or **62c**, −40°C, 1–1.5 h; (iii) brine

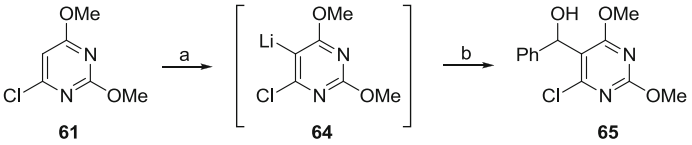
59b [44], and 10,11-methylenedioxy-14-azacamptothecin **60** [45], respectively. A follow-up deprotonative lithiation of **57** enabled a smooth introduction of a formyl group to the remaining position at C-5.

On the other hand, acylations of lithiated pyrimidine **61** were observed to give only low yields of **63a–c** (Scheme 14) [46]. Interestingly, preparation of homologue **63a** turned out to be problematic under conditions leading to **63b–c**, and a deprotonative lithiation at relatively high temperature (−30°C; −70°C for **63b–c**) followed by a quench with an ester at low temperature (−78°C; −40°C for **63b–c**) was found to be essential to a successful synthesis.

Hřebabecký et al. [47] described a simple, yet informative study of thermal stability of lithiated pyrimidine **64**, based on the regular treatment of samples with 3 equiv of benzaldehyde and GC-MS analysis after a reaction time of 1 h at −75°C (Table 8).

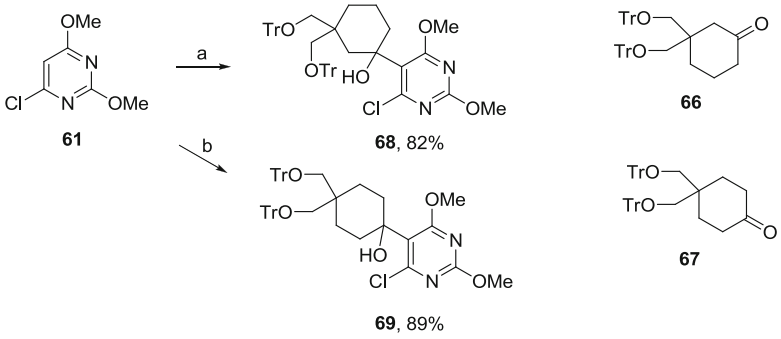
A control experiment at −75°C with exclusion of a prolonged stirring of **64** yielded **65** in 88%. Thus, the deterioration of lithiated intermediate **64** at −75°C with a drop of 4% in 8.5 h can be considered to be relatively slow. However, the obtained data indicate a dramatic decrease in stability of **64** at temperatures above −25°C. This know-how was exploited in synthesis of derivatives **68** and **69**, containing a masked uracil subunit (Scheme 15).

Table 8 Yields of pyrimidine **65** reflecting a time-dependent thermal stability of intermediate **64**



(**a**) (i) 1.1 equiv *n*-BuLi, THF, −75°C, 30 min; (ii) stirring at defined temperature (**b**) (i) 3 equiv PhCHO, THF, −75°C, 1 h; (ii) aq NH_4Cl

	Temperature (°C)		
Time of stirring (h)	−75	−25	0
2	87%	78%	16%
4.5	86%	70%	0%
8.5	84%	43%	0%

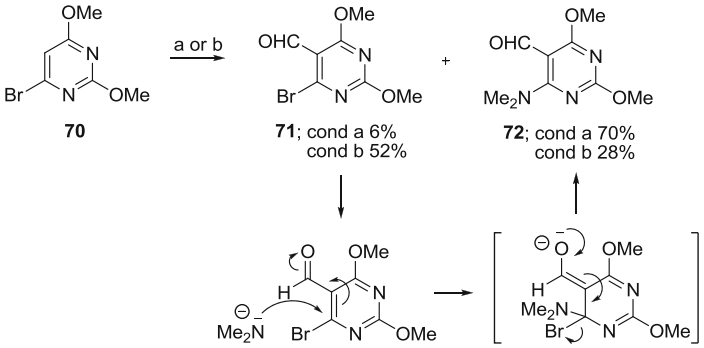


Scheme 15 (**a**) (i) 1.1 equiv *n*-BuLi, THF, −75°C, 25 min; (ii) 0.77 equiv **66**, 35 min at −75°C, 2 h at −30°C, 16 h at 0°C; (iii) aq NH_4Cl; (**b**) (i) 1.1 equiv *n*-BuLi, THF, −75°C, 30 min; (ii) 0.77 equiv **67**, 35 min at −75°C, 4 h at −30°C, 16 h at −10°C; (iii) aq NH_4Cl

A related 4-bromo-2,6-dimethoxypyrimidine **70** was reported to be prone to a nucleophilic displacement of the halogen upon formylation with DMF (Scheme 16) [48]. Presumably, the initial introduction of formyl group activated the pyrimidine ring towards the released dimethylamide and a substitution occurred via addition–elimination mechanism. Formation of **72** was partially suppressed by quenching the reaction mixture at −78°C (conditions b).

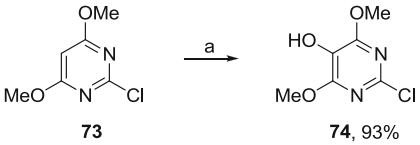
Lithiated pyrimidines are eligible for high-yielding oxidations, as demonstrated on 2-chloro-4,6-dimethoxypyrimidine **73** (Scheme 17) [49]. Alternative to *t*-BuOOH, dioxygen can serve as a source of the hydroxyl group, affording **74** in a less appealing 44% yield.

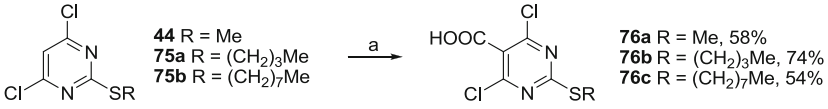
A series of 2-alkylthio-4,6-dichloropyrimidines **44**, **75a–b** (Scheme 18) can be safely deprotonated with LDA at the only free position left and quenched with an



Scheme 16 (**a**) (i) 2.5 equiv LDA, THF, −78°C, 10 min; (ii) 2.0 equiv DMF, −78°C, 1 h; (iii) aq NH_4Cl, rt; (**b**) (i) 2.5 equiv LDA, THF, −78°C, 2 h; (ii) 2.0 equiv DMF, −78°C, 2 h; (iii) aq NH_4Cl, -78°C

Scheme 17 (**a**) (i) 2.0 equiv LDA, THF, −78°C, 1 h; (ii) 2.1 equiv *t*-BuOOLi, −78 to 0°C, 3 h; (iii) 6M HCl





Scheme 18 (**a**) (i) 1.5 equiv LDA, THF, −78°C, 3–5 h; (ii) CO_2 (g), −78°C, 10 min; (iii) HCl

electrophile (e.g., CO_2) [50–52]. Irie et al. [53] reported 98% yield for **76a** under analogous reaction conditions, but with no experimental details.

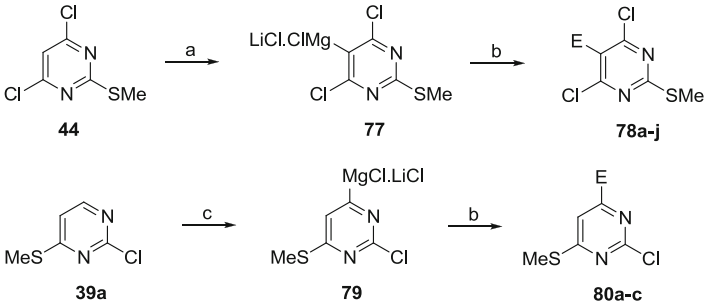
In comparison with lithiated 2-methylthio-4,6-dichloropyrimidine **44**, its magnesiated counterpart **77** has a remarkable thermal stability and can be generated and handled at ambient temperature (Table 9) [54].[5] The same magnesiation protocol, with somewhat shorter metalation time, is applicable to 2-chloro-4-methylthiopyrimidine **39a**. The intermediates **77** and **79** reliably react with a variety of electrophiles, with no substantial deviation in the reaction outcome.

A synthetic potential of the described magnesiations was demonstrated in preparation of the fungicide Mepanipyrim **83** (Scheme 19) [54].

Additional modes of functionalization of various halopyrimidines are enabled by zincation with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ [54].

[5] For related magnesiations see Tables 2, 3, and 5.

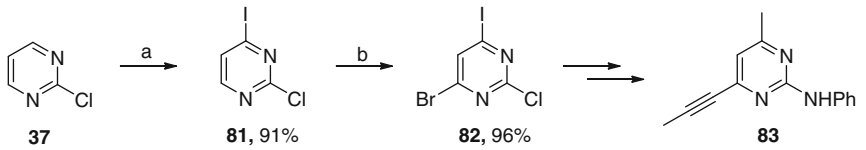
Table 9 Selective magnesiations of pyrimidines **44** and **39a** using TMPMgCl·LiCl, followed by a quench with an electrophile



(**a**) 1.1 equiv TMPMgCl·LiCl, THF, 25°C, 30 min; (**b**) E+; (**c**) as for (**a**), 5 min

Entry	Subst	E+	Product	Yield (%)
1	**44**	PhCHO	**78a**, E = CH(OH)Ph	90
2	**44**	$NCCO_2Et$	**78b**, E = CO_2Et	86
3	**44**	MeI	**78c**, E = Me	92
4	**44**	$BrCCl_2CCl_2Br$	**78d**, E = Br	89
5	**44**	TMS-CN	**78e**, E = TMS	79
6	**44**	*t*-$BuCOOCH_2I$	**78f**, E = *t*-$BuCOOCH_2$	76
7	**44**	PhCOCl	**78g**, E = PhCO	90[a]
8	**44**	*p*-FPhCOCl	**78h**, E = *p*-FPhCO	93[a]
9	**44**	furan-2-carbonyl chloride	**78i**, E = furan-2-carbonyl	86[a]
10	**44**	*t*-$BuCH_2COCl$	**78j**, E = *t*-$BuCH_2CO$	84[a]
11	**39a**	I_2	**80a**, E = I	71
12	**39a**	$BrCCl_2CCl_2Br$	**80b**, E = Br	79
13	**39a**	$ClCF_2CCl_2F$	**80c**, E = Cl	72

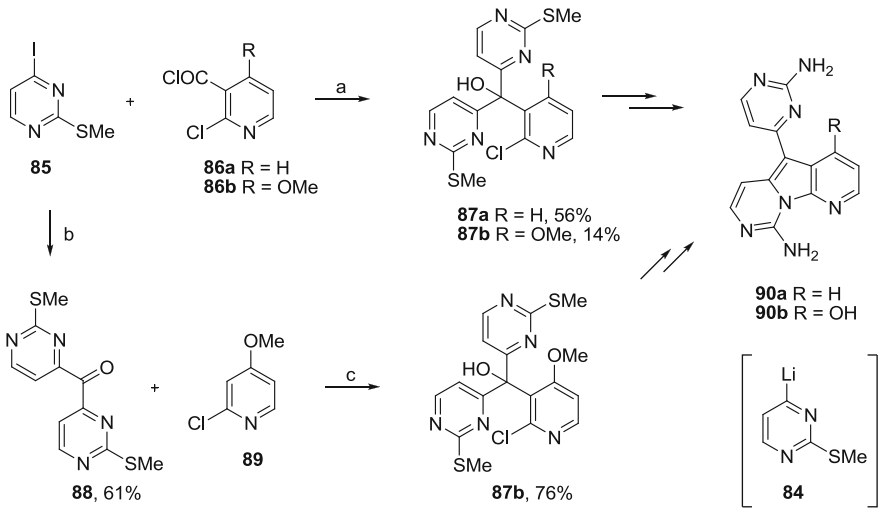
[a]The magnesiated pyrimidine derivative was transmetalated with 1.1 equiv CuCN·2LiCl [22]



Scheme 19 (**a**) (i) 1.1 equiv TMPMgCl·LiCl, THF, −60°C, 2 h; (ii) 1.1 equiv $ZnCl_2$, −60°C; (iii) 1.5 equiv I_2, THF, rt, 20 min; (**b**) (i) 1.1 equiv TMPMgCl·LiCl, THF, −60°C, 1 h; (ii) 1.5 equiv $BrCCl_2CCl_2Br$, −78 to −65°C, 3 h

5.2 Lithiations and Grignard Reactions by Halogen–Metal Exchange

Halogen–metal exchange has been established as a reliable method for a regioselective metalation of challenging substrates. As such can be regarded, for



Scheme 20 (**a**) (i) **85**, 1.0 equiv *n*-BuLi, THF, −95°C, 40 min; (ii) 0.34 equiv **86**, −95°C, 3.5 h; (iii) MeOH; (**b**) (i) **85**, 1.0 equiv *n*-BuLi, THF, −97°C, 50 min; (ii) 0.5 equiv $(EtO)_2CO$, −97°C to rt; (iii) aq NH_4Cl; (**c**) (i) **89**, 1.0 equiv *n*-BuLi, THF, −90 to −78°C, 80 min; (ii) 0.93 equiv **88**, −90 to −78°C, 3.5 h; (iii) MeOH, aq NH_4Cl

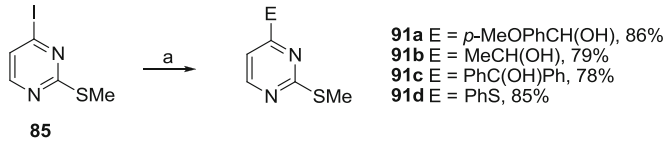
instance, a generation of 4-lithio-2-methylthiopyrimidine **84** species, readily decomposing at temperatures above −95°C. Morris et al. [55] employed iodine–lithium permutation of 4-iodo-2-methylthiopyrimidine **85** in total syntheses of a marine alkaloid Variolin B **90b** and its analogue Deoxyvariolin B **90a** (Scheme 20).

Addition of *n*-BuLi to pyrimidine **85** (conditions a) through a special glasware set[6] secured efficient precooling of the reagent solution and suppressed decomposition of the lithiated intermediate. The Deoxyvariolin B building block **87a**, as a result of double-addition, was isolated in a good yield of 56%. Synthesis of **87a** was as well attempted under Barbier-type conditions,[7] however, the outcome was less satisfactory (40% yield). The analogous pathway to **87b** (conditions a) proved to be troublesome, and the yield dropped to unacceptable 14%. The authors took advantage of the product symmetry and proposed a two-step alternative (conditions b, c). The ketone **88** was readily available by reaction of lithiated pyrimidine **84** with diethyl carbonate. Thanks to the directing effects of the chlorine and the methoxy group, pyrimidine **89** was lithiated in position 3 and upon addition to **88** provided the Variolin B building block **87b** in a yield of 76%.

Interestingly, pyrimidine **85** can be metalated and further functionalized under significantly less stringent conditions using lithium tri-*n*-butylmagnesate

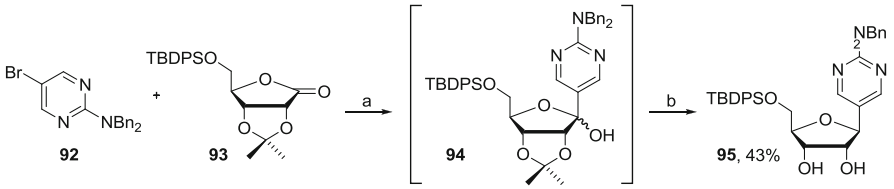
[6] The *n*-BuLi solution was precooled to −95°C when added through a spiral port. The glassware was first described by Suzuki and Noyori [56].

[7] The *n*-BuLi solution was carefully added to a mixture of **85** and **86a** in THF, at −95°C.



85

Scheme 21 (**a**) (i) 0.35 equiv *n*-Bu_3MgLi, THF, −10°C, 2.5 h; (ii) E+ (*p*-MeOPhCHO, MeCHO, PhCOPh and PhSSPh, respectively), −10°C to rt, 18 h; (iii) H_2O



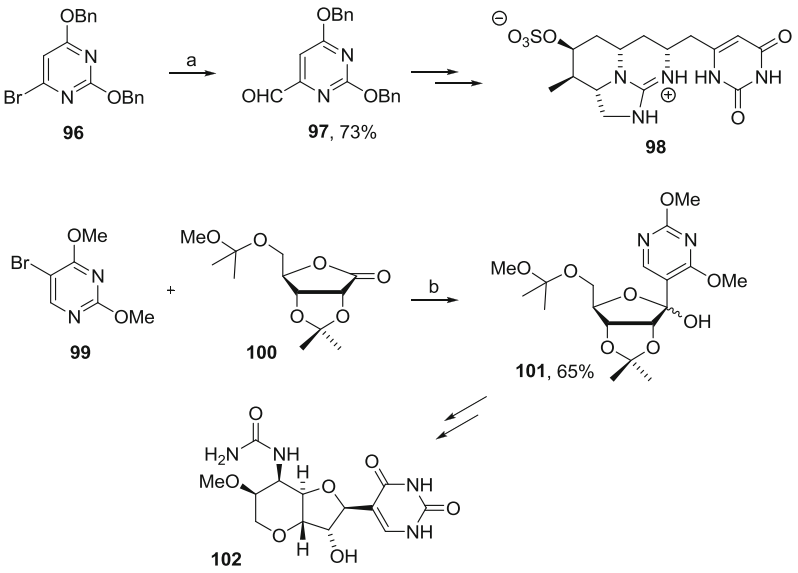
Scheme 22 (**a**) (i) **92**, 1.2 equiv *n*-BuLi, THF, −78°C, 1 h; (ii) 0.83 equiv **93**, −78°C to rt, 5 h; (iii) H_2O, work-up; (**b**) (i) 2.5 equiv Et_3SiH, 2.5 equiv $BF_3{\cdot}Et_2O$, −78°C to rt, overnight; (ii) satd $NaHCO_3$

and *n*-Bu_3MgLi [57]. Prior to metalation, *n*-Bu_3MgLi was readily prepared in situ by reacting 2 equiv *n*-BuLi with *n*-BuMgCl at −10°C in THF. Metalated pyrimidine smoothly reacted with four electrophiles and afforded products **91a–d** in good yields (Scheme 21).

For not quite obvious reasons, metalations of *N*-protected aminopyrimidines are rarely reported and a lithiation of *N*,*N*-dibenzyl-2-amino-5-bromopyrimidine **92** constitutes the only recent example [58]. Strictly considered, a pyrimidine bearing an amino group does not fall into scope of this section. Nevertheless, based on the structural features of **92**, discussing its chemistry here may be considered to be appropriate. Upon bromide–lithium exchange of **92** with *n*-BuLi at −78°C, the lithiated intermediate underwent addition to lactone **93**. The crude product **94** was consumed in a following reduction–deprotection sequence, providing C-nucleoside **95** in an overall yield of 43% (Scheme 22). On that account, the efficiency of initial metalation-addition steps remains unclear.

Halogenated 2,4-dialkoxypyrimidines have proven to be a useful tool in syntheses of complex targets containing a uracil subunit (Scheme 23). A bromine–lithium permutation at 2,4-bis(benzyloxy)-6-bromopyrimidine **96** by the action of *n*-BuLi and a subsequent formylation furnished **97**. This served as a building block in synthesis of the putative structure of 7-deoxycylindrospermopsin **98**, an analogue of hepatotoxic metabolites of the cyanobacterium *Cylindrospermopsis raciborskii* [59]. In analogy, 5-bromo-2,4-dimethoxypyrimidine **99** was upon lithiation added to lactone **100** giving **101** as a mixture of anomers in an α/β ratio of 1:9. Both of them were incorporated into structure of a potent fungicide malayamycin A **102** [60].

In a study published by Koszytkowska-Stawińska et al. [61], pyrimidine **99** was lithiated and magnesiated in parallel with the aim to compare the efficiency of both metalated reagents **103** and **105** in addition to reactions with a nitrone **104** (Table 10).



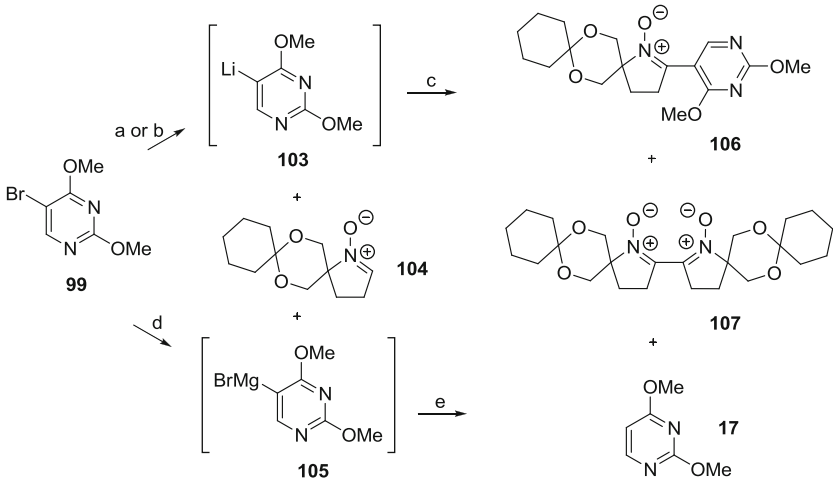
Scheme 23 (**a**) (i) 1.3 equiv *n*-BuLi, Et_2O, −100°C, 20 min; (ii) 5 equiv DMF, −100°C to reflux; (iii) 10% HCl; (**b**) (i) **99**, 2.1 equiv *t*-BuLi, THF, −78°C, 30 min; (ii) 0.77 equiv **100**, −78°C, 1.5 h; (iii) brine

Due to reported additions to ketonitrones, metalations with *n*-BuLi were not attempted. Pyrimidine **99** was successfully lithiated by the action of either 1.2 equiv or 2 equiv of *t*-BuLi (entries 1 and 2, respectively) and upon addition to nitrone **104** oxidized with $Cu(OAc)_2/NH_3$(aq). However, only the latter conditions (entry 2) led to the desired nitrone **106**, in a low yield of 17%. The accompanying dimer **107** presumably arises from deprotonative α-lithiation of the nitrone **104**, either by **103** or residual *t*-BuLi, followed by a cannibalistic addition to another nitrone **104**, and the oxidation. On the other hand, in the experiment with magnesiated pyrimidine **105** (entry 3), formation of **107** was completely suppressed and nitrone **106** was isolated in a somewhat better, though still unsatisfactory yield (36%).

Halogen–magnesium permutations pose a powerful tool in synthesis of 4,5-difunctionalized-2,6-dimethoxypyrimidines **65**, **112a–f**, and **113a–e**, which are easily convertible to the corresponding valuable uracil derivatives (Table 11) [62].

In the first step, starting from either 5-bromo-4-chloro or 4,5-dibromosubstituted pyrimidines **108** and **109**, respectively, magnesiation occurred selectively at C5. Subsequent reactions of the Grignard intermediates **110** (entries 1–7) or **111** (entries 8–13) with various electrophiles afforded the target pyrimidines in excellent yields. The method permits a successive introduction of two different electrophiles at C5 and C4 and was successfully executed even in a "one-pot" version (two examples). A considerable potential of stepwise magnesiations is apparent from the synthesis of HIV-1 inhibitor Emivirine **119**, described in the same paper (Scheme 24, steps a and c).

Table 10 Differences in reactivity of pyrimidines **103** and **105** with nitrone **104**



(**a**) 1.2 equiv *t*-BuLi, THF, −78°C, 30 min; (**b**) 2 equiv *t*-BuLi, THF, −78°C, 30 min; (**c**) (i) 0.89 equiv **104**, −78°C to rt, 3 h; (ii) a work-up; (iii) $Cu(OAc)_2$, NH_3 (aq), 1,4-dioxane, CH_2Cl_2, rt, 1 day; (**d**) 3 equiv Mg, 1.5 equiv $Br(CH_2)_2Br$, THF, reflux, 3 h; (**e**) (i) **104**, −10°C, 2 h; (ii) a work-up; (iii) $Cu(OAc)_2$, NH_3 (aq), 1,4-dioxane, CH_2Cl_2, rt, 1 day

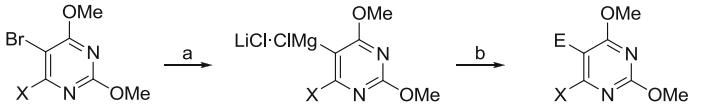
Entry	Conditions	**106/107/17** (yield in %)
1	a + c	-/34/71
2	b + c	17/39/70
3	d + e	36/-/39

McCaleb [38] and Soth [63] reported closely related examples of halogen–magnesium exchange at 5-bromo-2,4-bis-(2,4-difluorophenoxypyrimidine), performed with *i*-PrMgCl. Thereafter the metalated intermediate was reacted with either acid chloride or CO_2, to furnish the corresponding ketone and carboxylic acid, respectively.

Interesting synthetic applications can arise from a so far little explored area of transition-metal-catalyzed cross-couplings of magnesiated pyrimidines. In the synthesis of antibiotic Trimethoprim, Kofink, and Knochel [64] employed a copper-catalyzed coupling of magnesiated pyrimidine **120** with phosphate **121** as the key step (Scheme 25).

Triethyl phosphite $P(OEt)_3$ is presumed to stabilize the intermediate arylcopper species and along with tetrabutylammonium iodide were essential for the coupling reaction (conditions a). The protocol was expanded to various magnesiated aryl and indole derivatives.

Table 11 Functionalization of pyrimidines **108** and **109** at C5 via Br/Mg exchange

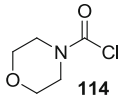
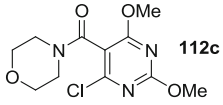
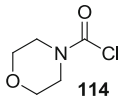
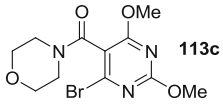


108 X = Cl
109 X = Br

110 X = Cl
111 X = Br

65, **112a-f** X = Cl
113a-e X = Br

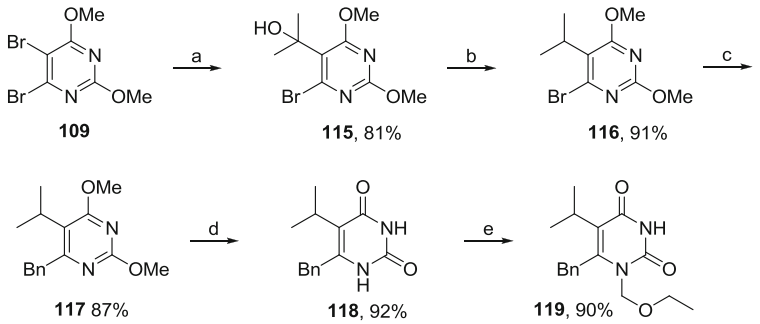
(**a**) 1.05 equiv *i*-PrMgCl·LiCl, THF, rt, 15 min; (**b**) (i) E+; (ii) aq NH_4Cl

Entry	Subst	E+	Product	Yield (%)
1	**108**	PhCHO	**65**, E = PhCH(OH)	91
2	**108**	*o*-MeOPhCHO	**112a**, E = *o*-MeOPhCH(OH)	83
3	**108**	PhCOCl	**112b**, E = PhCO	86
4	**108**	 **114**	 **112c**	85
5	**108**	TsCN	**112d**, E = CN	89
6	**108**	$NCCO_2Et$	**112e**, E = CO_2Et	87
7	**108**	BnBr	**112f**, E = Bn	75
8	**109**	PhCHO	**113a**, E = PhCH(OH)	95
9	**109**	$NCCO_2Et$	**113b**, E = CO_2Et	81
10	**109**	 **114**	 **113c**	95
12	**109**	TMSCl	**113d**, E = TMS	91
13	**109**	Allyl bromide	**113e**, E = allyl	91

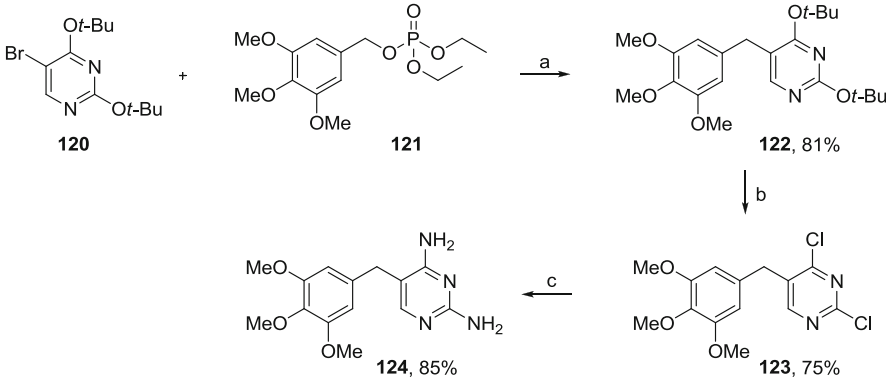
In a quest for novel carbocyclic C-nucleosides, Hřebabecký et al. [47] studied cross-coupling reactions of metallated pyrimidines with allyl chlorides (Scheme 26).

The attempts to employ lithium–tin or lithium–zinc exchange were unsuccessful, as well as coupling with an allyl acetate instead of allyl chlorides (**128**, **129**). After a switch to Grignard reagents [62, 65] and transmetalation with copper under catalytic conditions [66],[8] protected uracil (**130**, **132**) and thymine (**131**, **133**) derivatives were furnished in good yields. Allylic rearrangement leading to isomeric products was not observed. Comparable results were achievable with allyl iodide related to **129**; however, it should be avoided due to its problematic stability.

[8] Attempted palladium- or nickel-catalyzed couplings failed.



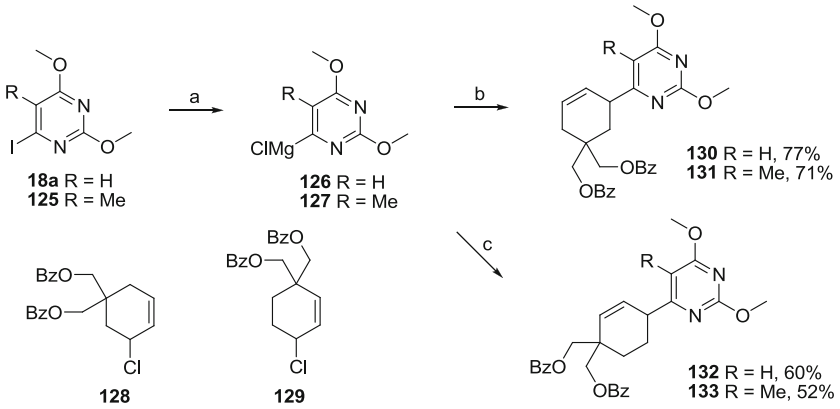
Scheme 24 (**a**) (i) 1.05 equiv *i*-PrMgCl·LiCl, THF, rt, 15 min; (ii) 1.0 equiv $LaCl_3$·LiCl, 1.0 equiv acetone, 0°C, 4 h; (iii) aq NH_4Cl; (**b**) (i) 3 equiv Et_3SiH, 3.5 equiv TFA, CH_2Cl_2, rt, 12 h; (ii) H_2/PtO_2, 1 bar, EtOH, 30 min; (**c**) (i) 1.05 equiv *i*-PrMgCl·LiCl, THF, rt, 5 h; (ii) 2 equiv BnBr, 20 h; (iii) aq NH_4Cl; (**d**) concd HCl, MeOH, reflux, 4 h; (**e**) (i) 3.5 equiv *N*,*O*-bis(trimethylsilyl) acetamide, MeCN, rt, 10 min; (ii) 1.07 equiv TMS-triflate, 2 equiv $CH_2(OEt)_2$, MeCN, −45°C to rt, 3.5 h; (iii) aq $NaHCO_3$



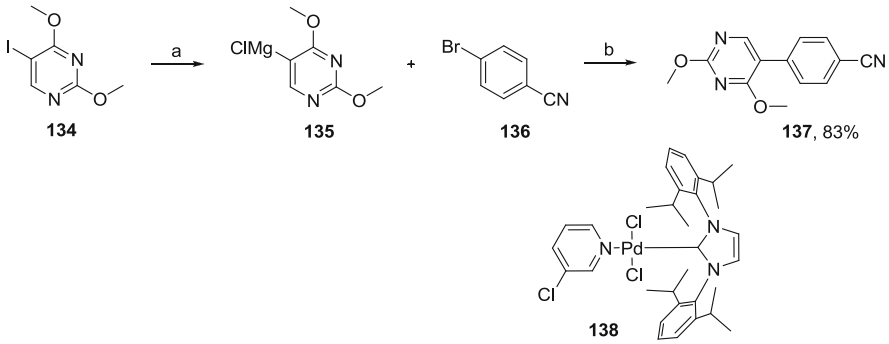
Scheme 25 (**a**) (i) **120**, 1.07 equiv *i*-PrMgCl·LiCl, THF, 0°C, 4 h; (ii) 10 mol% CuBr, 20 mol% P$(OEt)_3$; (iii) 0.67 equiv **121**, 10 mol% TBAI, DME, 60°C, 1 h; (**b**) (i) concd HCl, MeOH, rt, 15 min; (ii) $POCl_3$, reflux, 1 h; (**c**) (i) 7N NH_3/MeOH, autoclave, 175°C, 7 h

The palladium-catalyzed cross-coupling of organomagnesium reagents and unsaturated halides (Kumada coupling) [67, 68] avoids transmetalation steps and, thus, represents an attractive tool of coupling chemistry. Knochel and Manolikakes [69] have recently described coupling of 4-bromobenzonitrile **136** with pyrimidylmagnesium reagent **135**, prepared from pyrimidine **134** by I/Mg exchange (Scheme 27).

Interestingly, an accelerating effect of *i*-PrI, a sideproduct of I/Mg exchange, was observed and the desired diaryl product **137** could be cleanly prepared within several minutes at ambient temperature. A similar rate acceleration was found with various alkyl iodides, and after a brief investigation a radical mechanism was proposed (Scheme 28). In the initiation step, the palladium catalyst [LPd^0] reacts with R-I by a radical path, affording the Pd^I intermediate [LPdX]. This combines with Ar^1-Br generating an aryl radical Ar^1, which is trapped by [$LPdX_2$] to form



Scheme 26 (**a**) *i*-PrMgCl·LiCl, THF, −25°C; (**b**) (i) 13 mol% CuI·2LiCl, **128**, THF, −25°C, 36 h; (ii) aq NH_4Cl; (**c**) (i) 13 mol% CuI·2LiCl, **129**, THF, −25°C, 36 h; (ii) aq NH_4Cl



Scheme 27 (**a**) *i*-PrMgCl·LiCl, THF, −20°C, 1 h; **b** 3 mol% PEPPSI (**138**), THF, 25°C, 10 min

Pd^{III} intermediate **139**. Subsequent ligand exchange with Ar^2-MgX and reductive elimination provide the coupling product Ar^1-Ar^2 and the regenerated palladium radical [LPdX].

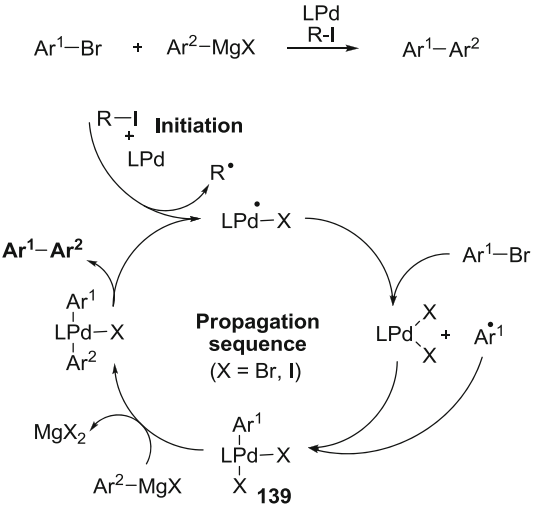
The method is applicable for a wide range of arylmagnesium reagents and aryl bromides.

6 Uracil, Thymine, and Cytosine Derivatives

6.1 C-Deprotonative Lithiations

Uracil (**140**) and cytosine (**142**) (Fig. 2) represent fundamental subunits of ribonucleic acid (RNA), while thymine (**141**) and cytosine (**142**) are found in deoxyribonucleic acid (DNA).

Scheme 28 Suggested radical mechanism of the Kumada cross-coupling



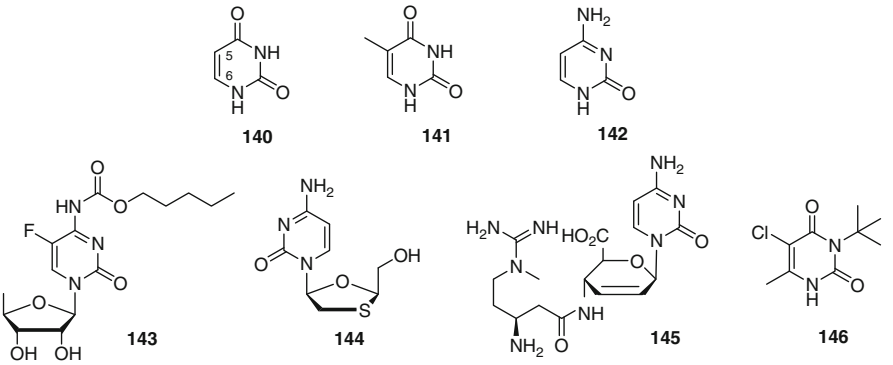
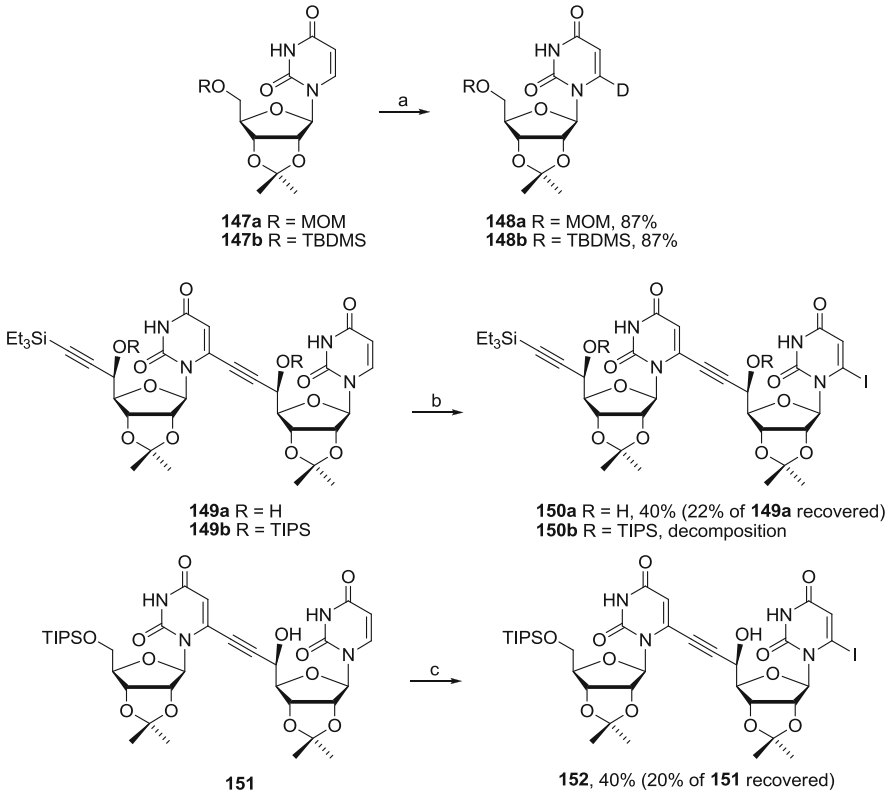


Fig. 2 Uracil (**140**), thymine (**141**), cytosine (**142**), capecitabine (**143**), lamivudine (**144**), blasticidin S (**145**), terbacil (**146**)

As such, therapeutic potential of numerous derivatives of uracil, thymine, and cytosine has been thoroughly investigated, particularly in antiviral and anticancer activity. Capecitabine (**143**) (breast and colorectal cancer) [70], lamivudine (**144**) (HIV and hepatitis B) [71], blasticidin S (**145**) [72] (fungicide), and terbacil (**146**) (herbicide), to mention just some of them, are illustrative representatives of the successful candidates, currently broadly used in medical practice and agriculture.

It is not of surprise that a lot of effort has been put into finding reliable synthetic methods enabling selective structural modifications of the pyrimidine bases. C-Lithiations are particularly suitable for introduction of substituents at C-5 and C-6.[9] In general, deprotonation at C-6 is thermodynamically favored. In uridine

[9] Occasionally, deprotonative lithiations are used for synthesis of *N*-alkylated or *N*,*N*-dialkylated pyrimidine bases. Illustrative examples and a discussion of chemoselectivity can be found in [73, 74].

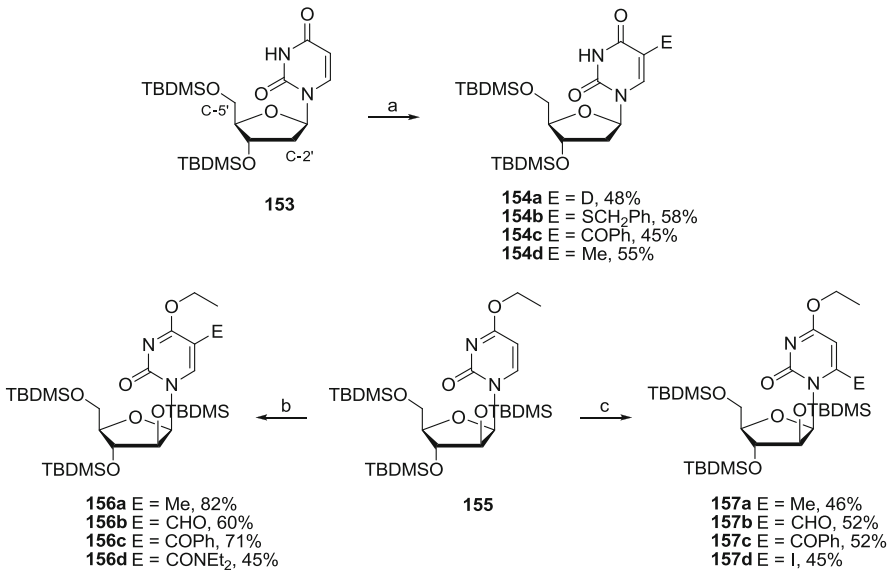


Scheme 29 (**a**) (i) 3 equiv LDA, THF, −70°C, 1 h; (ii) CD_3OD; (**b**) (i) 11.4 equiv LDA, THF, −78°C, 3 h; (ii) 11.9 equiv NIS, −78°C, 2 h; (**c**) (i) 12 equiv LDA, THF, −78°C, 2.5 h; (ii) 12 equiv NIS, −78°C, 1.5 h

[75, 76] and cytidine [77] series, C-6 can be selectively deprotonated under thermodynamic control (LDA). The assistance of chelating groups at C-5′ does not seem to play a substantial role (identical yields for **148a** and **148b**, Scheme 29) [78]. However, an example of a more complex substrate **149a** was reported, when unprotected propargylic OH group was essential for a moderate conversion and TIPS-*O*(5′) protected analogue **149b** decomposed under identical reaction conditions [79].

A selective deprotonation at C-5 usually requires a stronger base (*s*-BuLi) and a careful work at lower temperatures (Scheme 30) [80, 81]. Typically, C-5′ bears a nonchelating silyl group and sterical factors at C-2′ have to be attentively considered.

Over the last years, deprotonative lithiation followed by nucleophilic addition or substitution was routinely used for introduction of various substituents at C-6. Table 12 contains an overview of the reported structures and related reaction conditions.



Scheme 30 (**a**) (i) 2.2 equiv *s*-BuLi, 2.2 equiv TMEDA, THF, −78°C, 30 min; (ii) E+, then warming to rt [80]; (**b**) (i) 4 equiv LDA, THF, −80°C, 5 min; (ii) E+ [77]; (**c**) (i) 1 equiv LDA, THF, −40°C, 5 min; (ii) E+

Miyasaka et al. [75] observed that deprotonative lithiation of uridines at C-6 followed by methylation can be accompanied by undesired α-methylation of the newly attached substituent. Bello et al. [86] turned the fact to good account and smoothly ethylated substrate **163** via a two-stage methylation (Scheme 31).

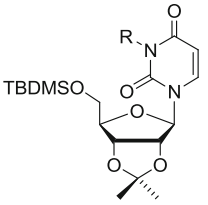
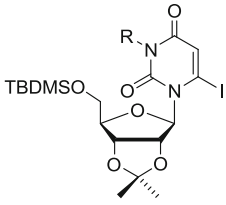
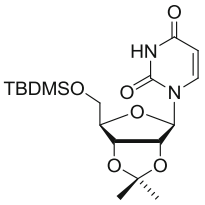
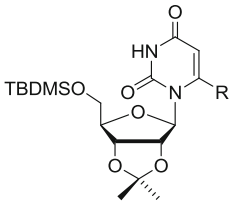
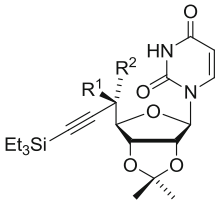
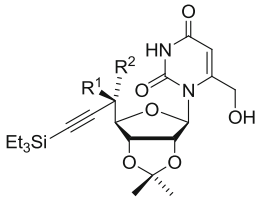
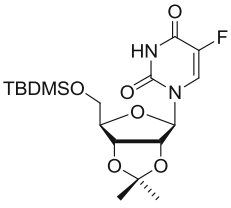
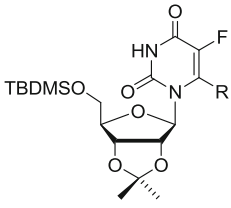
A monomethylation was not observed. The remarkable chemoselectivity was not discussed; however, a lateral lithiation with assistance of the neighboring fluorine (**190**) is likely behind the facile alkylation. In the absence of fluorine, the second methylation is a bit more tricky and under similar conditions (2.5 equiv LDA followed by 3.3 equiv MeI at −78°C) a mixture of 6-methyluridine **160a** (44%) and 6-ethyluridine **191** (17%) was isolated [11]. Double alkylation can be suppressed by a slow addition of the preformed dianion **192** to a solution of MeI (reverse-addition mode), furnishing 72% of uridine **160a**.

Utilization of a stepwise alkylation turned to be essential for a synthesis of 6-ω-alkenyl uridines **194a–b** (Scheme 32) [11].

Direct alkylation of lithiated 2′,3′-*O*-isopropylideneuridine of a putative structure **193** with 4-bromobut-1-ene failed to afford any C-6 alkylated product, in spite of literature precedent reporting a successful alkylation with *n*-butylbromide [75]. Starting from 6-methyluridine **160a**, the role of base was investigated in detail (Table 13).

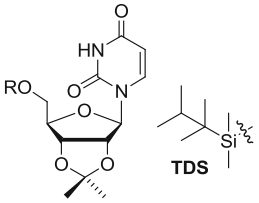
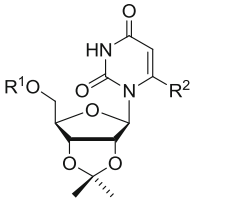
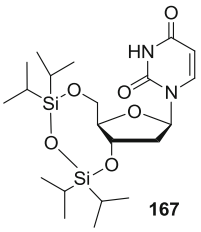
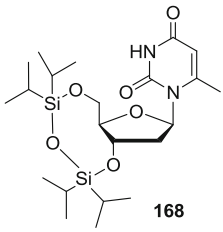
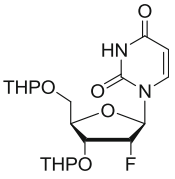
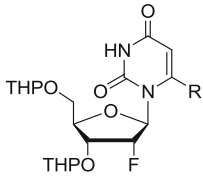
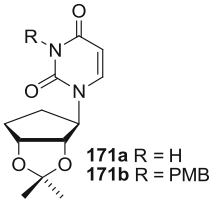
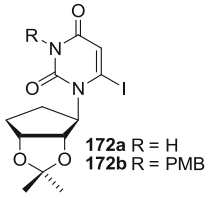
A formation of a dilithiated reagent **198** is presumed, with negative charges being delocalized over the conjugated system. The resonance structures **199** and **200** give origin to regioisomers **195a–b** and **194a–b**, respectively. With respect to yields and regioselectivity, a performance of LDA or LTMP (entries 1–4) appears to be superior over LiHMDS or *s*-BuLi/TMEDA (entries 5–6). Moreover, LiHMDS

Table 12 A summary of recent protocols in deprotonative lithiations of pyrimidine bases

Substrate	Conditions	Product
 **147b** R = H **158a** R = Me **158b** R = Bn **158c** R = PMB	**159a–d** [82]: (i) 2 equiv LDA, THF, −78°C, 1 h (ii) 2 equiv I_2, −78°C, 3 h; **159a** 55%, **159b** 45%, **159c** 50%, **159d** 43% **159a** [83]: (i) **147b**, 2.2 equiv LDA, THF, −78°C, 1 h (ii) 1 equiv I_2, −78°C, 5 h; 68%	 **159a** R = H **159b** R = Me **159c** R = Bn **159d** R = PMB
 **147b**	**160a** [84]: (i) 1.9 equiv LDA, THF, −78°C, 1 h (ii) 1 equiv MeI, −78°C, 5 h; unspecified yield **160b** [85]: (i) 6.2 equiv LDA, THF, −76°C, 2.5 h (ii) DMF, −76°C, 2.5 h; 85%	 **160a** R = Me **160b** R = CH_2OH
 **161a** R^1 = OH, R^2 = H **161b** R^1 = H, R^2 = OH	**162a,b** [85]: (i) 8 equiv LDA, THF, −76°C, 3 h (ii) DMF, −76°C, 2.5 h (iii) AcOH, EtOH (iv) $NaBH_4$, rt; **162a** 60%, **162b** 54%	 **162a** R^1 = OH, R^2 = H **162b** R^1 = H, R^2 = OH
 **163**	**164a** [86]: (i) 3 equiv LDA, THF, −78°C, 1 h (ii) 1 equiv I_2, −78°C, 5 h; 95% **164b** [86]: (i) 5 equiv LDA, THF, −78°C, 1 h (ii) 1.5 equiv HCO_2Me, −78°C, 5 h; 70%	 **164a** R = I **164b** R = CHO

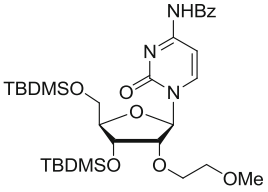
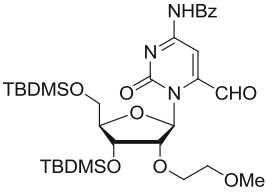
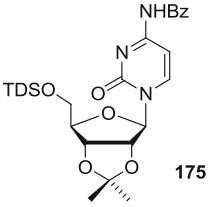
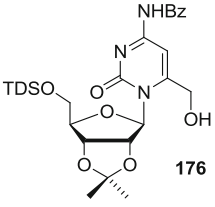
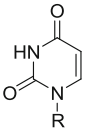
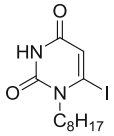
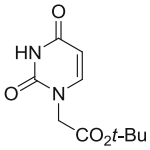
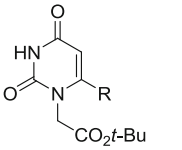
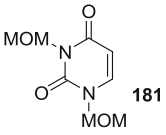
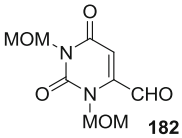
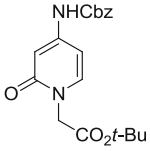
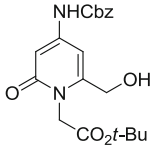
(continued)

Table 12 (continued)

Substrate	Conditions	Product
 **165a** R = TDS **165b** R = TIPS	**166a** [87]: (i) **165a**, 5 equiv LDA, THF, −76°C, 1.5 h (ii) 25 equiv DMF, −76°C, 1 h, then warming to rt; 98% **166b** [88] (i) **165a**, 5 equiv LDA, THF, −70°C, 1 h (ii) 25 equiv DMF, −70°C, 1 h (iii) AcOH, EtOH (iv) $NaBH_4$, rt; 80% **166c** [89, 90] (i) **165b**, 5 equiv LDA, THF, −78°C, 1 h (ii) 25 equiv DMF, −78°C, 2.5 h (iii) AcOH, EtOH (iv) $NaBH_4$, rt; 70%	 **166a** R^1 = TDS, R^2 = CHO **166b** R^1 = TDS, R^2 = CH_2OH **166c** R^1 = TIPS, R^2 = CH_2OH
 **167**	**168** [91]: (i) 5 equiv LDA, THF, −78°C, 1 h (ii) 1.5 equiv MeI, −78°C, 2 h; 58%	 **168**
 **169**	**170a** [92]: (i) 3.5 equiv LDA, THF, −78°C, 2 h (ii) 2 equiv I_2, −78°C, 6 h; 45% **170b** [92]: (i) 3.8 equiv LDA, THF, −78°C (ii) 4.2 equiv $ClCO_2Et$, −78°C, 2 days; 30%	 **170a** R = I **170b** R = CO_2Et
 **171a** R = H **171b** R = PMB	**172a** [93, 94]: (i) **171a**, 2.2 equiv LDA, THF, −78°C, 30 min (ii) 2.2 equiv I_2, −78°C, 2 h; 60% **172b** [94]: (i) **171b**, 2 equiv LDA, THF, −78°C, 30 min (ii) 4 equiv I_2, −78°C, 3 h; 78%[a]	 **172a** R = H **172b** R = PMB

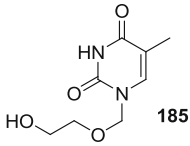
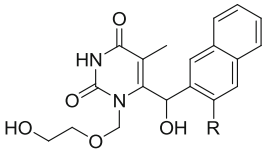
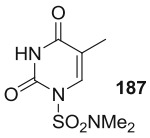
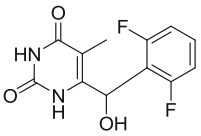
(continued)

Table 12 (continued)

Substrate	Conditions	Product
 **173**	**174** [95]: (i) 13 equiv LDA, THF, −78°C, 4 h (ii) 26 equiv HCOOMe, −78°C, 3 h, then warming to rt; 4:6 mixture of **173** and **174**, unspecified yield	 **174**
 **175**	**176** [96]: (i) 5 equiv LDA, THF, −70°C, 1 h (ii) 10 equiv DMF, −60°C, 1 h, then warming to −20°C (iii) AcOH (iv) $NaBH_4$, EtOH, rt; 86%	 **176**
 **177a** R = C_8H_{17} **177b** R = C_6H_{13}	**178a** [97]: (i) **177a**, 2.5 equiv LDA, 1.25 equiv *n*-BuLi, THF, −78°C, 1.5 h (ii) 2 equiv I_2, −78°C, 2 h; 61% **178b** [98, 99]: (i) **177b**, 5 equiv LDA, THF, −78°C, 1.5 h (ii) 5 equiv I_2, −78°C, 2 h; 72%	 **178a** R = C_8H_{17} **178b** R = C_6H_{13}
 **179**	**180a** [100]: (i) 6 equiv LDA, THF, −76°C, 2 h (ii) 20 equiv DMF, −76°C, 2.5 h, then warming to rt; 37% **180b** [100]: (i) 5 equiv LDA, THF, −70°C, 2 h (ii) 20 equiv DMF, −70°C, 1.5 h (iii) AcOH, EtOH (iv) $NaBH_4$, 0°C; **180b** 45%, **179** 43%[b]	 **180a** R = CHO **180b** R = CH_2OH
 **181**	**182** [101]: (i) 3 equiv LDA, THF, −78°C, 1 h (ii) 4.2 equiv DMF, −78°C, 2.5 h; 66%	 **182**
 **183**	**184** [100]: (i) 5 equiv LDA, THF, −70°C, 2 h (ii) 20 equiv DMF, −70°C, 2 h, then warming to rt (iii) AcOH, EtOH (iv) $NaBH_4$, rt; **184** 51%, **183** 27%	 **184**

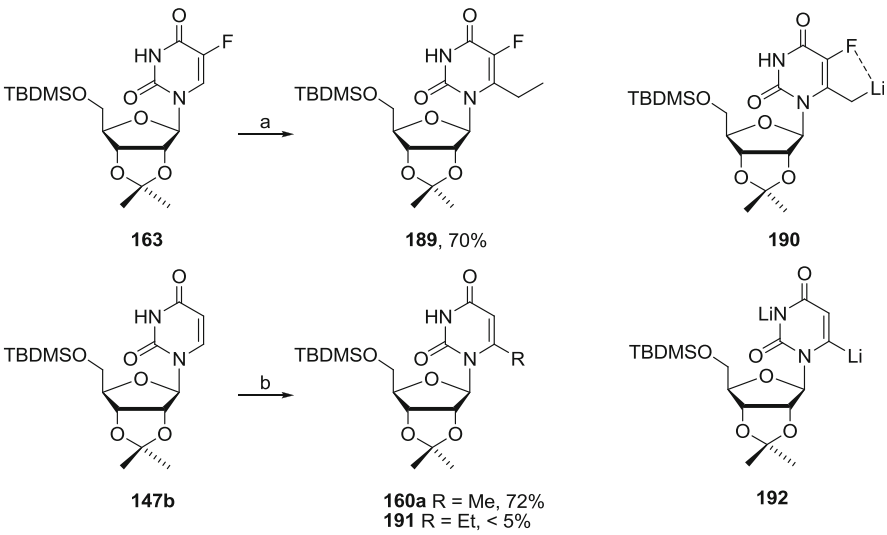
(continued)

Table 12 (continued)

Substrate	Conditions	Product
 **185**	**186a,b** [102]: (i) 2.7 equiv LDA, THF, −78°C, 1 h (ii) 2 equiv aldehyde, −78°C, 2 h; **186a** 32%, **186b** 51%	 **186a** R = H **186b** R = OMe
 **187**	**188** [103]: (i) 2.2 equiv *n*-BuLi, THF, −78°C, 1 h (ii) 1.1 equiv aldehyde, −78°C, 1 h, then warming to rt (iii) 4 M HCl, rt, 1 h; 71%	 **188**

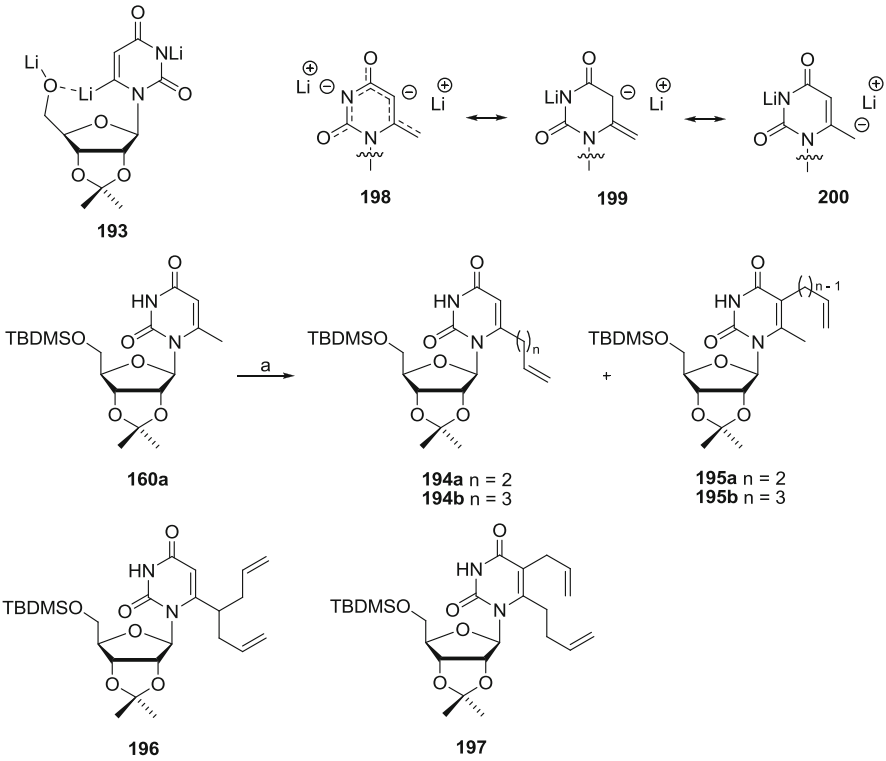
[a]With Bz-protecting group (R = Bz), iodination occurred at several sites, including Bz-group. On the other hand, substrates bearing Bn- and BOM-protection were successfully iodinated, though yields are not reported

[b]Attempted optimization using LTMP, LHMDS, or TrLi as a base did not provide better yields. As well, replacement of DMF for *N*-methylformanilide or *N*-formylmorpholine did not lead to an improvement



Scheme 31 (**a**) (i) 5 equiv LDA, THF, −78°C, 1 h; (ii) 3 equiv MeI, −78°C, 5 h [86]; (**b**) (i) 2.5 equiv LDA, THF, −78°C, 3 h; (ii) 3.3 equiv MeI, −78°C, 1 h, then warming to rt [11]

did not furnish any amount of uridines **194a** and/or **195a**, and bisallylated products **196**, **197** were obtained.



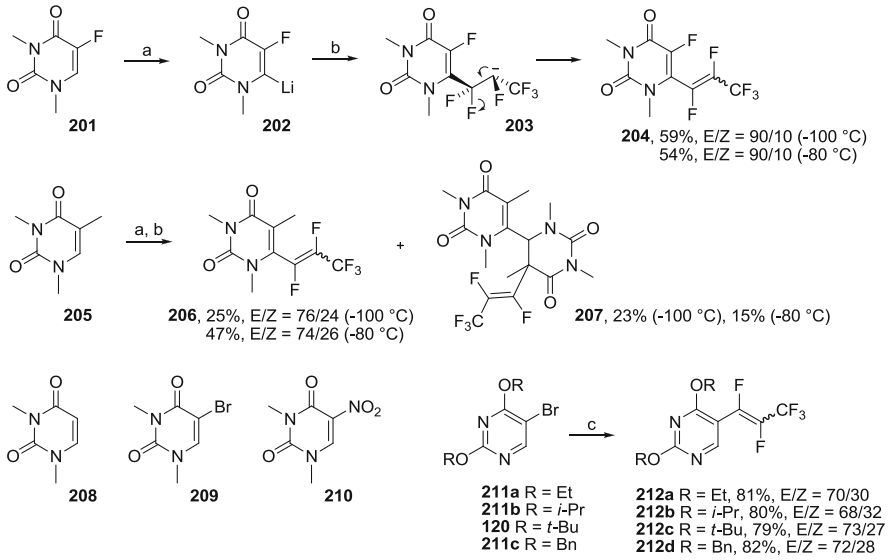
Scheme 32 (**a**) (i) 4 equiv base, THF, −70°C, 1 h; (ii) 8 equiv $Br(CH_2)_{n-1}$-CH=CH_2, −70°C, 30 min, then warming to rt

Table 13 Product distribution in lateral lithiation of uridine **160a**

Entry	Base	*n*	**194a/195a** (%)	**194b/195b** (%)
1	LDA	2	58/10	–
2	LTMP	2	65/20	–
3	LDA	3	–	44/0
4	LTMP	3	–	56/0
5	LiHMDS	2	0/0	–
6	*s*-BuLi/TMEDA	3	–	38/0

Mechanistically interesting is the reported synthesis of pentafluoropropenyl derivatives of pyrimidine [104]. In the first step, a lithiated pyrimidine **202** adds to hexafluoropropene (Scheme 33). Sequentially, the intermediate carbanion **203** undergoes a fluoride elimination to afford vinylated products **204** as a mixture of *E* and *Z* isomers.

In case of thymine derivative **205**, a competing 6-6′ dimerization was observed and **207** was isolated as a mixture of diastereisomers (dr = 65:35), bearing exclusively *E* configuration across the newly formed double bond. Attempted addition–elimination reactions of substrates **208**, **209** failed and **210** provided



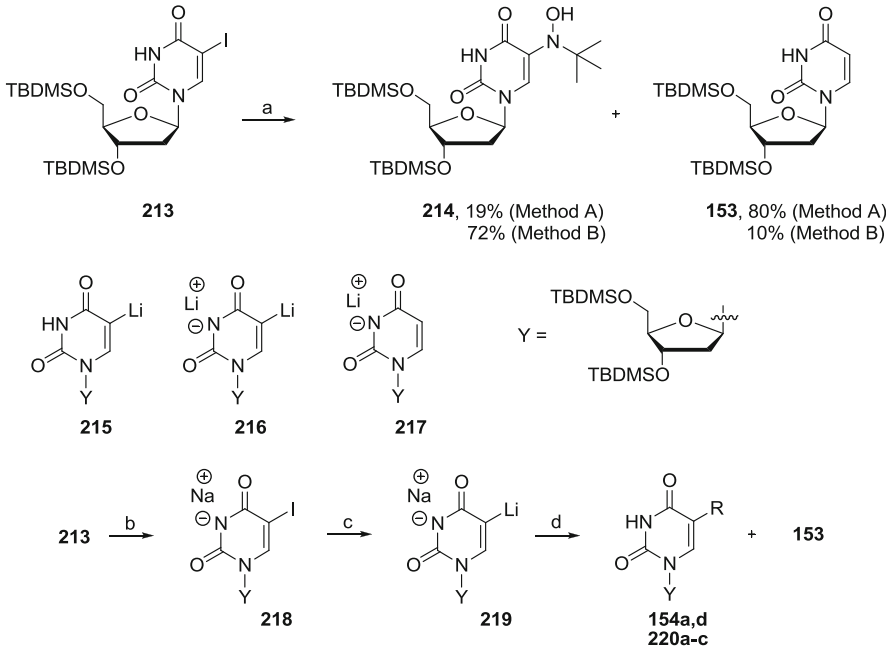
Scheme 33 (**a**) 1.2–2.5 equiv LDA, THF, −100°C or −80°C, 10–60 min; (**b**) 3 equiv hexafluoropropene, −100°C or −80°C, 30 min, then warming to rt; (**c**) (i) 1.5 equiv *n*-BuLi, THF, −100°C, 30 min; (ii) 3 equiv hexafluoropropene, −100°C, 30 min, then warming to rt

only the 6-6′ dimerization product (22%). However, the protocol was very well applicable for 5-bromo-2,4-dialkoxy-pyrimidines **120** and **211a–c** using a halogen–metal exchange reaction.

6.2 *Lithiations and Grignard Reactions by Halogen–Metal Exchange*

Halogen–metal exchange is typically used for introduction of substituents at the less reactive C-5 position of pyrimidine bases and is a useful alternative to deprotonative lithiations with *s*-BuLi [80]. An important contribution to the field was published by Aso et al. [105]. They observed that attempted reaction of 5-iodo-2′-deoxyuridine **213** with 2-methyl-2-nitrosopropane (MNP) gave mainly product of deiodination **153** (Scheme 34, Method A).

Presumably, imide deprotonation and iodo-lithium exchange were competitive at the early stage of the reaction and a proton scrambling between intermediates **215** and **216** or **215** itself yielded **217**, which was hard to deprotonate at C-5 with *n*-BuLi. Pretreatment of **213** with NaH (Method B) significantly limited formation of **153** and afforded 5-substituted uridines **214**, **154a, d**, and **220a–c** in good yields (Table 14).



Scheme 34 (**a**) Method A: (i) 2 equiv *n*-BuLi, THF, −78°C; (ii) 6 equiv MNP, −78°C; Method B: (i) 1.5 equiv NaH, THF, 0°C; (ii) 1.2 equiv *n*-BuLi, −78°C; (iii) 6 equiv MNP, −78°C; (**b**) NaH; (**c**) *n*-BuLi; (**d**) E+

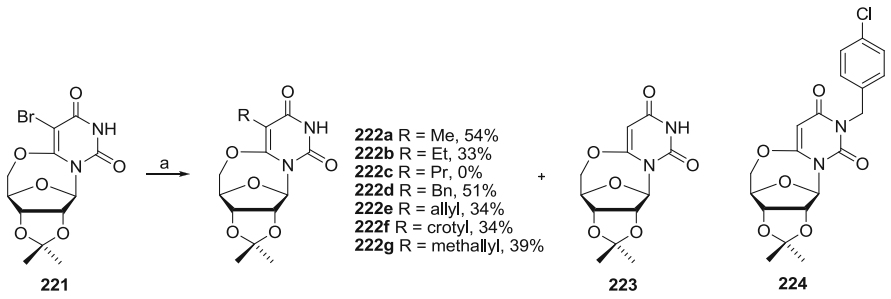
Table 14 5-Substituted 2′-deoxyuridines **154a, d** and **220a–c** prepared by Method B

n-BuLi (equiv)	E+	R	Product (%)	**153** (%)
1.2	CD_3OD	D	**154a** (64)	9
1.2	TMSCl	TMS	**220a** (62)	12
1.2	PhCHO	PhCH(OH)	**220b** (79)	0
3.0	MeI	Me	**154d** (81)	7
3.0	MeSSMe	SMe	**220c** (85)	0

Slightly altered conditions were reported to introduce an ethoxycarbonyl group [106]. The scope of the method was successfully expanded to alkylations of 5-bromosubstituted cyclonucleoside **221** (Scheme 35) [107].

The target compounds **222a–b** and **222d–g** were prepared in moderate yields along with unreported varying amounts of dehalogenated uridine **223**. Interestingly, when using PrI, the reaction did not yield any 5-substituted product **222c**. 4-Chlorobenzyl bromide afforded only the product of *N*-alkylation **224**.

Halogen–magnesium exchange reactions of nucleobase derivatives are convenient with respect to relatively high reaction temperatures and variability of reagents (Table 15) [65].



Scheme 35 (**a**) (i) 1 equiv NaH, THF, rt, 10 min; (ii) 3 equiv HMPA (for **222e–f**); (iii) 2 equiv *n*-BuLi, −78°C, 30 min; (iv) 5 equiv RI, −78°C, overnight

In comparison with *i*-PrMgCl, MeMgCl exhibits a low aptitude for halogen–magnesium exchange and a dehalogenative protonation of the substrates **225a–c** via proton scrambling can be avoided (conditions a). The use of LiCl is essential as it both increases the rate of the exchange reaction and improves the solubility. A versatility of the described method was demonstrated in synthesis of precursors of anti-HIV agents, HEPT and Emivirine.

7 Quinazolines

Unlike pyrimidines, the metalation chemistry of quinazolines has been relatively little explored. Smith et al. [108] disclosed that quinazolinones **230a–b**, upon litiation with LDA, could be selectively substituted at C2 (Scheme 36). The more nucleophilic MeLi or *t*-BuLi gave 1,2-addition products.

Introduction of a bulky *t*-Bu group to the C2-position effectively prevents from a nucleophilic attack and quinazolinone **232** can be regioselectively lithiated at C5 when treated with *s*-BuLi and TMEDA (Scheme 37) [109, 110].

When compared to other electrophiles, reaction of lithiated **232** with sterically hindered *t*-BuSS*t*-Bu required higher temperatures (conditions b) and along with **233e**, a product of a substitution at C8 was isolated in a yield of 18%.

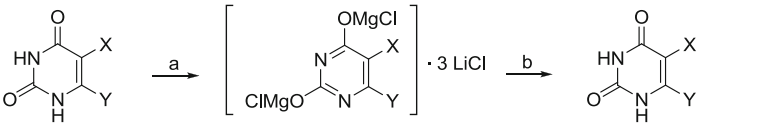
Quinazolines bearing two DMGs at C6 and C7 of the benzene ring prefer to undergo deprotonative lithiations at C8, and not C5 (Scheme 38; a recent illustrative example) [111–113].

Interestingly, in case that the starting quinazoline **234** was bearing a fluorine atom on the phenyl substituent (X = F), iodination was observed exclusively at C3′, yielding 30% of the corresponding product.

Unexpectedly, high regioselectivity was observed in lithiations of 5-phenylsulfinyl substituted quinazoline **236** (Scheme 39) [114]. The sulfoxide could assist both in *ortho* (C6) and in *peri* (C4) metalations; however, the latter did not occur. This is surprising with respect to a high acidity of H4.

The attempts to employ aldehydic electrophiles were unsuccessful and gave tarry products. Lithiation experiments in presence of TMSCl revealed a competitive *ortho* metalation on the phenyl ring (Scheme 40).

Table 15 Synthesis of substituted uracil derivatives by means of halogen–magnesium exchange

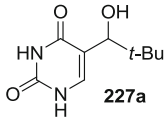
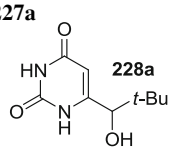
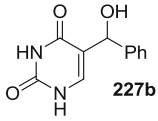
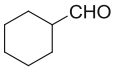
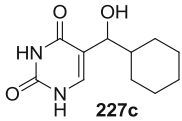
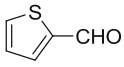
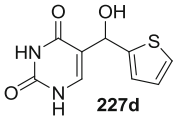
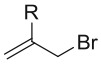
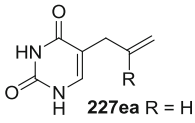


225a X = I, Y = H
225b X = Br, Y = H
225c X = H, Y = I

226a X = I, Y = H
226b X = Br, Y = H
226c X = H, Y = I

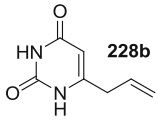
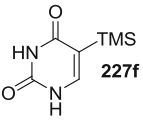
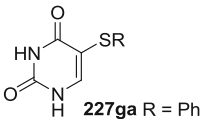
227a-g X = E, Y = H
228a-b X = H, Y = E

(**a**) (i) 2 equiv MeMgCl·LiCl, THF, −20°C, 30 min; (ii) 1.2 equiv *i*-PrMgCl·LiCl, −20°C to rt, 1 h; (**b**) E+, −20°C to rt

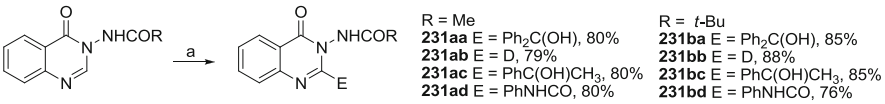
Entry	Substrate	E+	Product	Yield (%)
1	**225a**	*t*-BuCHO	 **227a**	77
2[a]	**225b**	*t*-BuCHO	**227a**	57
3[b]	**225c**	*t*-BuCHO	 **228a**	69
4	**225a**	PhCHO	 **227b**	78
5	**225a**		 **227c**	70
6	**225a**		 **227d**	55
7[c]	**225a**	 **229a** R = H	 **227ea** R = H	84
8[a,c]	**225b**	**229b** R = Me	**227eb** R = Me	54

(continued)

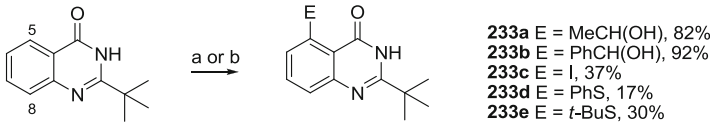
Table 15 (continued)

Entry	Substrate	E+	Product	Yield (%)
9[b,c]	**225c**	Allyl bromide	 **228b**	64
10	**225a**	TMSCl	 **227f**	72
11	**225a**	$PhSSO_2Ph$	 **227ga** R = Ph	77
12	**225a**	$MeSSO_2Me$	**227gb** R = Me	64

[a]1.1 Equiv $(i\text{-Pr})_2MgCl{\cdot}LiCl$, −20°C to rt, 2 h
[b]Step **a** carried out at −25°C
[c]Reaction in the presence of 1 mol% CuCN·2LiCl [22]



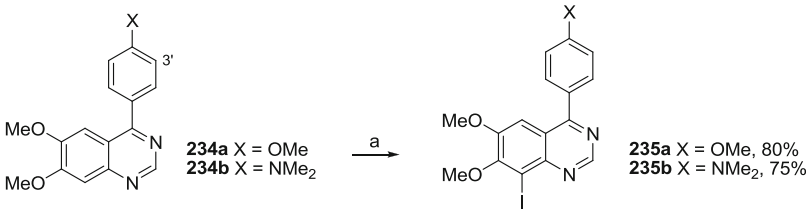
Scheme 36 (**a**) (i) 2.2 equiv LDA, THF, −78°C, 1 h; (ii) 1.1 equiv E+, −78°C, 4 h; (iii) aq NH_4Cl, rt



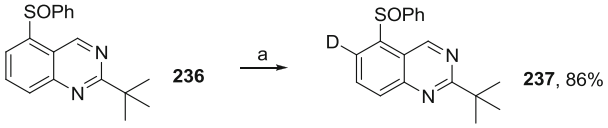
Scheme 37 (**a**) (**233a–d**) (i) 4.2 equiv *s*-BuLi, 4 equiv TMEDA, THF, −20°C, 1 h; (ii) 5 equiv E+, −78°C; (iii) $EtOH/H_2O$, −78°C [109]; (**b**) (**233e**) (i) 4 equiv *s*-BuLi, 4 equiv TMEDA, THF, −78 to 0°C, 1 h; (ii) 4 equiv *t*-BuSS*t*-Bu, 0°C, 3 h; (iii) H_2O, 0°C [110]

Presumably quinazoline **238** undergoes a sequence of a second lithiation, a nucleophilic addition at the diazine ring and an air oxidation upon work-up. Consequently, a side-product **239** was isolated along with the expected derivative **238** in identical yield.

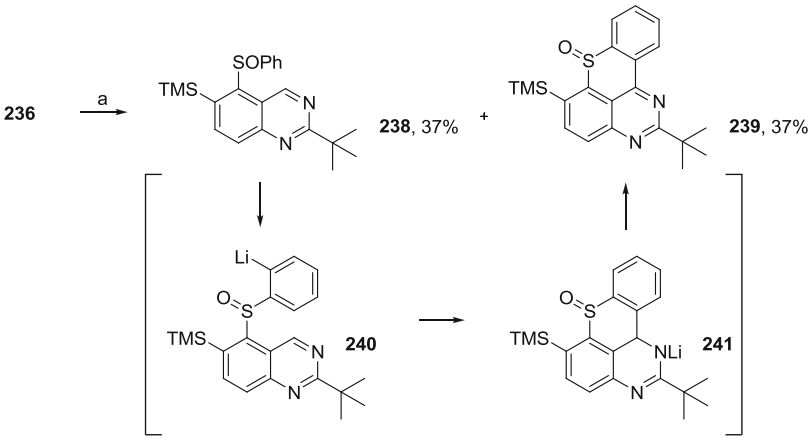
Halogen–lithium exchange reactions with alkyl lithiums in good yields have been reported both at the diazine [115] and the benzene ring [116] of quinazolines. Attempts to lithiate quinazolin-4-one **242** (Scheme 41) using *n*-BuLi or *t*-BuLi were unsuccessful



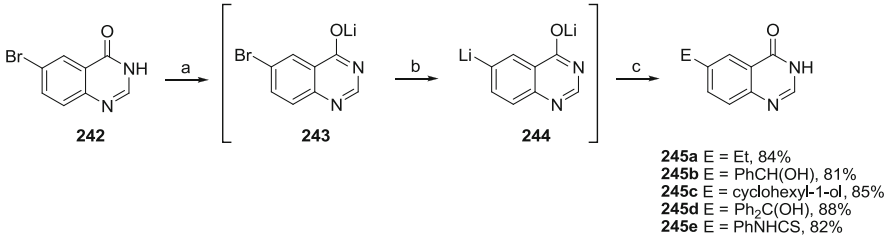
Scheme 38 (**a**) (i) 4 equiv LTMP, THF, −78°C; (ii) 2.5 equiv I_2, −78°C, 2 h; (iii) EtOH/H_2O [111]



Scheme 39 (**a**) (i) 2.1 equiv LTMP, THF, −78°C, 5 min; (ii) DCl, −78°C, 5 min



Scheme 40 (**a**) (i) 2.1 equiv LTMP, 2.1 equiv TMSCl, THF, −78°C, 90 min; (ii) H_2O/EtOH/THF



Scheme 41 (**a**) 1.1 equiv MeLi, THF, −78°C, 5 min; (**b**) 2.2 equiv *t*-BuLi, −78°C, 1 h; (**c**) (i) 1.1 equiv E+, −78°C, 2 h; (ii) aq NH_4Cl, rt

and competitive 1,2-additions were observed [117]. A stepwise *N*-deprotonation with MeLi followed by a bromine–lithium exchange performed with *t*-BuLi seemed to be essential for an efficient introduction of various electrophiles to the C6-position of **242**. In Scheme 41 are depicted selected examples **245a–e** of the prepared quinazolin-4-ones, isolated in somewhat surprisingly similar yields of 81–88%.

8 Conclusions

Both deprotonative and halogen–metal exchange lithiations and magnesiations provide a multitude of strategies for an aimed synthesis of variously modified compounds containing a pyrimidine subunit. Yet, the potential of catalytic transmetalations remains almost unrevealed and shows promise for a future dynamic development of the area.

Acknowledgment This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0457-11.

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Metalation of Azines and Diazines
Schnürch, M.; Mihovilovic, M.D. (Eds.)
2013, VII, 272 p., Hardcover
ISBN: 978-3-642-35021-4