Reactions of organolithium reagents with quinazoline derivatives

Gamal A. El-Hiti,[a]*† Amany S. Hegazy,[a] Mohammad Hayal Alotaibi,[b] and Mansour D. Ajarim[b]

[a] School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff CF10 3AT, UK
[b] Criminal Evidence, Ministry of Interior, Riyadh 11632, P.O. Box 86985, Saudi Arabia
Email: el-hitiga@cardiff.ac.uk
† Permanent address: Chemistry Department, Faculty of Science, Tanta University, Tanta 31527, Egypt

Dedicated to Professor Keith Smith on the occasion of his 65th anniversary

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Abstract

This review deals with directed and regioselective lithiation of various quinazoline derivatives by the use of alkyllithiums in anhydrous THF at low temperature. Reactions of the lithium reagents obtained from the lithiation reactions with a range of electrophiles give the corresponding substituted derivatives in high yields. The procedures are simple, efficient and general to provide derivatives which might be difficult to produce by other means. In some cases nucleophilic addition of alkyllithiums takes place to produce the corresponding addition products *via* 1,2- and 3,4-additions. In other cases nucleophilic substitution or halogen-lithium exchange reactions occur.

Keywords: 3*H*-Quinazolin-4-ones, directed *ortho*-lithiation, lateral lithiation, electrophilic substitution, alkyllithiums, nucleophilic addition

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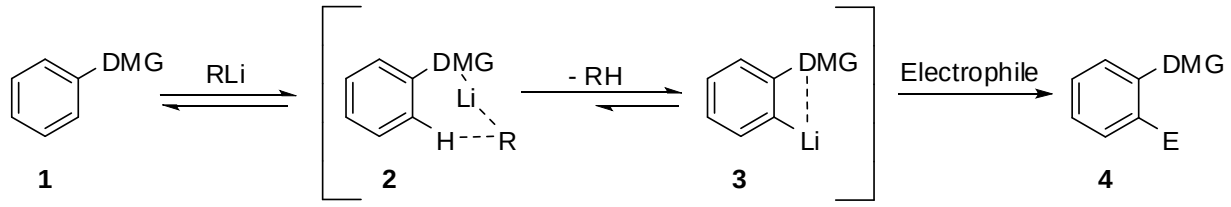
1. Introduction

Regioselective synthesis of *ortho*-disubstituted aromatics is one of the classical problems in synthetic chemistry. Simple electrophilic substitution usually takes place under forcing conditions in the presence of a catalyst and often leads to various isomers and polysubstituted aromatics.[1,2] A number of alternative approaches have therefore been developed for regioselective *ortho*-disubstitution, and lithiation followed by electrophilic substitution is one of the most recognized and efficient.[3-16]

Directed lithiation of aromatic compounds **1** comprises deprotonation of a site *ortho* to a substituent that possesses a heteroatom (*e.g.* oxygen, nitrogen or sulfur) by use of a base.[17-44] Such a substituent is known as a directing metallation group (DMG). The base, normally an alkyllithium reagent, leads to an *ortho*-lithiated species **3** (Scheme 1). Treatment of **3** with electrophilic reagents produces *ortho*-disubstituted products **4**.[45-55] Apparently, complexation occurs between the substituent group (DMG) and the lithium reagent prior to lithiation to give **2**, and this serves to bring the lithium reagent into closer proximity with the *ortho* proton, which is then selectively removed.[56]



Scheme 1. Directed lithiation and substitution of aromatic compounds **1**.

For a successful deprotonation to occur, the DMG must possess the somewhat contrary properties of being a good coordinating site for the lithium reagent and a poor electrophilic site for attack by the lithium reagent. The rate and regioselectivity of *ortho*-lithiation seems to be controlled not only by coordination between the lithium reagent and the heteroatom of the DMG but also by the acidity of the proton at the *ortho*-position.[12] It is not clear which factor is the principal driving force in *ortho*-lithiation. However, both of them could play a role for lithiation to be successful. For example, strong activators (DMG) tend to have a mixture of the basic requirements for good coordination to lithium reagent and the electron-withdrawing properties required to cause the *ortho*-protons to become acidic enough to encourage deprotonation efficiently and rapidly.

Groups that encourage such *ortho*-lithiation include: strong activators, SO_2NR_2, NHCOR, $CONR_2$, CSNHR, CONHR, $OCONR_2$, CO_2R, CH_2NHCOR, CH_2NHR, OCH_2OMe; moderate activators, OR, NR_2, SR, CF_3, F; and weak activators, CH_2OH, $CH(OR)_2$.[12-16] The rapid expansion of the list of functionalities capable of directing lithiation has made this approach an important strategy for the synthesis of various regiospecifically substituted benzenes and heterocycles.[57-64]

The addition of organolithium reagents to the imine bond of pyridine and related nitrogen heterocycles is a well-established reaction.[65-67] In particular, pyridine and quinoline undergo 1,2-addition on reaction with alkyllithiums.[68] Also, some fluoroquinolines undergo exclusive addition with butyllithium (BuLi), but in the cases of 2-fluoro- and 7-fluoroquinolines competitive lithiation takes place at the 3 and 8-positions, respectively.[69] However, these reactions become completely chemoselective for lithiation by the use of lithium diisopropylamide (LDA) at low temperature. The high reactivity of diazines towards nucleophiles makes the lithiation of such compounds even more difficult than that of most heterocycles. However, successful lithiation of diazines has been achieved by the use of less nucleophilic lithium reagents such as LDA or lithium 2,2,6,6-tetramethylpiperidine (LTMP).[56,70]

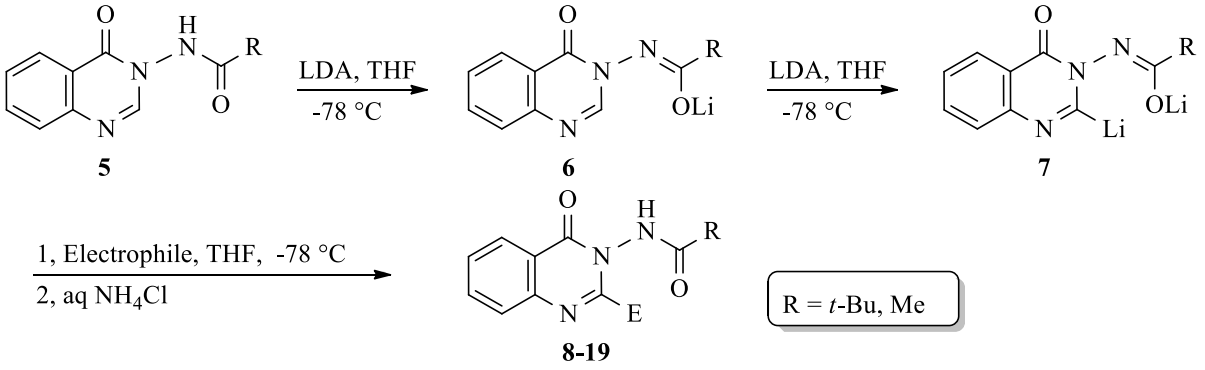
The synthesis of quinazoline derivatives has attracted the attention of chemists and has importance in medicinal chemistry because of the pharmacological applications for this heterocyclic ring system.[71-81] Also, quinazoline derivatives are important intermediates in the synthesis of a variety of valuable heterocyclic compounds.[82-86] Therefore, methods for the syntheses and/or modification of this ring system are always of interest. As part of our continuing interest in quinazoline chemistry[87-101] and in lithiation chemistry,[102-113] we have previously reported on the modification of the quinazoline ring system *via* lithiation and the organolithium reagents obtained from such reactions are very useful intermediates for the synthesis of substituted quinazoline derivatives that might be difficult to prepare by other means.[114] This review will concentrate on the work published in the general area of directed and regioselective ring-lithiation of various quinazoline derivatives. Also, it will discuss the lateral lithiation of various 2-*n*-alkylquinoxalines and their thione derivatives as well as the nucleophilic addition of alkyllithiums at the imine bonds of such ring systems.

2. Directed Lithiation of 3*H*-Quinazolin-4-Ones

Directed lithiation of 3*H*-quinazolin-4-one derivatives, containing a DMG at the 3-position (see sub-sections below), has been investigated by the use of hindered lithium reagents such as LDA at low temperature in anhydrous tetrahydrofuran (THF).[115-118] Lithiation is regioselective at the 2-position to produce the corresponding lithium reagents that on reactions with electrophiles give the corresponding 2-substituted derivatives in high yields. Also, directed lithiation of some substituted 3*H*-quinazolin-4-ones takes place on the benzenoid ring next to chloro, methoxy, *tert*-butylsulfinyl or phenylsulfinyl groups.[119-122]

2.1. Directed Lithiation of 3-Acylamino-3*H*-Quinazolin-4-Ones

Directed lithiation of 3-acylamino-3*H*-quinazolin-4-ones **5** was achieved by the use of LDA in anhydrous THF at –78 °C for 1 h under nitrogen and the lithiation reaction was regioselective at the 2-position (Scheme 2).[115] Two molar equivalents of LDA were used, the first to remove the NH proton to give the monolithium reagents **6** as yellowish solutions and the second to remove the hydrogen from the 2-position to form the dilithium reagents **7** as yellowish brown solutions (Scheme 2). Reactions of the dilithium reagents **7** with various electrophiles in THF at –78 °C for 4 hours afforded the corresponding 2-substituted 3-acylamino-3*H*-quinazolin-4-ones **8-19** in very good yields (Table 1).[115]



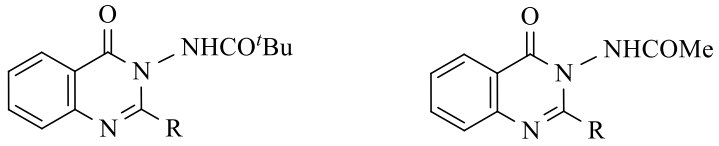
5 **6** **7** **8-19**

Scheme 2. Directed lithiation and substitution of **5**.

No deprotonation of the methyl group occurred for the case of compound **5b** (R = Me) despite the acidic character of the methyl protons.[123,124] Such side reactions took place with simple acetanilides and account for the preferred use of the pivaloylamino group in directed lithiation reactions.[17-20]

Reactions with excess iodomethane resulted in excellent yields of 2-alkylated products, but as mixtures of 2-methyl-, 2-ethyl-, and 2-(1-methylethyl)-3*H*-quinazolin-4-ones.[115] The authors concluded that the 2-methyl-3*H*-quinazolin-4-ones **8** and **14** initially produced underwent lithiation by the excess LDA present in the reaction mixture and were then methylated to give the 2-ethyl derivatives **20** and **22**, respectively. These in turn reacted further to give the

2-(1-methylethyl) derivatives **21** and **23**, respectively.[115] The authors did not attempt to optimize the yield of any individual products from these reactions, but it is likely that control of the total amount of LDA and/or iodomethane would allow the production of 2-methyl derivatives **8** and **14** without formation of any other alkylated products **20-23** (Figure 1).



20 R = Et (16%)
21 R = *i*-Pr (6%)

22 R = Et (28%)
23 R = *i*-Pr (5%)

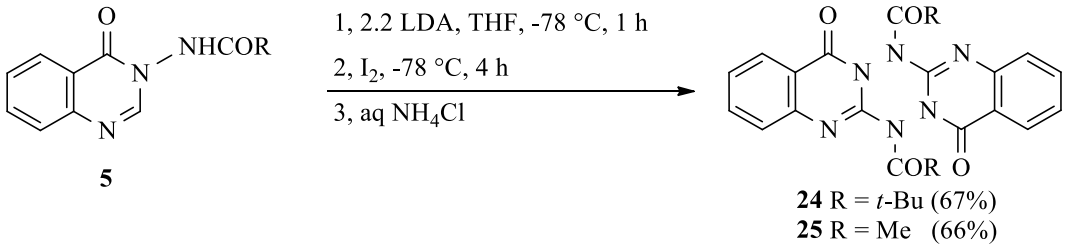
Figure 1. Structures of compounds **20-23**.

Table 1. Synthesis of 2-substituted 3*H*-quinazolin-4-ones **8-19** according to Scheme 2[115]

Product	R	Electrophile	E	Yield (%)[a]
8	*t*-Bu	MeI	Me	67[b]
9	*t*-Bu	D_2O	D	88
10	*t*-Bu	Ph_2CO	$Ph_2C(OH)$	85
11	*t*-Bu	PhCOMe	PhC(OH)(Me)	85
12	*t*-Bu	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	87
13	*t*-Bu	PhNCO	PhNHCO	76
14	Me	MeI	Me	59[c]
15	Me	D_2O	D	79
16	Me	Ph_2CO	$Ph_2C(OH)$	80
17	Me	PhCOMe	PhC(OH)(Me)	80
18	Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	81
19	Me	PhNCO	PhNHCO	80

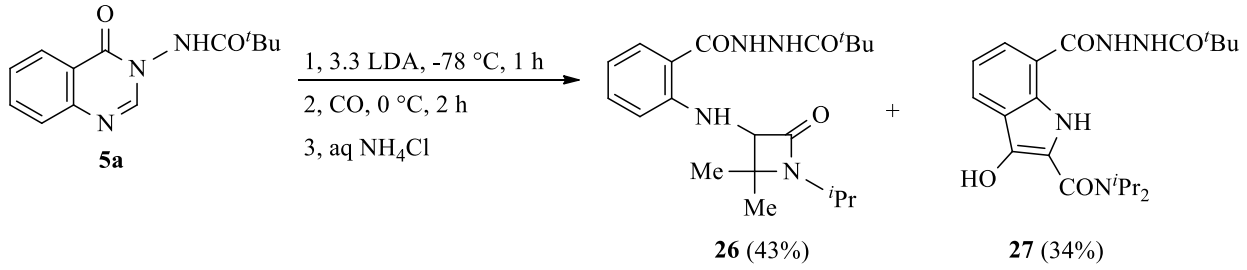
[a]Yield of isolated product after crystallization from ethyl acetate.
[b]2-Ethyl-3-pivaloylamino-3*H*-quinazolin-4-one **20** and 2-(1-methylethyl)-3-pivaloylamino-3*H*-quinazolin-4-one **21** (Figure 1) were produced as side products in 16 and 6% yields, respectively.
[c]3-Acetylamino-2-ethyl-3*H*-quinazolin-4-one **22** and 3-acetylamino-2-(1-methylethyl)-3*H*-quinazolin-4-one **23** (Figure 1) were produced as side products in 28 and 5% yields, respectively.

Reactions of the dilithium reagents **7**, obtained from lithiation of **5**, with iodine took place in a different manner involving oxidative dimerisation. 6,13-Dipivaloyl-1,2,4,5-tetrazino[3,2-*b*:6,5-*b*']bisquinazolin-7,14(6*aH*,13*aH*)-dione **24** and 6,13-diacetyl-1,2,4,5-tetrazino[3,2-*b*:6,5-*b*']bisquinazolin-7,14(6*aH*,13*aH*)-dione **25** were obtained in 67 and 66% yields, respectively (Scheme 3) instead of 2-iodo-3*H*-quinazolin-4-ones.[115]



Scheme 3. Directed lithiation of **5** followed by reactions with iodine.

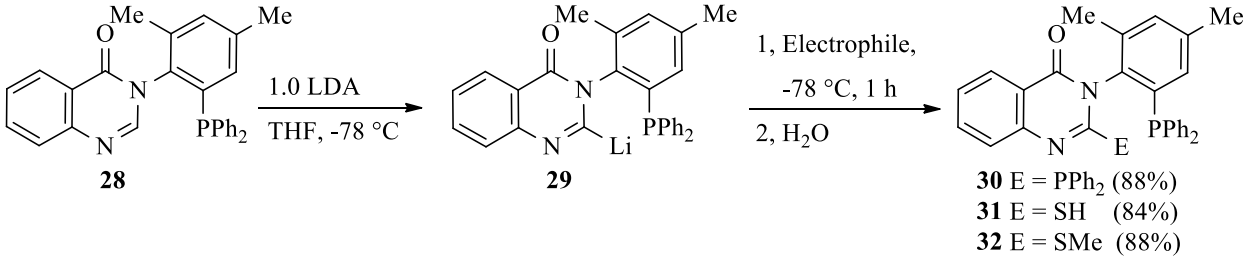
Directed lithiation of **5a** with three molar equivalents of LDA in THF at –78 °C for one hour followed by reaction with carbon monoxide at 0 °C for two hours gave a 77% isolated yield of a mixture of azetidinone derivative **26** and indole derivative **27** (Scheme 4).[116] Both products involved the incorporation of a diisopropylamide unit from the LDA used for lithiation as well as carbon monoxide. Compound **26** was obtained due to reaction of the lithium intermediate obtained with one molar equivalent of carbon monoxide, while compound **27** involved uptake of two molar equivalents of carbon monoxide. The mechanism of the formation of **26** and **27** has not been investigated.



Scheme 4. Directed lithiation and carbonylation of **5a**.

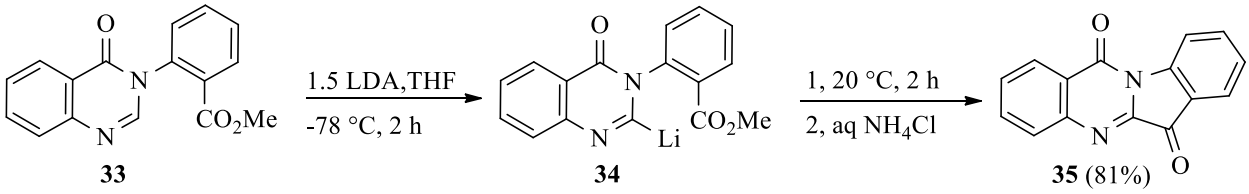
2.2. Directed lithiation of 3-aryl-3*H*-quinazolin-4-ones

Lithiation of 3-(2-(diphenylphosphino)-4,6-dimethylphenyl)-3*H*-quinazolin-4-one **28** took place rapidly with one molar equivalent of LDA in THF at -78 °C under argon to give the corresponding 2-lithium reagent **29** as a yellow solution (Scheme 5), which was found to be unstable at temperature above -20 °C.[117] Reaction of **29** with chlorodiphenylphosphine (PPh_2Cl), solid sulfur (S_8), and dimethyl disulfide (MeSSMe) in THF at -78 °C for 1 h gave 2-substituted derivatives **30**-**32** in 84-88% yields (Scheme 5).[117]



Scheme 5. Directed lithiation and substitution of **28**.

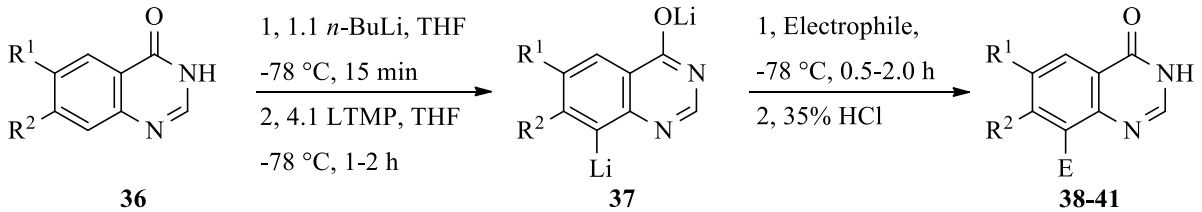
Lithiation of methyl 2-(4-oxo-4*H*-quinazolin-3-yl)benzoate **33** with LDA (1.5 molar equivalents) in THF at -78 °C for two hours gave the corresponding 2-lithium derivative **34** as a reddish solution.[118] The lithium reagent **34** underwent intramolecular cyclisation at room temperature to give indolo[2,1-*b*]quinazoline-6,12-dione **35** in 81% yield (Scheme 6).[118]



Scheme 6. Directed lithiation of **33** with LDA followed by intramolecular cyclisation.

2.3. Directed lithiation of chloro- and methoxy-3*H*-quinazolin-4-ones

Various attempts have been made to lithiate 6,8-dichloro-3*H*-quinazolin-4-one.[119] However, none of the conditions tried was successful; instead starting material or a degraded product was obtained.[119] On the other hand, lithiation of 7-chloro- and 6,7-dimethoxyquinazolines **36** took place at the 8-position by the use of a mixture of *n*-BuLi (one molar equivalent) and LTMP (four molar equivalents) for one hour at -78 °C to give dilithium derivative **37** (Scheme 7).[119] Reactions of **37** with acetaldehyde and benzaldehyde gave 8-substituted products **38-41** (Scheme 7) in 50-95% yield (Table 2) along with a small quantity of starting material **36**.[119] The yields were high for 7-chloro-3*H*-quinazolin-4-one **36** (R^1 = H, R^2 = Cl) and moderate for 6,7-dimethoxy-3*H*-quinazolin-4-one **36** (R^1 = R^2 = OMe).



Scheme 7. Directed lithiation and substitution of **36**.

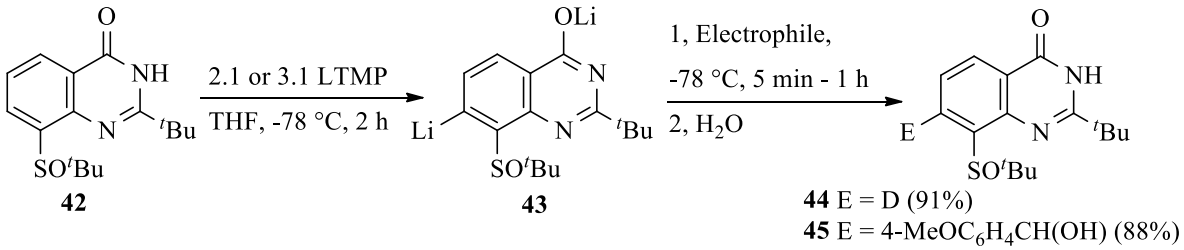
Table 2. Synthesis of 8-substituted 3*H*-quinazolin-4-ones **38-41** according to Scheme 7[119]

Product	R^1	R^2	Electrophile	E	Yield (%)[a]
38	H	Cl	MeCHO	MeCH(OH)	73
39	H	Cl	PhCHO	PhCH(OH)	95
40	OMe	OMe	MeCHO	MeCH(OH)	50
41	OMe	OMe	PhCHO	PhCH(OH)	50

[a]Yield of isolated product after column chromatography.

2.4. Directed lithiation of *tert*-butylsulfinyl-2-*tert*-butyl-3*H*-quinazolin-4-one

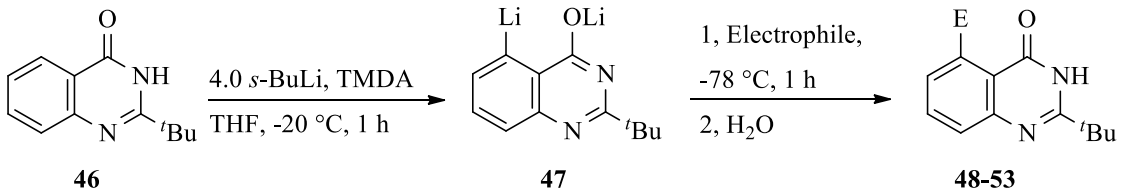
The position of a *tert*-butylsulfinyl group on the 3*H*-quinazolin-4-one ring system was found to have an effect on the position of lithiation. For example, lithiation of 5-*tert*-butylsulfinyl-2-*tert*-butyl-3*H*-quinazolin-4-one was not successful using excess LTMP at -78 °C and starting material along with tarry material were recovered.[120] On the other hand, lithiation of 8-*tert*-butylsulfinyl-2-*tert*-butyl-3*H*-quinazolin-4-one **42** with LTMP at -78 °C in THF was regioselective at the 7-position to give dilithium intermediate **43**, which on reactions with DCl and 4-anisaldehyde gave 7-substituted derivatives **44** and **45** in 91 and 88% yields, respectively (Scheme 8).[120]



Scheme 8. Directed lithiation and substitution of **42**.

2.5. Directed lithiation of 2-substituted 3*H*-quinazolin-4-ones

Lithiation of 2-*tert*-butyl-3*H*-quinazolin-4-one **46** was regioselective at the 5-position to give the dilithium intermediate **47** by the use of four molar equivalents of *s*-BuLi in the presence of tetramethylethylenediamine (TMEDA) at -20 °C in THF (Scheme 9).[125] Reactions of **47** with a range of electrophiles at -78 °C gave the corresponding 5-substituted derivatives **48-53** in 17-94% yields (Table 3).[125]



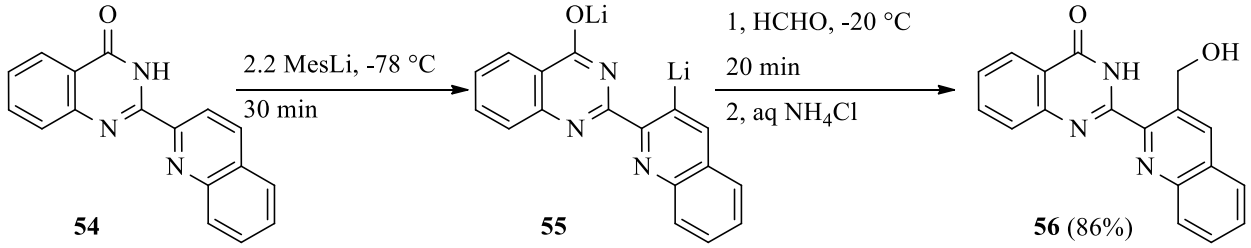
Scheme 9. Lithiation and substitution of **46**.

Table 3. Synthesis of 5-substituted 3*H*-quinazolin-4-ones **48-53** according to Scheme 9[125]

Product	Electrophile	E	Yield (%)[a]
48	MeCHO	MeCH(OH)	94
49	PhCHO	PhCH(OH)	92
50	PhSSPh	PhS	17
51	Bu_3SnCl	Bu_3Sn	50
52	I_2	I	37
53	$(^iPrO)_3B$	$B(OH)_2$	68[b]

[a]Yield of isolated product after column chromatography.
[b]Reaction was carried out at -78 °C to room temperature for 15 h.

Lithiation of 2-(quinolin-2-yl)-3*H*-quinazolin-4-one **54** with two molar equivalents of mesityllithium (MesLi) in THF at -78 °C for 30 min gave the dilithium reagent **55** as a deep brown solution.[126] Reaction of **55** with formaldehyde in THF at -20 °C gave alcohol **56** in 86% yield (Scheme 10).[126]



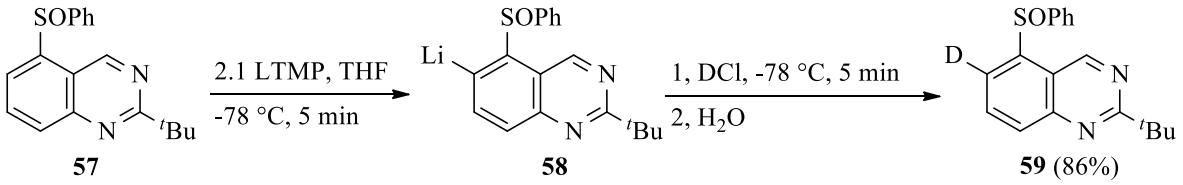
Scheme 10. Lithiation of **54** followed by reaction with formaldehyde.

3. Directed Lithiation of Quinazoline Derivatives

Directed lithiation and substitution of various quinazoline derivatives (see sub-sections below) has been achieved by the use of alkyllithiums followed by reactions with electrophiles to produce the corresponding substituted derivatives.[120,121]

3.1. Directed lithiation of 5-phenylsulfinyl-2-*tert*-butylquinazoline

Directed lithiation of 5-phenylsulfinyl-2-*tert*-butylquinazoline **57** with excess LTMP (two molar equivalents) took place at the 6-position to give the 6-lithium intermediate **58** which on reaction with DCl gave **59** in 86% yield (Scheme 11).[120]



Scheme 11. Directed lithiation of **57** followed by reaction with DCl.

When the reaction was carried out with trimethylsilyl chloride (TMSCl) as the electrophile under conditions similar to those used in Scheme 11, 2-*tert*-butyl-5-(phenylsulfinyl)-6-(trimethylsilyl)quinazoline **60** and a cyclized product **61** (Figure 2) were obtained in 37% yield each.[120] Compound **61** was obtained as a result of a second *ortho*-directed lithiation on the *ortho*-position of the phenyl ring followed by a nucleophilic addition of the lithium derivative at the 4-position of the quinazoline ring and finally aromatization by air oxidation.[120]

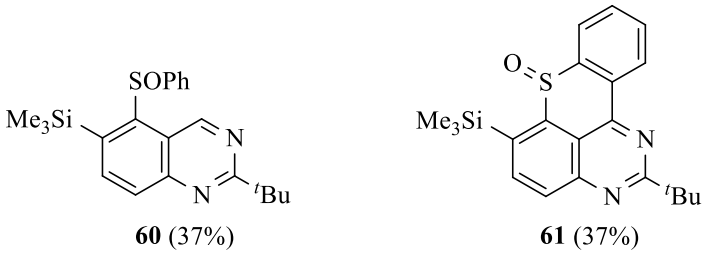
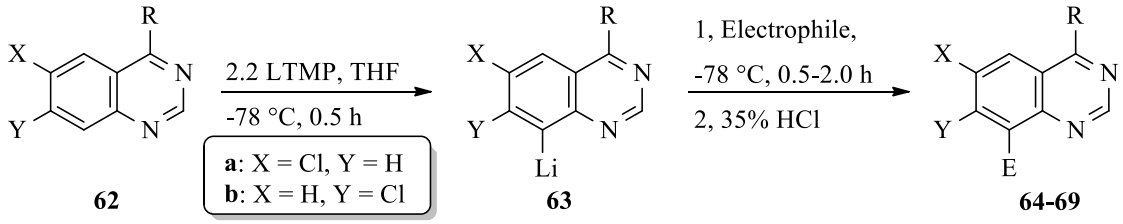


Figure 2. Structures of compounds **60** and **61**.

3.2. Directed lithiation of chloroquinazolines

Lithiation of 4-substituted 6-chloroquinazoline **62a** (Scheme 12; X = Cl, Y = H; R = OMe, $O(CH_2)_2OMe$, NEt_2) with LTMP (2.2 molar equivalents) in THF at -78 °C for 0.5 hour gave the corresponding lithium derivative **63a** in which lithiation took place at the 8-position.[121] Reactions of **63a** with a range of electrophiles at -78 °C for 0.5-2.0 hours gave the corresponding 8-substituted quinazolines **64-69** in low to moderate yields (Table 4).[121]



Scheme 12. Directed lithiation and substitution of **62**.

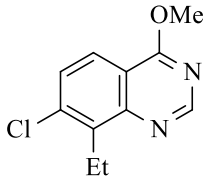
Similarly, lithiation of 7-chloro-4-methoxyquinazoline **62b** (Scheme 12; X = H, Y = Cl, R = OMe) with LTMP in THF at -78 °C for 0.5 hour gave the corresponding lithium derivative **63b**

which, on reactions with various electrophiles, gave the corresponding 8-substituted quinazolines **70-74** in 32-85% yields (Table 4).[121] Starting material was recovered from reactions that gave low yields.

Table 4. Synthesis of 8-substituted quinazolines **64-74** according to Scheme12[121]

Product	X	Y	R	Electrophile	E	Yield (%)[a]
64	Cl	H	OMe	MeCHO	MeCH(OH)	50
65	Cl	H	OMe	PhCHO	PhCH(OH)	19
66	Cl	H	OMe	I_2	I	25[b]
67	Cl	H	OMe	Me_3SiCl	Me_3Si	35[b,c]
68	Cl	H	$O(CH_2)_2OMe$	MeCHO	MeCH(OH)	29
69	Cl	H	NEt_2	MeCHO	MeCH(OH)	55
70	H	Cl	OMe	MeCHO	MeCH(OH)	85
71	H	Cl	OMe	PhCHO	PhCH(OH)	73
72	H	Cl	OMe	MeI	Me	40[d,e]
73	H	Cl	OMe	I_2	I	32[b,e,f]
74	H	Cl	OMe	Me_3SiCl	Me_3Si	40[c,e]

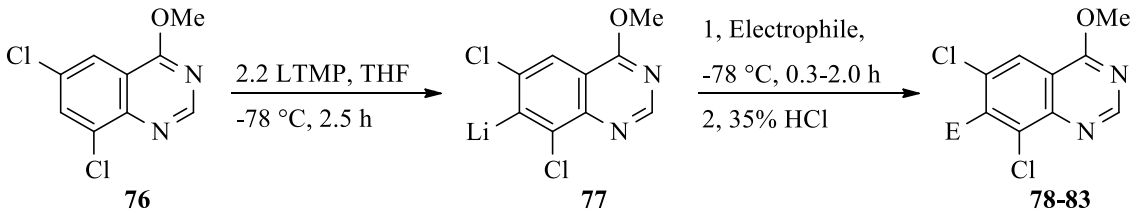
[a]Yield of isolated product after column chromatography.
[b]Yield after purification by column chromatography and sublimation.
[c]Obtained with the *in situ* trapping technique in which **62a** and trimethylsilyl chloride were simultaneously added to the LTMP solution.
[d]7-Chloro-8-ethyl-4-methoxyquinazoline **75** (Figure 4) was obtained as a side product in 8% yield due to lithiation and methylation of methylated product **72**.
[e]Starting material **62b** was recovered (31-55%).
[f]Reaction was carried out with 1.3 molar equivalents LTMP.



75 (8%)

Figure 3. Structure of compound **75**.

Lithiation of 6,8-dichloro-4-methoxyquinazoline **76** with 2.2 molar equivalents of LTMP in THF at -78 °C for 2.5 h gave 7-lithio derivative **77** (Scheme 13) that on reactions with various electrophiles gave 7-substituted quinazolines **78-83** in 88-93% yield (Table 5).[121]



76 **77** **78-83**

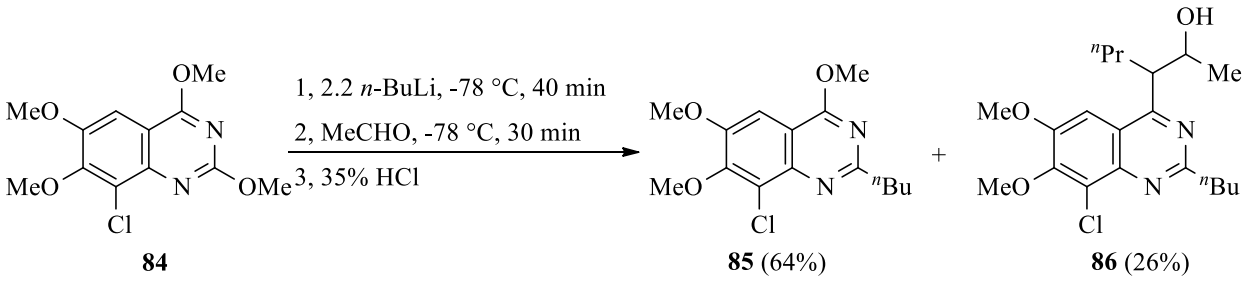
Scheme 13. Directed lithiation and substitution of **76**.

Table 5. Synthesis of 7-substituted quinazolines **78-83** according to Scheme 13[121]

Product	Electrophile	E	Yield (%)[a]
78	MeCHO	MeCH(OH)	93
79	PhCHO	PhCH(OH)	92
80	I_2	I	90
81	Me_3SiCl	Me_3Si	88[b]
82	MeI	Me	93
83	EtOD/DCl	D	88

[a]Yield of isolated product after column chromatography.
[b]Obtained with the *in situ* trapping technique in which **76** and Me_3SiCl were simultaneously added to the LTMP solution.

Lithiation of 8-chloro-2,4,6,7-tetramethoxyquinazoline **84** with LTMP was not successful under different reaction conditions.[121] However, use of *n*-BuLi (two molar equivalents) at -78 °C for 40 minutes followed by reaction with acetaldehyde for 30 minutes gave a mixture of **85** and **86** in 64 and 26% yields, respectively (Scheme 14).[121]



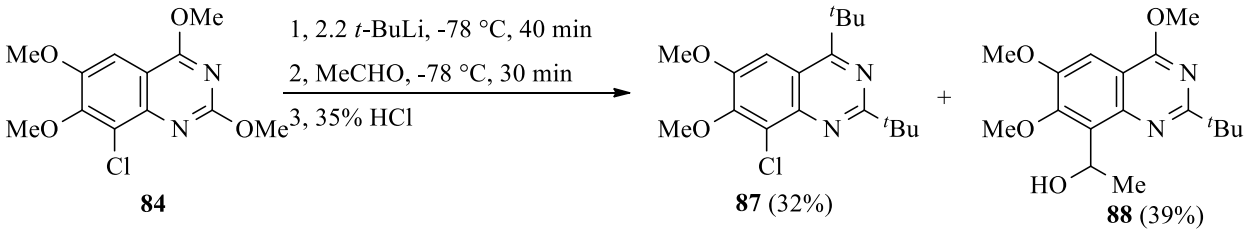
84 **85** (64%) **86** (26%)

Scheme 14. Reaction of **84** with *n*-BuLi followed by reaction with acetaldehyde.

Compound **85** was obtained as a result of replacement of the methoxy group at the 2-position by a butyl group from *n*-BuLi. While compound **86** was obtained due to replacement of the two methoxy groups at the 2- and 4-positions by two butyl groups from *n*-BuLi followed by lithiation

at the α-position of the butyl group at the 4-position and finally reaction of the lithium reagent obtained with acetaldehyde.

On the other hand, treatment of **84** with *t*-BuLi (two molar equivalents) followed by reaction with acetaldehyde under conditions similar to those used in Scheme 14 gave a mixture of **87** and **88** in 32 and 39% yields, respectively (Scheme 15).[121]



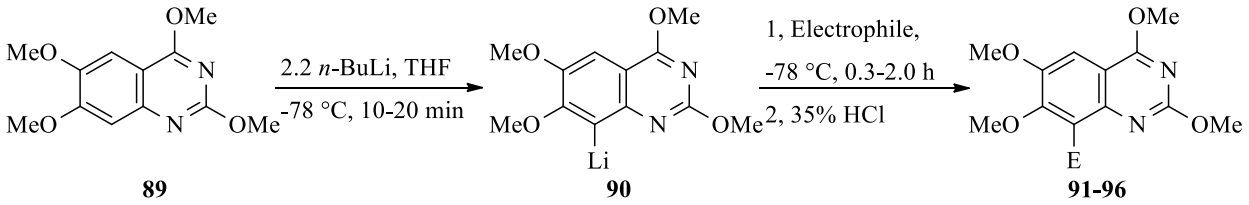
84 **87** (32%) **88** (39%)

Scheme 15. Reaction of **84** with *t*-BuLi in THF followed by reaction with acetaldehyde.

Compound **87** was obtained due to replacement of the two methoxy groups at the 2- and 4-positions by two *tert*-butyl groups from *t*-BuLi. While compound **88** was obtained due to replacement of the methoxy group at the 2-position by a *tert*-butyl group from *t*-BuLi followed by chlorine-lithium exchange to produce the corresponding 8-lithium derivative that reacted with acetaldehyde.[121]

3.3. Directed lithiation of methoxyquinazolines

Lithiation of 2,4,6,7-tetramethoxyquinazoline **89** with two molar equivalents of *n*-BuLi at -78 °C took place at the 8-position to give the 8-lithium intermediate **90** (Scheme 16).[121] Reactions of **90** with various electrophiles afforded the corresponding 8-substituted derivatives **91-96** in 51-97% yields (Table 6).[121]



89 **90** **91-96**

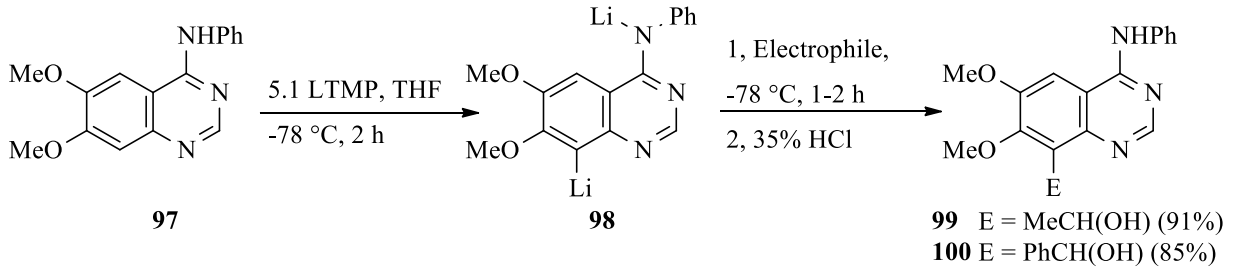
Scheme 16. Directed lithiation and substitution of **89**.

Table 6. Synthesis of 8-substituted quinazolines **91-96** according to Scheme 16[121]

Product	Electrophile	E	Yield (%)[a]
91	MeCHO	MeCH(OH)	97
92	PhCHO	PhCH(OH)	99
93	MeI	Me	51[b]
94	EtOD/DCl	D	96
95	I_2	I	89
96	C_2Cl_6	Cl	90

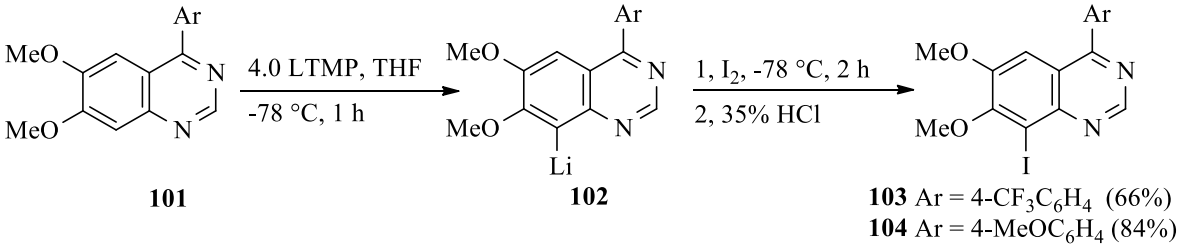
[a]Yield of isolated product after column chromatography.
[b]Starting material **89** was recovered.

Treatment of 6,7-dimethoxy-4-phenylaminoquinazoline **97** with LTMP (5 molar equivalents) at -78 °C for 2 h gave the corresponding 8-lithium derivative **98** which on reactions with acetaldehyde and benzaldehyde afforded 8-substituted derivatives **99** and **100** in 91 and 85% yields, respectively (Scheme 17).[119]



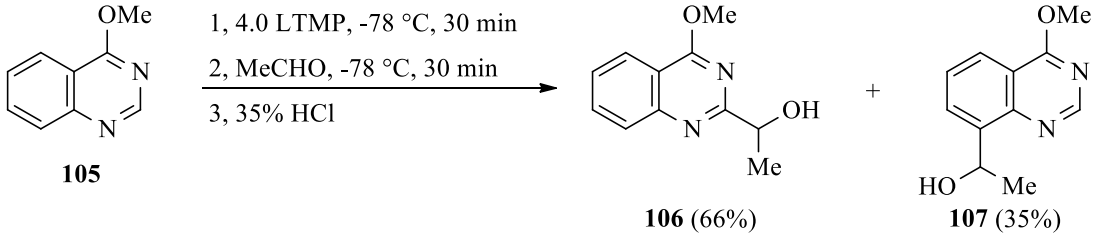
Scheme 17. Directed lithiation and substitution of **97**.

Similarly, lithiation of 4-aryl-6,7-dimethoxyquinazolines **101** with LTMP (four molar equivalents) at -78 °C gave the corresponding 8-lithio intermediates **102** which on reaction with iodine gave 8-iodoquinazolines **103** and **104** in 66 and 84% yields, respectively (Scheme 18).[122]



Scheme 18. Directed lithiation of **101** followed by reactions with iodine.

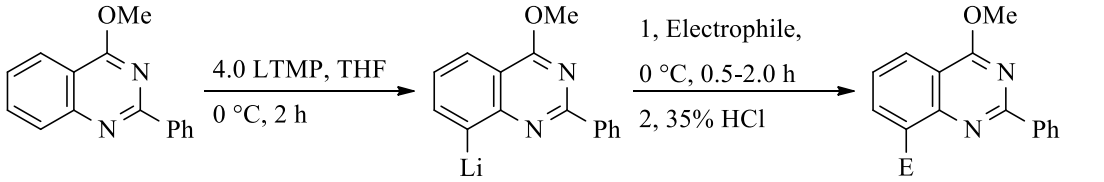
Lithiation of 4-methoxyquinazoline **105** with four molar equivalents of LTMP in THF at 78 C for 30 min followed by reaction with acetaldehyde gave a mixture of alcohols **106** and **107** in 66 and 35% yields, respectively (Scheme 19).[121] Clearly, a competitive lithiation took place at C-2 and C-8.



105 **106** (66%) **107** (35%)

Scheme 19. Lithiation of **105** followed by reaction with acetaldehyde.

Lithiation of 4-methoxy-2-phenylquinazoline **108** with excess LTMP (two molar equivalents) in THF at 0 °C was regioselective at C-8 to give the 8-lithium intermediate **109** (Scheme 20).[121] Reactions of **109** with acetaldehyde and trimethylsilyl chloride gave the corresponding 8-substituted derivatives **110** and **111** in 56 and 94% yields, respectively.[121]

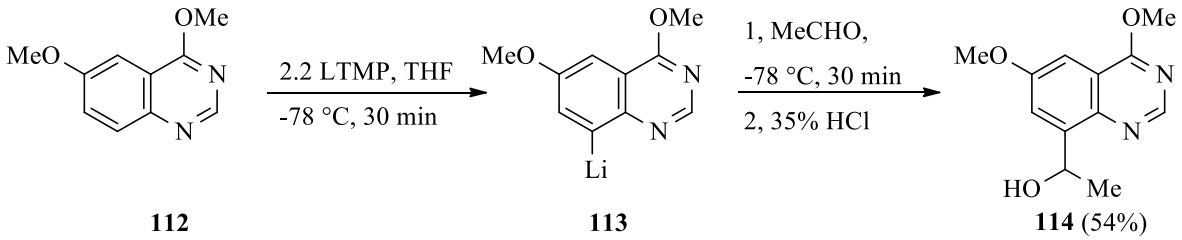


108 **109**

110 E = MeCH(OH) (56%)
111 E = $SiMe_3$ (94%)

Scheme 20. Lithiation of **108** followed by reactions with electrophiles.

Similarly, lithiation of 4,6-dimethoxyquinazoline **112** with 2.2 molar equivalents of LTMP in THF at -78 °C gave 8-lithium intermediate **113** that reacted with acetaldehyde to give alcohol **114** in 54% yield (Scheme 21).[121]



112 **113** **114** (54%)

Scheme 21. Lithiation of **112** followed by reaction with acetaldehyde.

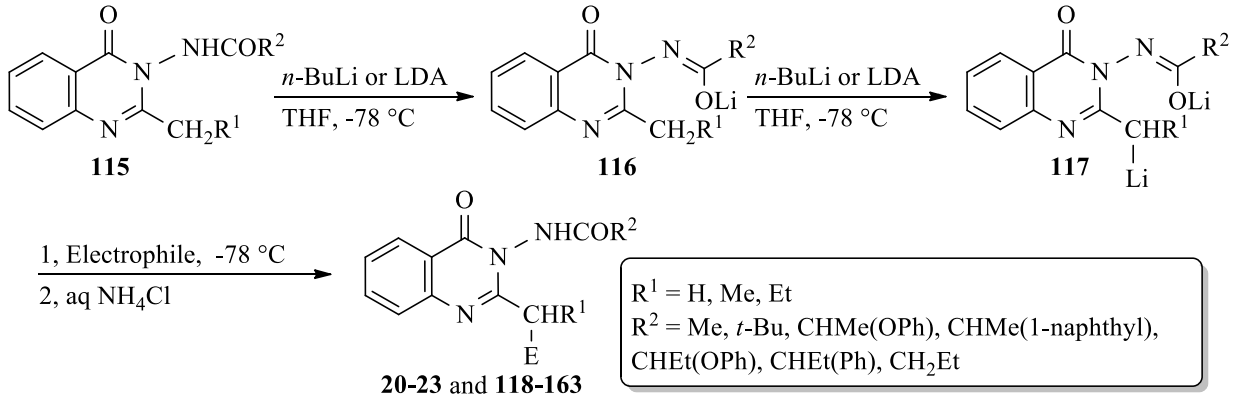
4. Lateral Lithiation of 2-*n*-Alkylquinazoline Derivatives

Lateral lithiation of various 2-*n*-alkyl-3*H*-quinazolin-4-ones containing various groups at the 3-position, such as acylamino, methylamino, amino, aryl and a hydrogen, have been attempted by the use of BuLi or LDA at low temperature. The lithiation took place at the benzylic position of the *n*-alkyl group. These procedures provide efficient syntheses of more complex 2-substituted derivatives in high yields. Similar procedures have been applied to 3-unsubstituted 2-*n*-alkyl-3*H*-quinazolin-4-ones, their thiones and 4-substituted quinazolines.

4.1. Lateral lithiation of 3-acylamino-2-*n*-alkyl-3*H*-quinazolin-4-ones

Lateral lithiation of various 3-acylamino-2-*n*-alkyl-3*H*-quinazolin-4-ones **115** was achieved by the use of 2.2 molar equivalents of *n*-BuLi (for R^1 = Me) or LDA (for R^1 = Et and *n*-Pr) in anhydrous THF at -78 °C (Scheme 22).[115,127,128] Lithiation was regioselective at the carbon α to the 2-position of the 3*H*-quinazolin-4-one moiety. Addition of the first equivalent of the alkyllithium produced the monolithium reagents **116**, which were converted into the dilithium reagents **117** on addition of the second equivalent of alkyllithium (Scheme 22).[115,127,128]

Reactions of **117** with a variety of electrophiles afforded the corresponding 2-substituted 3*H*-quinazolin-4-ones **20-23** and **118-163** (Scheme 22) in high yields (Tables 7-10). On the other hand, lithiation of 2-(1-methylethyl)-3*H*-quinazolin-4-ones **21** and **23** and 3-diacylamino-2-*n*-alkyl-3*H*-quinazolin-4-ones were not successful under similar reaction conditions.[115]



Scheme 22. Lateral lithiation and substitution of **115**.

The NMR spectra for compounds reported in Table 7 except for cases where the electrophile was D_2O (*i.e*. products **122** and **127**) showed that the two hydrogen atoms of the CH_2 group at the 2-position occurred as independent, coupled signals, suggesting they are diastereotopic due to the barrier to rotation around the *N*-*N* bond. The crystal structure of compound **118** showed that the plane of the aromatic ring is orthogonal to the plane of the ^{t}BuCONH group. This renders the *N*-*N* bond as a chiral axis. Orthogonal conformations are known to be significantly more stable than their co-planar counterparts for *N,N'*-diacylhydrazines, which has resulted in measured

barriers to rotation about the *N*-*N* bond.[129,130] Barriers to rotation have been reported for di- and tetraacylhydrazines, where both nitrogen atoms are of amide type,[131-134] hydrazines,[135] triazines[136] and tetrazines.[137] Also, hindrance to rotation about the *N*-*N* bond in 3-acylamino- and 3-diacylamino-3*H*-quinazolin-4-ones was found to be as high as for hydrazine derivatives (14.7-20.6 Kcal mol^{-1}).[138,139]

Table 7. Lithiation and substitution of **115** (R^1 = H; R^2 = Me, *t*-Bu) using *n*-BuLi as the lithium reagent according to Scheme 22[127]

Product	R^2	Electrophile	E	Yield (%)[a,b]
20	*t*-Bu	MeI	Me	89
118	*t*-Bu	Ph_2CO	$Ph_2C(OH)$	83
119	*t*-Bu	PhCOMe	PhC(OH)(Me)	81
120	*t*-Bu	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	80
121	*t*-Bu	PhNCO	PhNHCO	84
122	*t*-Bu	D_2O	D	88
22	Me	MeI	Me	75
123	Me	Ph_2CO	$Ph_2C(OH)$	80
124	Me	PhCOMe	PhC(OH)(Me)	84
125	Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	79
126	Me	PhNCO	PhNHCO	83
127	Me	D_2O	D	74

[a]Yield of isolated product after crystallization from ethyl acetate.

Table 8. Lithiation and substitution of **115** (R^1 = Me, Et; R^2 = *t*-Bu) using LDA as the lithium reagent according to Scheme 22[115]

Product	R^1	Electrophile	E	Yield (%)[a]
21	Me	MeI	Me	92
128	Me	Ph_2CO	$Ph_2C(OH)$	90
129	Me	PhCOMe	PhC(OH)(Me)	81
130	Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	82
131	Me	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	84
132	Me	I_2	I	70
133	Me	D_2O	D	88
134	Et	MeI	Me	90
135	Et	Ph_2CO	$Ph_2C(OH)$	92
136	Et	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	88

[a]Yield of isolated product after crystallization from ethyl acetate.

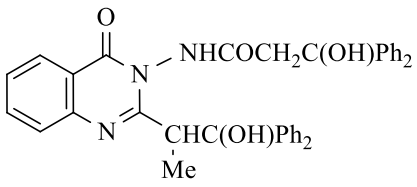
Table 9. Lithiation and substitution of **115** (R^1 = Me, Et; R^2 = Me) using LDA as the lithium reagent according to Scheme 22[115]

Product	R^1	Electrophile	E	Yield (%)[a]
23	Me	MeI	Me	84
137	Me	Ph_2CO	$Ph_2C(OH)$	80[b]
138	Me	PhCOMe	PhC(OH)(Me)	77
139	Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	82[c]
140	Me	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	80
141	Me	I_2	I	70
142	Me	D_2O	D	81
143	Et	MeI	Me	86
144	Et	Ph_2CO	$Ph_2C(OH)$	87
145	Et	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	85[d]

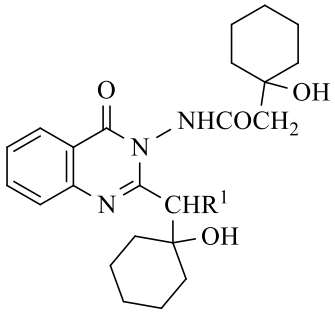
[a]Yield of isolated product after crystallization from ethyl acetate.

[b-d]Compounds **146-148** (Figure 4) were obtained as by products in 3-5% yields. Such compounds were produced due to lithiation and substitution on the methyl group of the acetylamino unit at the 3-position.

It was possible to remove the acyl group from products reported in Tables 7-9 under hot basic or acidic conditions to produce 2-*n*-alkyl-3-amino-3*H*-quinazolin-4-ones.[115,127] For example, hydrolysis of compounds **20-23** with hydrochloric acid or aqueous sodium hydroxide in methanol under reflux removed the acyl group to give the corresponding 3-amino-derivatives in 75% yields.[115] However, such forcing conditions for removal of the acylamino group were not always appropriate for some of the more complicated substituents at the 2-position.



146 (3%)



147 R^1 = Me (4%)
148 R^1 = Et (5%)

Figure 4. Structures of compounds **146-148**.

Table 10. Lithiation and substitution of **115** (R^1 = Me, Et; R^2 = CHMe(OPh), CHMe(1-naphthyl), CHEt(OPh), CHEt(Ph) using LDA according to Scheme 22[128]

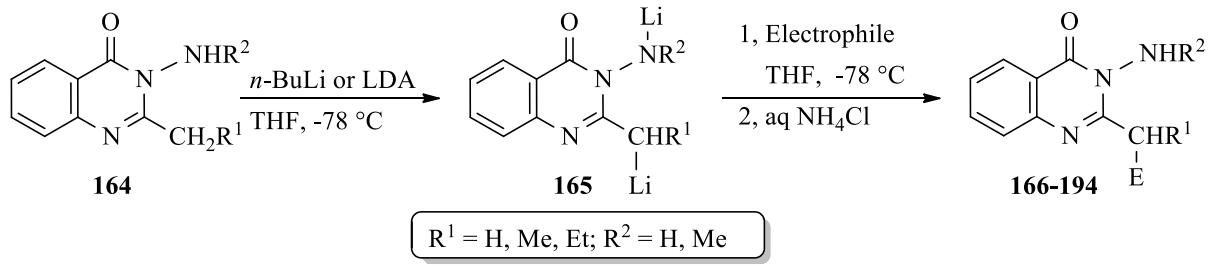
Product	R^1	R^2	Electrophile	E	Yield (%)[a]
149	Me	CHMe(OPh)	Ph_2CO	$Ph_2C(OH)$	80
150	Me	CHMe(OPh)	PhCOMe	PhC(OH)(Me)	78
151	Me	CHMe(OPh)	PhCHO	PhCH(OH)	82
152	Me	CHMe(1-naphthyl)	Ph_2CO	$Ph_2C(OH)$	79
153	Me	CHEt(OPh)	Ph_2CO	$Ph_2C(OH)$	76
154	Me	CHEt(OPh)	PhCOMe	PhC(OH)(Me)	79
155	Me	CHEt(OPh)	PhCHO	PhCH(OH)	80
156	Me	CHEt(Ph)	Ph_2CO	$Ph_2C(OH)$	77
157	Me	CHEt(Ph)	Et(Me)CO	EtC(OH)Me	75
158	Et	CHMe(OPh)	Ph_2CO	$Ph_2C(OH)$	88
159	Et	CHMe(OPh)	PhCOMe	PhC(OH)(Me)	80
160	Et	CHMe(OPh)	PhCHO	PhCH(OH)	76
161	Et	CHEt(OPh)	Ph_2CO	$Ph_2C(OH)$	90
162	Et	CHEt(OPh)	PhCOMe	PhC(OH)(Me)	78
163	Et	CHEt(OPh)	PhCHO	PhCH(OH)	80

[a]Yield of isolated product after crystallization from ethyl acetate.

The NMR spectra of products **149-163** (Table 10) showed the expected diastereotopic feature for all the CH_2 groups and provided evidence for long-range asymmetric induction at the newly created asymmetric centre(s). This opens up possibilities for novel synthetic approaches to certain types of chiral compounds.[128]

4.2. Lateral lithiation of 2-*n*-alkyl-3-amino-3*H*-quinazolin-4-ones

Lateral lithiation of 2-*n*-alkyl-3-amino- and 2-*n*-alkyl-3-methylamino-3*H*-quinazolin-4-ones **164** took place by the use 2.2 molar equivalents of alkyllithium (Scheme 23; *n*-BuLi for R^1 = H and LDA for R^1 = Me, Et) at -78 °C in THF to give deep red solutions of dilithium reagents **165**.[140] Reactions of the dilithium reagents **165** with various electrophiles at -78 or 0 °C in THF gave the corresponding 2-substituted derivatives **166-194** in high yields (Tables 11 and 12).[140]



Scheme 23. Lateral lithiation and substitution of **164**.

Table 11. Lithiation and substitution of **164** (R^1 = H, Me, Et; R^2 = H) using *n*-BuLi or LDA according to Scheme 23[140]

Product	R^1	Electrophile	E	Yield (%)[a]
166	H	Ph_2CO	$Ph_2C(OH)$	86
167	H	PhCOMe	PhC(OH)(Me)	86
168	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	84
169	H	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	89
170	H	PhCHO	PhCH(OH)	77
171	H	$[^iPr_2NC(S)S]_2$	$^iPr_2NC(S)S$	75
172	H	D_2O	D	88
173	Me	Ph_2CO	$Ph_2C(OH)$	84
174	Me	PhCOMe	PhC(OH)(Me)	80
175	Me	EtCOMe	EtC(OH)Me	88
176	Me	^{n}BuCOMe	^{n}BuC(OH)Me	71
177	Me	^{n}BuCOEt	^{n}BuC(OH)Et	83
178	Me	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	90
179	Me	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	90
180	Me	PhCHO	PhCH(OH)	80
181	Me	D_2O	D	92
182	Et	Ph_2CO	$Ph_2C(OH)$	90
183	Et	PhCOMe	PhC(OH)(Me)	87
184	Et	EtCOMe	EtC(OH)Me	92

[a]Yield of isolated product after crystallization, usually from diethyl ether.

Table 12. Lithiation and substitution of **164** (R^1 = H, Me, Et; R^2 = Me) using *n*-BuLi or LDA according to Scheme 23[140]

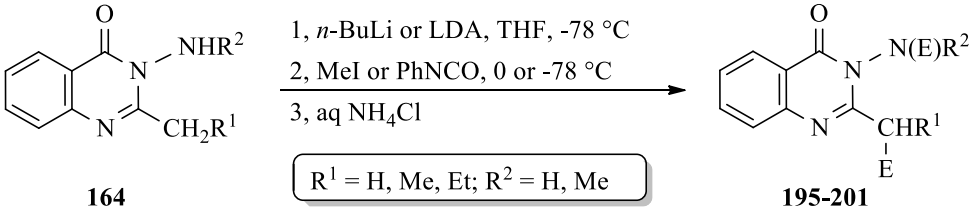
Product	R^1	Electrophile	E	Yield (%)[a]
185	H	Ph_2CO	$Ph_2C(OH)$	83
186	H	EtCOMe	EtC(OH)Me	84
187	H	PhCHO	PhCH(OH)	70
188	H	PhNCO	PhNHCO	72
189	H	D_2O	D	90
190	Me	Ph_2CO	$Ph_2C(OH)$	82
191	Me	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	80
192	Me	PhNCO	PhNHCO	66
193	Me	D_2O	D	82
194	Et	Ph_2CO	$Ph_2C(OH)$	80

[a]Yield of isolated product after crystallization, usually from diethyl ether.

The ambient temperature ^{1}H NMR spectra of compounds **182-184** (Table 11) and **194** (Table 12) showed that the two hydrogens of the CH_2 group adjacent to the newly created asymmetric center are diastereotopic, indicating a significant barrier to rotation around the *N*-*N* bond even at room temperature.[140]

Clearly the process represented in Scheme 23 was general, high yielding and accommodated various complex substituents at the α-carbon at the 2-position.

Lateral lithiation of **164** with a lithium reagent (Scheme 24; *n*-BuLi for R^1 = H or LDA for R^1 = Me, Et) at -78 °C followed by reactions with two molar equivalents of iodomethane or phenyl isocycanate at -78 or 0 °C gave the corresponding disubstituted derivatives **195-201** in high yields (Table 13).[140] Clearly, substitution at both the α-carbon at the 2-position and the nitrogen attached to the 3-position had taken place.



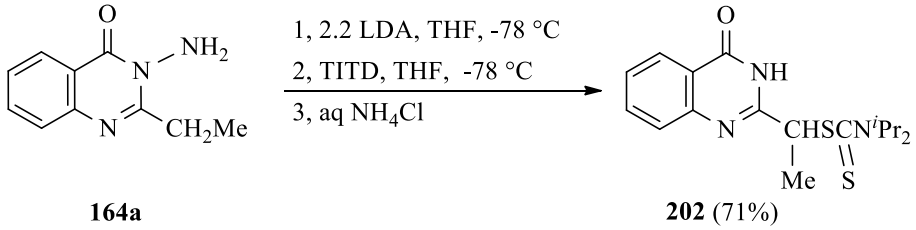
Scheme 24. Lateral lithiation and double substitution of **164**.

Table 13. Lithiation and double substitution of **164** according to Scheme 24[140]

Product	R^1	R^2	Electrophile	E	Yield (%)[a]
195	H	H	MeI	Me	89
196	H	H	PhNCO	PhNCO	75
197	H	Me	MeI	Me	80
198	Me	H	MeI	Me	86
199	Me	Me	MeI	Me	88
200	Me	H	PhNCO	PhNCO	70
201	Et	Me	MeI	Me	79

[a]Yield of isolated product after crystallization, usually from diethyl ether.

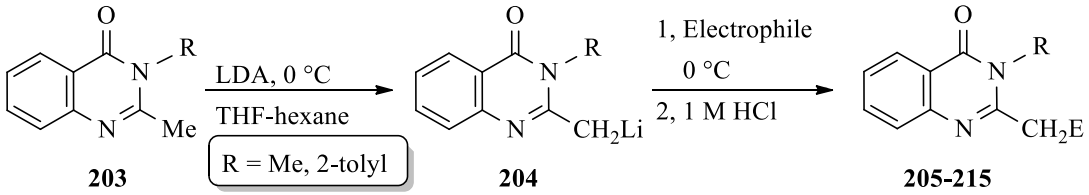
Reaction of the dilithium reagent obtained *in situ* from lithiation of 3-amino-2-ethyl-3*H*-quinazolin-4-one **164a** with tetraisopropylthiuram disulfide (TITD) gave compound **202** in 71% yield, in which deamination had taken place (Scheme 25).[140] Lithiation of 3-dimethylamino-2-ethyl-3*H*-quinazolin-4-one under similar reaction conditions was not successful.[140]



Scheme 25. Synthesis of 2-[1-(diisopropyldithiocarbamoyl)ethyl]-3*H*-quinazolin-4-one **202**.

4.3. Lateral lithiation of 3-substituted 2-methyl-3*H*-quinazolin-4-ones

Lithiation of 3-substituted 2-methyl-3*H*-quinazolin-4-ones **203** with LDA in THF-hexane mixture at 0 °C gave the corresponding lithium intermediates **204** (Scheme 26) as deep red solutions.[141] Reactions of **204** with various electrophiles afforded the corresponding 2,3-disubstituted derivatives **205-215** (Scheme 26) in 22-92% yields (Table 14).[141]



Scheme 26. Lateral lithiation and substitution of **203**.

Table 14. Lithiation and substitution of **203** according to Scheme 26[141]

Product	R	Electrophile	E	Yield (%)[a]
205	Me	PhCHO	PhCH(OH)	73
206	Me	Ph_2CO	$Ph_2C(OH)$	69
207	Me	Me_2CO	$Me_2C(OH)$	41
208	2-tolyl	PhCHO	PhCH(OH)	51[b]
209	2-tolyl	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	22[c]
210	2-tolyl	$(PhS)_2$	PhS	53[d]
211	2-tolyl	MeI	Me	53
212	2-tolyl	EtI	Et	25[e]
213	2-tolyl	$CH=CHCH_2Br$	$CH=CHCH_2$	60
214	2-tolyl	PhI	Ph	34[f,g]
215	2-tolyl	D_2O	D	92

[a]Yield of isolated product after crystallization or column chromatography.

[b]A traces of 2-styryl derivative was obtained as a side-product due to dehydration of **208** along with starting material **203** (8%).

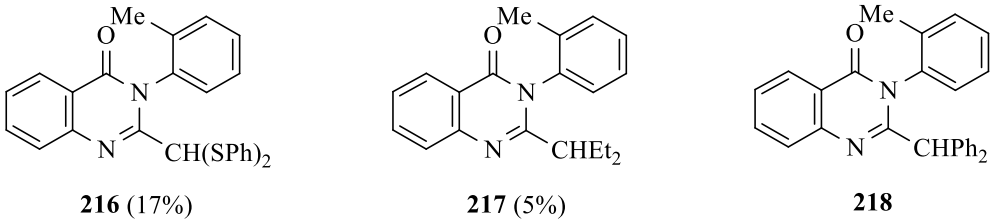
[c]Starting material **203** (56%) was recovered.

[d]2-(*Bis*(phenylthio)methyl)-3-(2-tolyl)-3*H*-quinazolin-4-one **216** (Figure 5) was obtained in 17% yield as a side-product due to lithiation and substitution of **210** along with **203** (29%).

[e]2-(Pentan-3-yl)-3-(2-tolyl)-3*H*-quinazolin-4-one **217** (Figure 5) was obtained in 5% yield due to further lithiation and substitution of **212** along with **203** (42%).

[f]2-Benzhydryl-3-(2-tolyl)-3*H*-quinazolin-4-one **218** (Figure 5; >1%) was obtained due to lithiation and substitution of **214** along with **203** (41%).

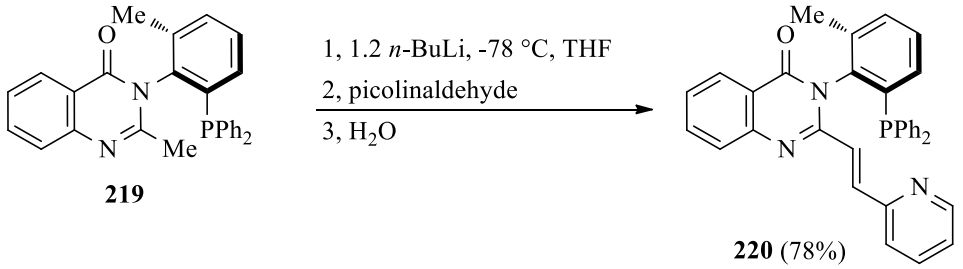
[g]Obtained from the corresponding 2-potassiomethyl derivative.



216 (17%) **217** (5%) **218**

Figure 5. Structures of compounds **216-218**.

Lithiation of (*S*)-3-2-(diphenylphosphino)-6-methylphenyl)-2-methyl-3*H*-quinazolin-4-one **219** with 1.2 molar equivalents of *n*-BuLi in anhydrous THF at -78 °C followed by reaction with picolinaldehyde gave (*E*)-3-(2-(diphenylphosphino)-6-methylphenyl)-2-(2-(pyridin-2-yl)vinyl)-3*H*-quinazolin-4-one **220** in 78% yield (Scheme 27).[142] Compound **220** was obtained as a results of dehydration of the substituted product initially produced.

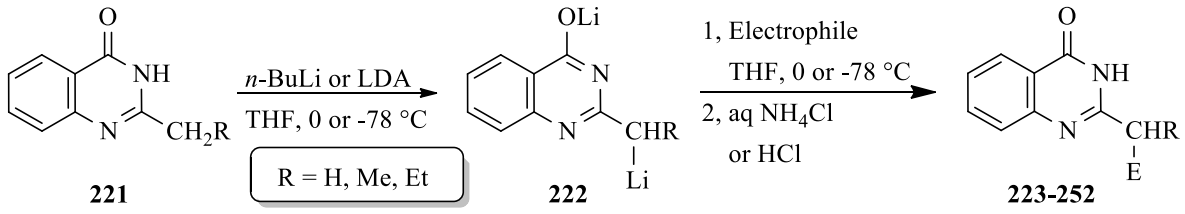


219 **220** (78%)

Scheme 27. Lateral lithiation, substitution and dehydration of **219**.

4.4. Lateral lithiation of 2-*n*-alkyl-3*H*-quinazolin-4-ones

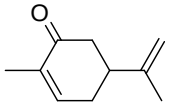
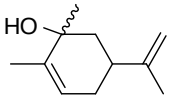
Lateral lithiation of various 2-*n*-alkyl-3*H*-quinazolin-4-ones **221** has been achieved by the use of 2.2 molar equivalents of *n*-BuLi (for R = H) or LDA (for R = Me and Et) in anhydrous THF at 0 or -78 °C (Scheme 28).[143-145] Lithiation was regioselective at the carbon α to the 2-position of the 3*H*-quinazolin-4-one moiety to give the dilithium reagents **222** (Scheme 28).[143-145] Reactions of **222** with various electrophiles gave the corresponding 2-substituted derivatives **223-252** (Scheme 28) in good yields (Tables 15 and 16).[143-145]



221 **222** **223-252**

Scheme 28. Lateral lithiation and substitution of **221**.

Table 15. Lithiation and substitution of **221** (R = H) according to Scheme 28[143-145]

Product	Electrophile	E	Yield (%)[a]
223	Ph_2CO	$Ph_2C(OH)$	79
224	PhCOMe	PhC(OH)Me	63
225	EtCOMe	EtC(OH)Me	80
226	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	81
227			82
228	PhCHO	PhCH(OH)	77
229	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	58
230	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	56
231	4-$Me_2NC_6H_4CH=CHCHO$	4-$Me_2NC_6H_4CH=CHCH(OH)$	50
232	nicotinaldehyde	pyridin-3-ylmethanol	55
233	isonicotinaldehyde	pyridin-4-ylmethanol	64
234	biphenyl-4-carbaldehyde	biphenyl-4-ylmethanol	81
235	1-naphthaldehyde	naphthalen-1-ylmethanol	72
236	2-naphthaldehyde	naphthalen-2-ylmethanol	73
237	PhNCO	PhNHCO	80
238	MeI	Me	89
239	EtBr	Et	57
240	$PhCH_2Cl$	$PhCH_2Cl$	58
241	D_2O	D	90

[a]Yield of isolated product after crystallization.

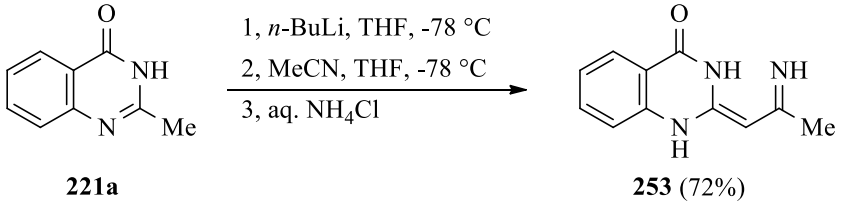
Table 16. Lithiation and substitution of **221** (R = Me, Et) according to Scheme 28[143]

Product	R	Electrophile	E	Yield (%)[a]
242	Me	PhCHO	PhCH(OH)	73
243	Me	Ph_2CO	$Ph_2C(OH)$	78
244	Me	PhCOMe	PhC(OH)Me	70
245	Me	PhNCO	PhNHCO	62
246	Me	MeI	Me	82
247	Me	D_2O	D	87
248	Et	PhCHO	PhCH(OH)	79
249	Et	Ph_2CO	$Ph_2C(OH)$	88
250	Et	PhCOMe	PhC(OH)Me	77
251	Et	MeI	Me	79
252	Et	D_2O	D	77

[a]Yield of isolated product after crystallization.

No *N*-substitution was observed even when excess iodomethane (3 molar equivalents) was used. The NMR spectra of products **227** (Table 15), **242**, **244**, **248** and **250** (Table 16) indicated the presence of two diastereoisomers.

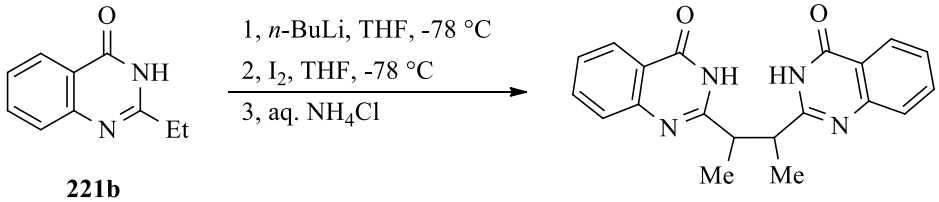
Reaction of the dilithium reagent, obtained *in situ* from lithiation of 2-methyl-3*H*-quinazolin-4-one **221a**, with acetonitrile gave 2-(2-iminopropylidene)-1,2-dihydro-3*H*-quiazolin-4-one **253** in 72% yield (Scheme 29) instead of the simple 2-substituted derivative.[143] The stability of **253** could be due to an intramolecular hydrogen bond.



221a **253** (72%)

Scheme 29. Synthesis of 2-(2-iminopropylidene)-1,2-dihydro-3*H*-quiazolin-4-one **253**.

Reaction of the dilithium reagent, obtained *in situ* from lithiation of 2-ethyl-3*H*-quinazolin-4-one **221b**, with iodine took place in different manner. Instead of 2-iodo derivative being formed oxidative dimerization took place to give 2,2≠-(2,3-butanediyl)*bis*-3*H*-quinazolin-4-one **254** in 60% yield (Scheme 30) after purification.[143]

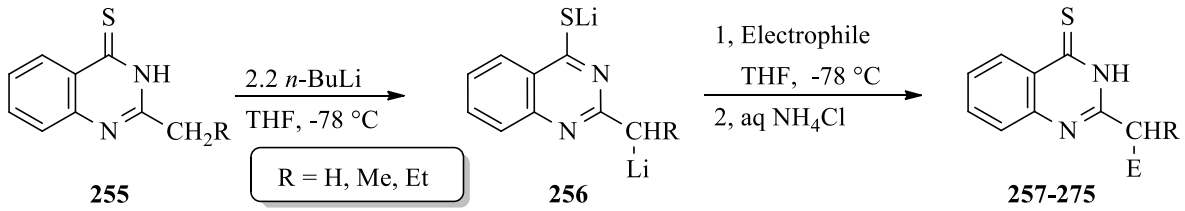


221b **254** (60%)

Scheme 30. Synthesis of 2,2≠-(2,3-butanediyl)*bis*-3*H*-quinazolin-4-one **254**.

4.5. Lateral lithiation of 2-*n*-alkyl-3*H*-quinazolin-4-thiones

Lateral lithiation of 2-*n*-alkyl-3*H*-quinazolin-4-thiones **255** occurred smoothly and rapidly with 2.2 molar equivalents of *n*-BuLi at -78 °C in THF with no nucleophilic attack at either the thione or the imine group of the quinazolinethione ring to produce dilithium reagent **256** (Scheme 31) as a purple solution.[146] Reactions of **256** with various electrophiles afforded the corresponding 2-substituted 3*H*-quinazoline-4-thiones **257-275** (Scheme 31) in excellent yields (Table 17).[146]



255 **256** **257-275**

Scheme 31. Lateral lithiation and substitution of **255**.

Table 17. Lithiation and substitution of **255** according to Scheme 31[146]

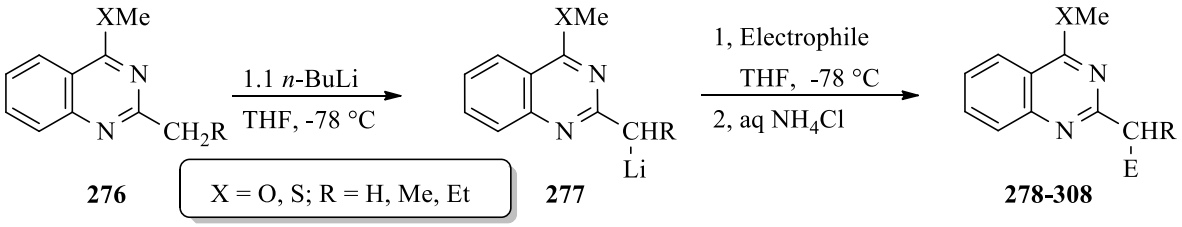
Product	R	Electrophile	E	Yield (%)[a]
257	H	PhCHO	PhCH(OH)	87
258	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	89
259	H	Ph_2CO	$Ph_2C(OH)$	92
260	H	BuCOMe	BuC(OH)Me	90
261	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	91
262	H	PhNCO	PhNHCO	84
263	H	$(i\text{-}Pr_2NCSS)_2$	$i\text{-}Pr_2NCSS$	90
264	H	MeI	Me	92
265	H	EtI	Et	90
266	H	D_2O	D	95
267	Me	PhCHO	PhCH(OH)	89
268	Me	Ph_2CO	$Ph_2C(OH)$	88
269	Me	BuBr	Bu	90
270	Me	MeI	Me	95
271	Me	D_2O	D	95
272	Et	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	90
273	Et	Ph_2CO	$Ph_2C(OH)$	95
274	Et	BuBr	BuBr	87
275	Et	D_2O	D	93

[a]Yield of isolated product after crystallization from methanol.

^{1}H NMR spectra of compounds **257**, **260**, **269** and **272-274** showed that the two hydrogen atoms of the CH_2 group at the 2-position occurred as independent, coupled signals, suggesting that they are diastereotopic. For compound **263**, the two isopropyl methyl protons appear as two broad signals and two separated doublets in its ^{1}H NMR spectra recorded at room temperature and 100 °C, respectively. The ^{1}H NMR spectrum of **263** recorded at 150 °C showed significant line-broadening indicative of the onset of equilibration *via* rotation about the C-N and C-S bonds, thereby confirming the origin of the non-equivalence of the two isopropyl methyl protons. The NMR spectra of compounds **267** and **272** show the expected presence of two racemic diastereoisomers.

4.6. Lateral lithiation of 4-substituted 2-*n*-alkylquinazolines

Lateral lithiation of 2-*n*-alkylquinazolines **276**, substituted in the 4-position by a methoxy or methanethiyl group, have been achieved by the use of 1.1 molar equivalents of *n*-BuLi at -78 °C in anhydrous THF under nitrogen to produce the corresponding lithium reagents **277** (Scheme 32) as purple solutions.[147] Reactions of **277** with various electrophiles afforded the corresponding 2-substituted derivatives **278-308** (Scheme 32) in high yields (Tables 18 and 19).[147]



Scheme 32. Lateral lithiation and substitution of **276**.

In some cases, a nucleophilic addition of *n*-BuLi took place at the C=N bond *via* 1,2- or 3,4-addition to give side products **309**-**311** and **313** (Figure 6).[147] Side product **312** (Figure 6) was formed due to 1,2-addition of *n*-BuLi followed by methylation at N-1 with iodomethane. Side product **314** (Figure 6) was obtained as a result of addition of *n*-BuLi at the imine bond at position 4, followed by elimination of the methoxy group and further addition of *n*-BuLi.

Table 18. Lithiation and substitution of **276** (X = S) according to Scheme 32[147]

Product	R	Electrophile	E	Yield (%)[a]
278	H	PhCHO	PhCH(OH)	83
279	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	86
280	H	PhCOMe	PhC(OH)Me	85
281	H	BuCOMe	BuC(OH)Me	84
282	H	Ph_2CO	$Ph_2C(OH)$	90
283	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	85
284	H	MeI	Me	91
285	H	EtI	Et	88
286	H	D_2O	D	89
287	Me	PhCHO	PhCH(OH)	80[b]
288	Me	Ph_2CO	$Ph_2C(OH)$	81[b]
289	Me	MeI	Me	82[b]
290	Me	D_2O	D	85[b]
291	Et	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78[c]
292	Et	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	79[c]
293	Et	D_2O	D	82[c]

[a]Yield of isolated product after purification by column chromatography.
[b]Compound **309** (Figure 6) was obtained in 3–5% yield.
[c]Compound **310** (Figure 6) was obtained in 4–7% yield.

Table 19. Lithiation and substitution of **276** (X = O) according to Scheme 32[147]

Product	R	Electrophile	E	Yield (%)[a]
294	H	PhCHO	PhCH(OH)	80
295	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	82
296	H	PhCOMe	PhC(OH)Me	85
297	H	BuCOMe	BuC(OH)Me	73
298	H	Ph_2CO	$Ph_2C(OH)$	81
299	H	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	75
300	H	MeI	Me	90
301	H	EtI	Et	87
302	H	D_2O	D	86
303	Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	71[b]
304	Me	Ph_2CO	$Ph_2C(OH)$	73[b]
305	Me	MeI	Me	67[b,c]
306	Me	D_2O	D	76[b]
307	Et	Ph_2CO	$Ph_2C(OH)$	71[d,e]
308	Et	D_2O	D	79[d,e]

[a]Yield of isolated product after purification by column chromatography.
[b]Compound **311** (Figure 6) was obtained in 2–3% yield.
[c]Compound **312** (Figure 6) was obtained in 3% yield.
[d]Compound **313** (Figure 6) was obtained in 3% yield.
[e]Compound **314** (Figure 6) was obtained in 1–2%.

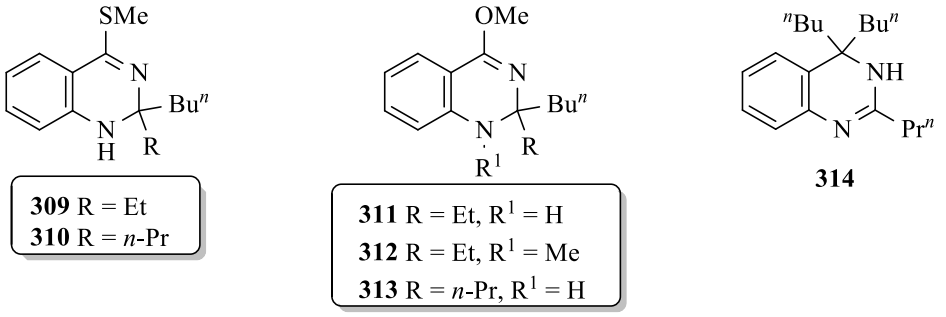
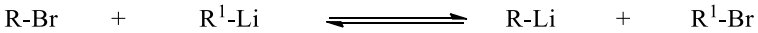


Figure 6. Structures of compounds **309-314**.

The ^{1}H NMR spectra of compounds **278-281** and **294-297** showed that the two hydrogen atoms of the CH_2 group at C-2 occurred as independent, coupled signals, verifying that they are diastereotopic.[147] The NMR spectra of compounds **287**, **291** and **303** showed the expected presence of two racemic diastereoisomers. In the cases of compounds **287** and **303** the two diastereoisomers were separated by column chromatography.[147]

5. Bromine-Lithium Exchange of 6-Bromo-3*H*-Quinazolin-4-One

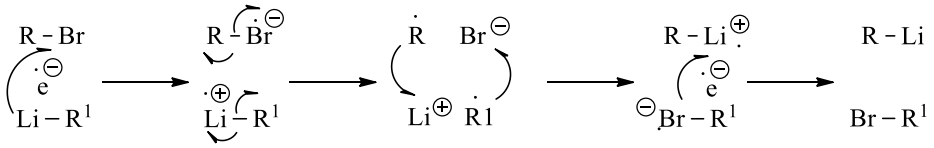
Bromine-lithium exchange (Scheme 33) has features that make it extremely valuable for the synthesis of organolithium compounds.



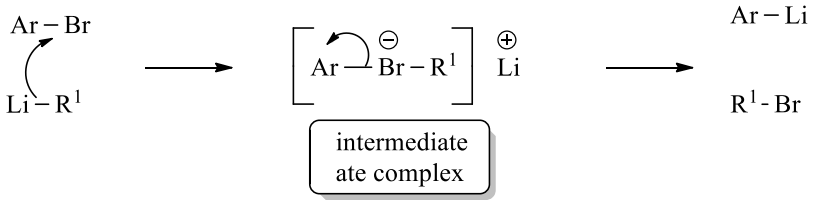
Scheme 33. Bromine-lithium exchange of bromo compounds using alkyllithium.

The equilibrium lies towards the side having the organolithium compound with the organic group better able to accommodate partial carbanionic character, and it is thus particularly useful for the preparation of aryllithiums by reaction of butyllithium with aryl bromides.[14] Because bromine-lithium exchange takes place rapidly under mild conditions, potential side-products such as alkylation of the organolithium by the organic halide are not usually troublesome. However, when the desired organolithium reagent is warmed for subsequent reaction it can couple with the alkyl bromide, producing a coupled product (R-R^1).[14] If alkylation is a problem, it can be minimised by use of two mole equivalents of *t*-BuLi as alkyllithium. In this case, bromine-lithium exchange is achieved by the first mole equivalent and the second reacts with the *t*-BuBr formed to produce isobutane and isobutene.

Bromine-lithium exchange may involve single electron transfer and radical intermediates (Scheme 34) or proceed through nucleophilic substitution at the bromine *via* ate complex formation (Scheme 35).[12] It is believed that alkyl bromides react with alkyllithiums *via* the radical mechanism, while aryl bromides react *via* ate complexes as intermediates.[12,56]



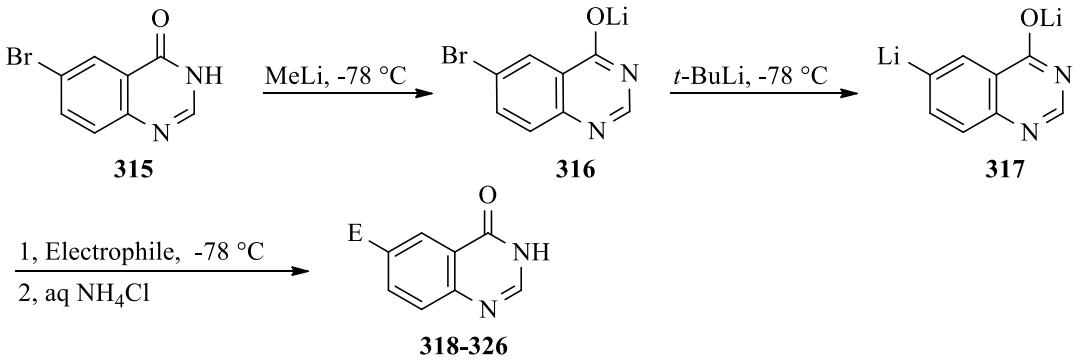
Scheme 34. Bromine-lithium exchange of alkyl bromide *via* radical intermediate.



Scheme 35. Bromine-lithium exchange of aryl bromide *via* ate complex intermediate.

Bromine-lithium exchange of 6-bromo-3*H*-quinazolin-4-one **315** was successful by the use of MeLi then *t*-BuLi at -78 °C in anhydrous THF.[148] Treatment of **315** with MeLi (1.1 molar

equivalents) for 5 minutes gave the monolithium reagent **316** by removing the NH proton, followed by bromine-lithium exchange using *t*-BuLi (2.2 molar equivalents) to give the dilithium reagent **317** (Scheme 36) as a yellow solution. Reactions of **317** with a range of electrophiles at -78 °C for 2 h gave the corresponding 6-substituted derivatives **318-326** (Scheme 36) in 81-91% yields (Table 20).[148]



315 316 317 318-326

Scheme 36. Bromine-lithium exchange of **315** followed by reactions with electrophiles.

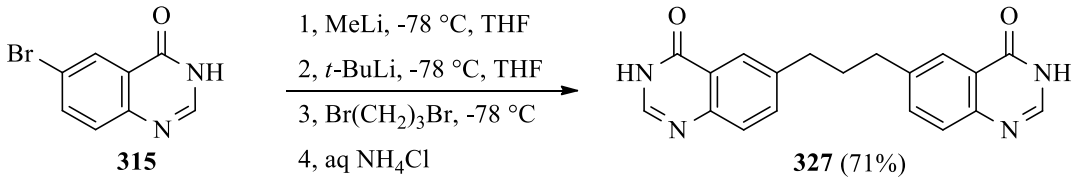
Table 20. Synthesis of 6-substituted 3*H*-quinazolin-4-ones **318-326** according to Scheme 36[148]

Product	Electrophile	E	Yield (%)[a]
318	H_2O	H	91
319	EtI	Et	84
320	PhCHO	PhCH(OH)	81
321	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
322	Ph_2CO	$Ph_2C(OH)$	88
323	MeCOBu	MeC(OH)Bu	88
324	$(CH_2)_5CO$	$CH_2)_5C(OH)$	85
325	PhNCS	PhNHCS	82
326	$[^iPr_2NC(S)S]_2$	$^iPr_2NC(S)S$	81

[a]Yield of isolated product after crystallization from methanol or ethyl acetate.

No *N*-substitution was observed, even when excess iodoethane (2 molar equivalents) as electrophile was used.[148] In the ^1H NMR spectrum of **326** the methyl and CH protons of the *iso*-propyl groups appeared as broad signals at room temperature and as doublet and heptet signals, respectively at 80 °C.[148] This confirms the restricted hindered to rotation about the C-S and C-N bonds at room temperature.

Reaction of the dilithium reagent obtained *in situ* from the bromine lithium exchange of **315** with 1,3-dibromopropane (0.55 mole equivalents) at -78 °C gave 6,6'-(propane-1,3-diyl)*bis*-3*H*-quinazoline **327** in 71% yield (Scheme 37).[148]



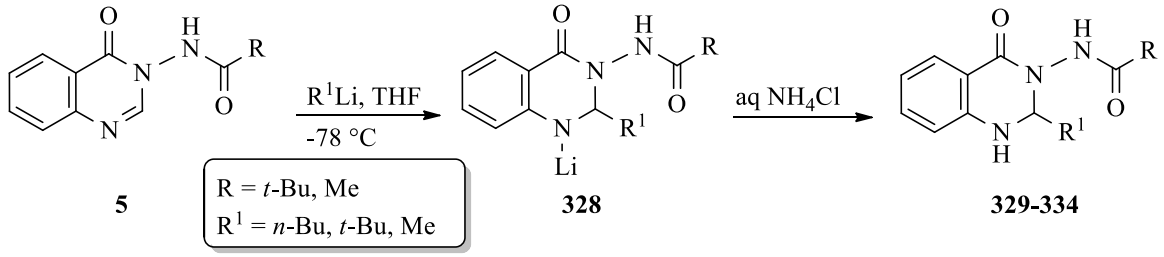
Scheme 37. Bromine-lithium exchange of **315** followed by reaction with 1,3-dibromopropane.

6. Addition of Alkyllithiums to Substituted Quinazoline Derivatives

Nucleophilic addition of alkyllithiums takes place at the imine bond of the quinazoline moiety to produce either 1,2- or 3,4-addition products. However, regioselective lithiation can take place by the use of less nucleophilic lithium reagents.

6.1. Addition of alkyllithiums to 3-acylamino-3*H*-quinazolin-4-ones

It was found that reactions of 3-acylamino-3*H*-quinazolin-4-ones **5** with one molar equivalent of alkyllithiums in THF at -78 °C were very fast and complete within five minutes to give 3-acylamino-2-alkyl-1,2-dihydro-3*H*-quinazolin-4-ones **329-334** (Scheme 38) in high yields (Table 21).[115]



Scheme 38. Addition of alkyllithiums to 3-acylamino-3*H*-quinazolin-4-ones **5**.

Table 21. Synthesis of 3-acylamino-2-alkyl-1,2-dihydro-3*H*-quinazolin-4-ones **329-334** according to Scheme 38 *via* 1,2-addition[115]

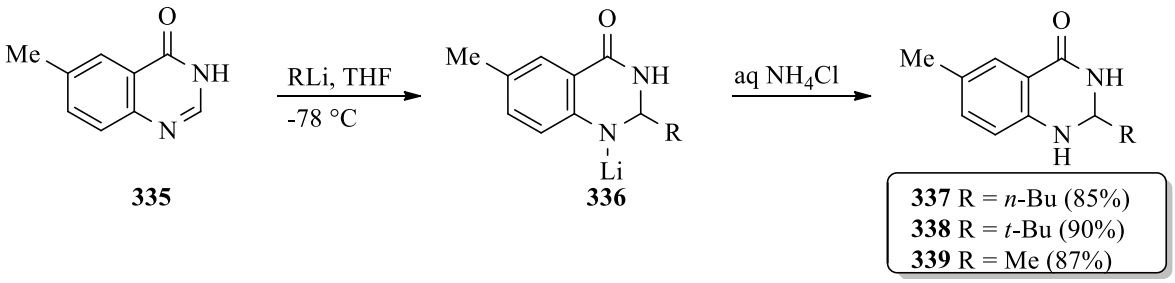
Product	R	R^1	Yield (%)[a]
329	*t*-Bu	*n*-Bu	96
330	*t*-Bu	*t*-Bu	98
331	*t*-Bu	Me	90
332	Me	*n*-Bu	82
333	Me	*t*-Bu	84
334	Me	Me	70

[a]Yield of isolated product after crystallization from ethyl acetate.

Clearly nucleophilic addition of alkyllithiums at the imine bond of the quinazoline moiety took place to give the corresponding 1,2-addition intermediates **328**. Directed lithiation of 3-acylamino-3*H*-quinazolin-4-ones **5**, at the 2-position, was achieved by the use of LDA as described in Section 2.1.[115]

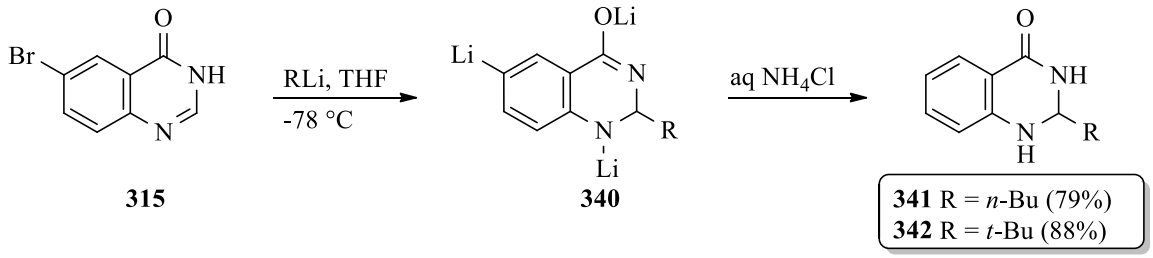
6.2. Addition of alkyllithiums to 6-substituted 3*H*-quinazolin-4-ones

Regioselective lithiation of 6-methyl-3*H*-quinazolin-4-ones **335** using alkyllithiums was not successful.[148] Instead, nucleophilic addition took place at the imine bond to give the corresponding 1,2-addition products. Reactions of **335** with alkyllithiums (one molar equivalent) in THF at -78 °C took place within 15 minutes to give 2-alkyl-6-methyl-1,2-dihydro-3*H*-quinazolin-4-ones **337-339** in high yields *via* lithium intermediate **336** (Scheme 39).[148] Lithiation of **335** with a less nucleophilic reagent such as LDA did not take place and only starting material was recovered, indicating that no reaction took place under the conditions tried.



Scheme 39. Addition of alkyllithiums to 6-methyl-3*H*-quinazolin-4-ones **335**.

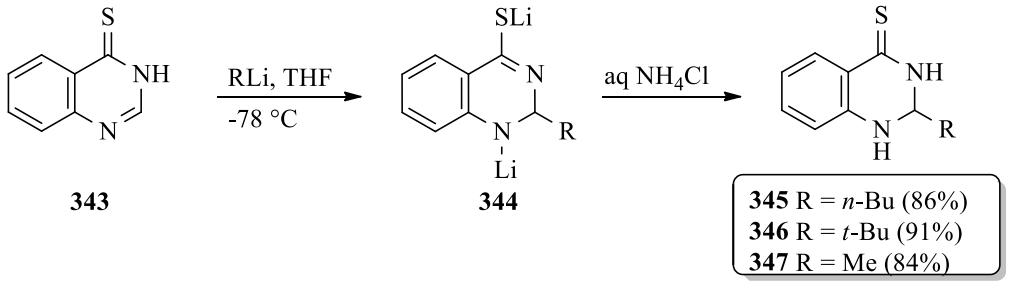
Reactions of 6-bromo-3*H*-quinazolin-4-ones **315** with butyllithiums in THF at -78 °C followed by reactions with a number of electrophiles (iodoethane, benzaldehyde, H_2O) produced low yields of 6-substituted products along with 2-butyl-1,2-dihydro-3*H*-quinazolin-4-ones.[148] However, if four molar equivalents of *n*-BuLi or *t*-BuLi were used in THF at -78 °C for 30 minutes, **341** and **342** were obtained in 88 and 79% yields, respectively (Scheme 40).[148] The author suggested that compound **340** was formed as an intermediate. Compound **315** was successfully converted into the 6-lithio derivative using a combination of MeLi and *t*-BuLi in THF at -78 °C (Section 5).[148]



Scheme 40. Addition of butyllithiums to 6-bromo-3*H*-quinazolin-4-ones **315**.

6.3. Addition of alkyllithiums to 3*H*-quinazolin-4-thiones

Reactions of 3*H*-quinazolin-4-thione **343** with two molar equivalents of alkyllithiums in THF at -78 C for 1 h gave the corresponding 2-alkyl-1,2-dihydro-3*H*-quinazoline-4-thiones **345-347** in high yields (Scheme 41).[149] It is believed that such reactions took place through the formation of dilithium reagents **344**.

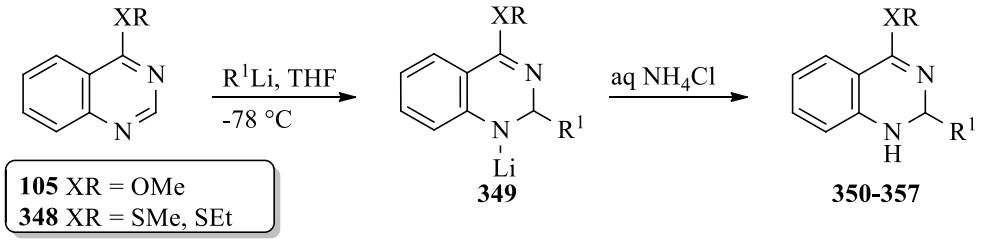


Scheme 41. Addition of alkyllithiums to 3*H*-quinazolin-4-thione **343**.

This result contrasts sharply with the situation of 3*H*-quinazolin-4-one, which does not react at all with alkyllithiums (*n*-BuLi, *t*-BuLi and MeLi) under similar conditions, which is an indication of the important role played by the sulfur atom in this reaction.[149] The authors suggested that the reason for this difference could be due to the thiolate anion in **344** being less effective at donating negative charge to the ring than its oxygen counterpart. The acquisition of negative charge by the ring would be expected to deactivate the ring towards nucleophilic attack by alkyllithiums.[149]

6.4. Addition of alkyllithiums to substituted quinazolines

Reactions of alkyllithiums with various quinazoline derivatives to produce addition products have been reported.[121,149-151] For example, reactions of 4-substituted quinazolines **105** and **348** with 1.2 molar equivalents of alkyllithiums took place smoothly and cleanly at -78 °C in anhydrous THF for 1 h.[149] The lithium reagent reagents **349** were presumably obtained as intermediates and after quenching with aqueous ammonium chloride solution gave the corresponding 4-substituted 2-alkyl-1,2-dihydroquinazolines **350-357** (Scheme 42) in high yields (Table 22).[149] Lithiation of **348** with LDA under similar reaction conditions was not successful.[149]



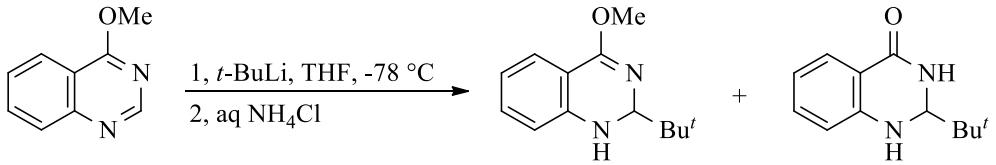
Scheme 42. Addition of alkyllithiums to 4-substituted quinazolines **105** and **348**.

Table 22. Synthesis of 4-substituted 2-alkyl-1,2-dihydroquinazolines **350**-**357** according to Scheme 42[149]

Product	X	R	R^1	Yield (%)[a]
350	S	Me	*n*-Bu	90
351	S	Me	*t*-Bu	88
352	S	Me	Me	89
353	S	Et	*n*-Bu	91
354	S	Et	*t*-Bu	89
355	O	Me	*n*-Bu	89
356	O	Me	*t*-Bu	89
357	O	Me	Me	94

[a]Yield of isolated product after column chromatography.

Reaction of 4-methoxyquinazoline **105** with excess *t*-BuLi gave a mixture of 2-*tert*-butyl-4-methoxy-1,2-dihydroquinazoline **356** and 2-*tert*-butyl-1,2-dihydro-3*H*-quinazoline-4-one **358** (Scheme 43) in proportions that depended on the molar equivalents of *t*-BuLi used (Table 23).[149] Compound **358** was the very product that might have been expected from the reaction of 3*H*-quinazolin-4-one with *t*-BuLi, but, of course, this direct reaction of 3*H*-quinazolin-4-one with *t*-BuLi did not occur.[149] Compound **358** was obtained due to nucleophilic addition of *t*-BuLi at the 2-position of **105** followed by a C=O formation at the 4-position.



105 **356** **358**

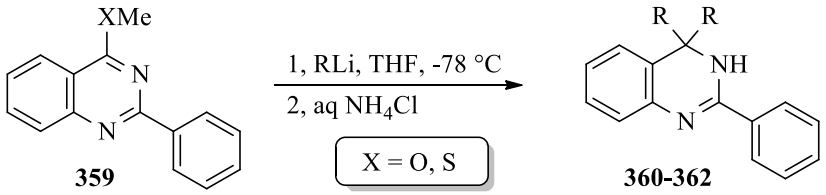
Scheme 43. Reaction of 4-methoxyquinazoline **105** with excess *t*-BuLi.

Table 23. Yields of **356** and **358** from reaction of **105** with *t*-BuLi according to Scheme 43[149]

t-BuLi (molar equiv.)	Yield (%)[a]	
	356	**358**
1.2	89	—
1.4	76	6
2.0	66	15
2.4	50	27
3.0	37	42

[a]Yield of isolated product after column chromatography.

Reactions of 4-substituted 2-phenylquinazoline **359** with one molar equivalent of alkyllithiums (*n*-BuLi and MeLi) at -78 °C in anhydrous THF for one hour gave 4,4-dialkyl-3,4-dihydro-2-phenylquinazolines in moderate yields along with significant quantities of starting material **359**.[149] Use of 2.2 molar equivalents of alkyllithium (*n*-BuLi, *t*-BuLi and MeLi) at –78 °C in THF for one hour gave **360-362** (Scheme 44) in high yields (Table 24).[121,149] Products **360-362** were obtained *via* 3,4-nucleophilic addition of alkyllithiums followed by displacement of the substituent (SMe, OMe or $O(CH_2)_2OMe$) as an anion and further addition of alkyllithium. Reaction of **359** with *t*-BuLi gave only a modest yield of product **362** due to formation of by-products which were not identified.[149]



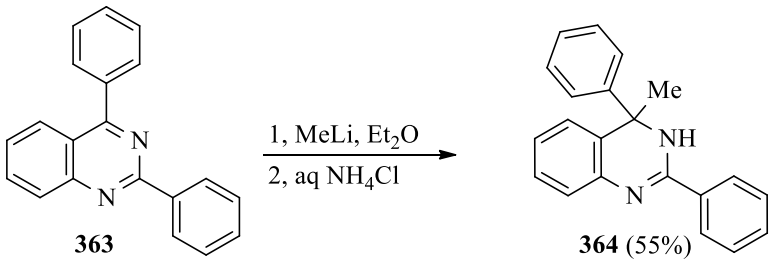
Scheme 44. Addition of alkyllithiums to 4-substituted 2-phenylquinazoline **359**.

Table 24. Synthesis of 4,4-dialkyl-3,4-dihydro-2-phenylquinazolines **360-362** according to Scheme 44[121,149]

Product	X	RLi (molar equiv.)	R	Yield (%)[a]
360	S	1.1	*n*-Bu	49
360	S	2.2	*n*-Bu	96
360	O	1.1	*n*-Bu	46
360	O	2.2	*n*-Bu	88
360	$O(CH_2)_2OMe$	2.2	*n*-Bu	50
361	S	1.1	Me	40
361	S	2.2	Me	81
361	O	2.2	Me	83
362	S	2.2	*t*-Bu	49
362	O	2.2	*t*-Bu	49

[a]Yield of isolated product after column chromatography.

Reactions of 2,4-diphenylquinazoline **363** with MeLi in dry Et_2O gave 4-methyl-2,4-diphenyl-3,4-dihydroquinazoline **364** in 55% yield (Scheme 45) in which methyllithium was added at the imine bond at the 3-position.[150]



Scheme 45. Synthesis of 4-methyl-2,4-diphenyl-3,4-dihydroquinazoline **364**.

7. Conclusions

Directed *ortho*-lithiation of 3-acylamino-3*H*-quinazolin-4-ones with LDA at -78 °C in anhydrous THF is regiospecific and reactions of the lithium regents obtained with various electrophiles provided access to a broad variety of 2-substituted derivatives in high yields. Similar procedures have been developed for directed lithiation and substitution of 3-aryl-, *tert*-butylsulfinyl-3*H*-quinazolin-4-ones, phenylsulfinyl-, chloro- and methoxyquinazolines. Such procedure provided derivatives previously unavailable or that might be difficult to prepare by other means.

Lateral lithiation of 3-acylamino-2-*n*-alkyl-3*H*-quinazolin-4-ones, at the benzylic position of the *n*-alkyl group, has been achieved by use of *n*-BuLi or LDA at low temperature. Also, lithiation of 3-amino- and 3-methylamino-2-*n*-alkyl-3*H*-quinazolin-4-ones at low temperature in THF followed by reactions with several electrophiles provides various 2-substituted derivatives in high yields. The procedure is particularly useful in that there is no protecting group to be removed in another step from the amino function. A similar procedure has been developed for the side-chain lithiation and substitution for 3-aryl- and 3-unsubstituted 2-*n*-alkyl-3*H*-quinazolin-4-ones and their thione derivatives.

A simple and convenient method for the side-chain substitution of 4-substituted 2-*n*-alkylquinazolines, with a methoxy or methylthio group at position 4, has been reported and allows synthesis of various 2-substituted derivatives in high yields. Also, lithiation and substitution of several other quinazoline derivatives have been achieved to provide a range of substituted derivatives.

Bromine-lithium exchange of 6-bromo-3*H*-quinazolin-4-one has been achieved by the use of MeLi and *t*-BuLi at -78 °C in THF. Reactions of the dilithium reagent thus obtained with electrophiles give the corresponding 6-substituted 3*H*-quinazolin-4-ones in high yields.

Nucleophilic addition of alkyllithiums to 3-acylamino-3*H*-quinazolin-4-ones, 3*H*-quinazoline-4-thione and various quinazoline derivatives containing an alkylthio or a methoxy group at C-4 and a phenyl group or a hydrogen at C-2 take place at low temperature. The method provides high yields of various 2-alkyl-1,2-dihydroquinazolines, *via* 1,2-addition of alkyllithiums, and 4,4-dialkyl-3,4-dihydro-2-phenylquinazolines *via* 3,4-addition followed by displacement of the substituent (SMe or OMe) at C-4.

8. References

1. Olah, G. A. *Friedel-Crafts Chemistry*, Wiley-Interscience: New York, 1973.
2. Pearson, D. E.; Buehler, C. A. *Synthesis* **1972**, 533.
3. Florio, S.; Capriati, V.; Salomone, A. *Topics in Stereochemistry*; Siegel J. S., Ed.; Wiley-VCH: Weinheim, 2010, Vol *26*, Chap. 4.
4. Rathman, T. L.; Bailey, W. F. *Org. Process Res. Dev.* **2009**, *13*, 144.
5. Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918.
6. Chevallier, F.; Mongin, F. *Chem. Soc. Rev*. **2008**, *37*, 595.
7. Elschenbroich, C. *Organometallics*, Wiley-VCH: Weinheim, 2006.
8. Foubelo, F.; Yus, M. *Curr. Org. Chem*. **2005**, *9*, 459.
9. Schlosser, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 376.
10. Smith, K.; El-Hiti, G. A. *Curr. Org. Synth*. **2004**, *1*, 253.
11. Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev*. **2004**, *104*, 2667.
12. Clayden, J. *Organolithiums: Selectivity for Synthesis*, Pergamon: Oxford, 2002.
13. Schlosser, M. *Organometallics in Synthesis*, 2nd ed.; Wiley: Chichester, **2002**; pp. 1–352.
14. Wakefield, B. J. In *Organolithium Methods*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Ed.; Academic Press: London, 1988.
15. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
16. Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev*. **1984**, *84*, 471.
17. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.
18. Beak, P.; Snieckus, V. *Acc. Chem. Res*. **1982**, *15*, 306.
19. Beak, P.; Musick, T. J.; Chen, C.-W. *J. Am. Chem. Soc*. **1988**, *110*, 3538.
20. Smith, K.; Lindsay, C. M.; Morris, I. K.; Matthews, I.; Pritchard, G. J. *Sulfur Lett*. **1994**, *17*, 197.
21. Smith, K.; Anderson, D.; Matthews, I. *Sulfur Lett*. **1995**, *18*, 79.
22. Godard, A.; Rocca, P.; Pomel, V.; Thomas-dit-Dumont, L.; Rovera, J.-C.; Thaburet, J.-F.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem*. **1996**, *517*, 25.
23. Bowles, P.; Clayden, J.; Helliwell, M.; McCarthy, C.; Tomkinson, M.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2607.
24. Plé, N.; Turck, A.; Heynderickx, A.; Quéguiner, G. *Tetrahedron* **1998**, *54*, 4899.
25. Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 12149.
26. Choppin, S.; Gros, P.; Fort, Y. *Eur. J. Org. Chem*. **2001**, 603.
27. Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489.
28. Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150.
29. Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem*. **2002**, *67*, 234.
30. Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed*. **2004**, *43*, 2206.
31. Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett*. **2004**, *6*, 4191.

32. Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc*. **2007**, *129*, 2259.
33. Clayden, J.; Turner, H.; Helliwell, M.; Moir, E. *J. Org. Chem*. **2008**, *73*, 4415.
34. Lee, W. K.; Park, Y. S.; Beak, P. *Acc. Chem. Res.* **2009**, *42*, 224.
35. Hodgson, D. M.; Kloesges, J. *Angew. Chem. Int. Ed*. **2010**, *49*, 2900.
36. Fukuda, T.; Ohta, T.; Sudo, E.; Iwao, M. *Org. Lett*., **2010**, *12*, 2734.
37. Houlden, C. E.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett*. **2010**, *12*, 3090.
38. Tilly, D.; Fu, J.-M.; Zhao, B.-P.; Alessi, M.; Catanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett*. **2010**, *12*, 68.
39. Wessels, M.; Mahajan, V.; Bosshammer, S.; Raabe, G.; Gais, H.-J. *Eur. J. Org. Chem*. **2011**, 2431.
40. Skvorcova, A.; Rakovsky, E.; Kozisek, J.; Sebesta, R. *J. Organomet. Chem*. **2011**, *696*, 2600.
41. (a) Snieckus, V. *Beilstein J. Org. Chem*. **2011**, *7*, 1215. (b) Cho, I.; Meimetis, L.; Belding, L.; Katz, M. J.; Dudding, T.; Britton, R. *Beilstein J. Org. Chem*. **2011**, *7*, 1315. (c) Page, A.; Clayden, J. *Beilstein J. Org. Chem*. **2011**, *7*, 1327.
42. (a) Schmid, M.; Waldner, B.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Tetrahedron* **2011**, *67*, 2895. (b) Degennaro, L.; Mansueto, R.; Carenza, E.; Rizzi, R.; Florio, S.; Pratt, L. M.; Luisi, R. *Chem. Eur. J*. **2011**, *17*, 4992. (c) de Ceglie, M. C.; Musio, B.; Affortunato, F.; Moliterni, A.; Altomare, A.; Florio, S.; Luisi, R. *Chem. Eur. J*. **2011**, *17*, 286.
43. (a) Clayton, J.; Clayden, J. *Tetrahedron Lett*. **2011**, *52*, 2436. (b) Clayden, J.; MacLellan, P. *Beilstein J. Org. Chem*. **2011**, *7*, 582. (c) Campbell, S. A.; Donnard, M.; Haywood, J.; McPartlin, M.; Vincent, M. A.; Hillier, I. H.; Clayden, J.; Wheatley, A. E. H. *Chem. Eur. J*. **2011**, *17*, 8078.
44. (a) Ibrahim, N.; Chevot, F.; Legraverend, M. *Tetrahedron Lett*. **2011**, *52*, 305. (b) Solovyev, A.; Lacôte, E.; Curran, D. P. *Org. Lett*. **2011**, *13*, 6042.
45. Clayden, J.; Turner, H.; Pickworth, M.; Adler, T. *Org. Lett*. **2005**, *7*, 3147.
46. Clayden, J.; Dufour, J. *Tetrahedron Lett*. **2006**, *47*, 6945.
47. Comoy, C.; Banaszak, E.; Fort, Y. *Tetrahedron* **2006**, *62*, 6036.
48. Luisi, R.; Capriati, V.; Florio, S.; Musio, B. *Org. Lett*. **2007**, *9*, 1263.
49. Burgos, P. O.; Fernández, I.; Iglesias, M. J.; García-Granda, S.; Ortiz, F. L. *Org. Lett*. **2008**, *10*, 537.
50. Castanet, A.-S.; Tilly, D.; Véron, J.-B.; Samanta, S. S.; De, A.; Ganguly, T.; Mortier, J. *Tetrahedron* **2008**, *64*, 3331.
51. Clayden, J.; Hennecke, U. *Org. Lett*. **2008**, *10*, 3567.
52. McLaughlin, M.; Marcantonio, K.; Chen, C.; Davies, I. W. *J. Org. Chem*. **2008**, *73*, 4309.
53. Capriati, V.; Florio, S.; Luisi, R.; Mazzanti, A.; Musio, B. *J. Org. Chem*. **2008**, *73*, 3197.
54. Affortunato, F.; Florio, S.; Luisi, R.; Musio B. *J. Org. Chem.* **2008**, *73*, 9214.
55. Michon, C.; Murai, M.; Nakatsu, M.; Uenishi, J.; Uemura M. *Tetrahedron* **2009**, *65*, 752.

56. Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Advances in Heterocyclic Chemistry: Directed Metallation of π-deficient Azaaromatics* Katritzky, A. R. Ed.; Academic Press: London, 1991, pp 187-304.
57. Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.
58. Macklin, T.; Ang, P.; Blanchet, J.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199.
59. Sánchez, J. D.; Cledera, P.; Perumal, S.; Avendaño, C.; Menéndez, J. C. *Synlett* **2007**, 2805.
60. Chau, N. T. T.; Nguyen, T. H.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Tetrahedron* **2008**, *64*, 10552.
61. Sahin, A.; Cakmak, O.; Demirtas, I.; Okten, S.; Tutar, A. *Tetrahedron* **2008**, *64*, 10068.
62. Ruiz-Gómez, G.; Francesch, A.; Iglesias, M. J.; López-Ortiz, F.; Cuevas, C.; Serrano-Ruiz, M. *Org. Lett.* **2008**, *10*, 3981.
63. Luliński, S.; Zajac K. *J. Org. Chem.* **2008**, *73*, 7785.
64. Shibasaki, T.; Ooishi, T.; Yamanouchi, N.; Murafuji, T.; Kurotobi, K.; Sugihara, Y. *J. Org. Chem*. **2008**, *73*, 7971.
65. van der Stoel, R. E.; van der Plas, H. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2393.
66. van der Stoel, R. E.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 116.
67. Ziegler, K.; Zeiser, H. *Ann*. **1931**, *485*, 174.
68. Ziegler, K.; Zeiser, H. *Ber*. **1930**, *63*, 1874.
69. Marsais, F.; Bouley, E.; Quéguiner, G. *J. Organomet. Chem*. **1979**, *171*, 273.
70. Godard, A.; Turck, A.; Plé, N.; Marsais, F.; Quéguiner, G. *Trends Heterocycl. Chem.* **1993**, *3*, 19.
71. Jen, T.; Dienel, B.; Dowalo, F.; Van Hoeven, H.; Bender, P.; Loev, B. *J. Med. Chem*. **1973**, *16*, 633.
72. Marsham, P. R.; Hughes, L. R.; Jackman, A. L.; Hayter, A. J.; Oldfield, J.; Wardleworth, J. M.; Bishop, J. A. M.; O'Connor, B. M.; Calvert, A. H. *J. Med. Chem.* **1991**, *34*, 1594.
73. Dempcy, R. O.; Skibo, E. B. *Bioorg. Med. Chem.* **1993**, *1*, 39.
74. Hennequin, L. F.; Boyle, F. T.; Wardleworth, J. M.; Marsham, P. R.; Kimbell, R.; Juckman, A. L. *J. Med. Chem*. **1996**, *39*, 695.
75. Hour, M.-J.; Huang, L.-J.; Kuo, S.-C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K.-H. *J. Med. Chem*. **2000**, *43*, 4479.
76. Alagarsamy, V.; Murugananthan, G.; Venkateshperumal, R. *Biol. Pharm. Bull*. **2003**, *26*, 1711.
77. Alagarsamy, V. *Pharmazie* **2004**, *59*, 753.
78. Alagarsamy, V.; Giridhar, R.; Yadav, M. R. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1877.
79. Alagarsamy, V.; Giridhar, R.; Yadav, M. R. *J. Pharm. Pharmacol*. **2006**, *58*, 1249.
80. Aagarsamy, V.; Pathak, U. S. *Bioorg. Med. Chem.* **2007**, *15*, 3457.
81. Aagarsamy, V.; Shankar, D.; Murugan, M.; Siddiqui, A. A.; Rajesh, R. *Arch. Pharm.* **2007**, *340*, 41.

82. Shaban, M. A. E.; Taha, M. A. M.; Sharshira, E. M. *Advances in Heterocyclic Chemistry*: *Synthesis and Biological Activities of Condensed Heterocyclo[n,m-a,b or c]quinazolines*, Katritzky, A. R. Ed.; Academic Press: New York, 1991, Vol. *52*; pp. 1-303.
83. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893.
84. Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627
85. Eguchi, S. *Top. Heterocyl. Chem*. **2006**, *6*, 113.
86. Shawali, A. S.; Farghaly, T. A. *Arkivoc* **2008**,(*i)*, 18.
87. Abdel-Megeed, M. F.; Aly, Y. L.; Saleh, M. A.; Abdo, I. M.; El-Hiti, G. A.; Smith, K. *Sulfur Lett*. **1995**, *19*, 129.
88. Abdo, M. A.; Abdel-Megeed, M. F.; Saleh, M. A.; El-Hiti, G. A. *Pol. J. Chem*. **1995**, *69*, 583.
89. Abdel-Megeed, M. F.; Saleh, M. A.; Abdo, M. A.; El-Hiti, G. A. *Collect. Czech. Chem. Commun*. **1995**, *60*, 1016.
90. Saleh, M. A.; Abdo, M. A.; Abdel-Megeed, M. F.; El-Hiti, G. A. *Indian J. Chem*. **1996**, *35B*, 147.
91. El-Hiti, G. A. *Bull. Chem. Soc., Jpn*. **1997**, *70*, 2209.
92. Abdo, M. A.; Zeid, I. F.; El-Hiti, G. A.; Mahmoud, O. E. *Indian J. Chem*. **1999**, *38B*, 850.
93. Abdel-Megeed, M. F.; El-Hiti, G. A.; Saleh, M. A.; Abdo, M. A.; Awadalla, S. E. *Rev. Roum. Chim*. **1999**, *44*, 67.
94. El-Hiti, G. A.; Abdel-Megeed, M. F.; Mahmoud, Y. A.-G. *Indian J. Chem*. **2000**, *39B*, 368.
95. Abdel-Megeed, M. F.; El-Hiti, G. A.; Abdo, M. A.; Saleh, M. A. *Rev. Roum. Chim*. **2000**, *45*, 545.
96. El-Hiti, G. A. *Alex. J. Pharm. Sci*. **2000**, 14, 37.
97. El-Hiti, G. A.; Abdel-Megeed, M. F.; Zied,T. M. *Indian J. Chem*. **2002**, *41B*, 1519.
98. El-Brollosy, N. R.; Abdel-Megeed, M. F.; El-Hiti, G. A.; Genady, A. R. *Afinidad* **2003**, *60*, 199.
99. El-Hiti, G. A.; Abdel-Megeed, M. F. *Heterocycles* **2005**, *65*, 3007.
100. Abdel-Megeed, M. F.; Azaam, M. M.; El-Hiti, G. A. *Monatsh. Chem*. **2007**, *138*, 153
101. El-Hiti, G. A.; Hussain, A.; Hegazy, A. S.; Alotaibi, M. H. *J. Sulfur Chem.* **2011**, *32*, 361.
102. Smith, K.; El-Hiti, G. A.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4041.
103. Smith, K.; El-Hiti, G. A.; Pritchard, G. J.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2299.
104. Smith, K.; El-Hiti, G. A.; Shukla, A. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2305.
105. Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synlett* **1999**, 945.
106. Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synthesis* **2003**, 2047.
107. Smith, K.; El-Hiti, G. A.; Mahgoub, S. A. *Synthesis* **2003**, 2345.
108. El-Hiti, G. A. *Synthesis* **2003**, 2799.
109. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synlett* **2009**, 2242.

110. Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A.; Kariuki, B. M. *Arkivoc* **2009**, (*xiv)*, 266.
111. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Chem. Commun*. **2010**, *46*, 2790.
112. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2010**, 1371.
113. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. Kariuki, B. *Beilstein J. Org. Chem*. **2011**, *7*, 1219-1227.
114. El-Hiti, G. A. *Heterocycles* **2000**, *53*, 1839.
115. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem*. **1996**, *61*, 647.
116. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F. *Russ. J. Org. Chem*. **2003**, *39*, 430.
117. Dai, X.; Virgil, S. *Tetrahedron: Asymmetry* **1999**, *10*, 25.
118. Potewar, T. M.; Ingale, S. A.; Srinivasan, K. V. *Arkivoc* **2008**, (*xiv)*, 100.
119. Chapoulaud, V. G.; Salliot, I.; Plé, N.; Turck, A.; Quéguiner, G. *Tetrahedron* **1999**, *55*, 5389.
120. Le Fur, N.; Mojovic, L.; Plé, N.; Turck, A.; Marsais, F. *Tetrahedron* **2005**, *61*, 8924.
121. Plé, N.; Turck, A.; Chapoulaud, V. G.; Quéguiner, G. *Tetrahedron* **1997**, *53*, 2871.
122. Chapoulaud, V. G.; Plé, N.; Turck, A.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 5499.
123. Colwell, W. T.; Yamamoto, K.; Christie, P.; Henry, D. W. *Synth. Commun.* **1972**, *2*, 109.
124. Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688.
125. Busch, A.; Chapoulaud, V. G.; Audoux, J.; Plé, N.; Turck, A. *Tetrahedron* **2004**, *60*, 5373.
126. Mhaske, S. B.; Argade, N. P. *J. Org. Chem*. **2004**, *69*, 4563.
127. Smith, K.; El-Hiti, G. A.; Abdo, M. A.; Abdel-Megeed, M. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1029.
128. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F. *Synthesis* **2004**, 2121.
129. Atkinson, R. S. In *Comprehensive Organic Chemistry*, Eds. Barton, D. H. R.; Ollis, W. D. Pergamon: Oxford, 1978, Vol. 2, p. 225.
130. Shvo, Y. in *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, Ed. S. Patai, Interscience: New York, 1975, Part 2.
131. Moriarty, R. M.; Murphy, M. R.; Druck, S. J.; May, L. *Tetrahedron Lett*. **1967**, *8*, 1603.
132. Dewar, M. J. S.; Jennings, W. B. *J. Am. Chem. Soc*. **1969**, *91*, 3655.
133. Anderson, J. E.; Griffith, D. L.; Roberts, J. D. *J. Am. Chem. Soc*. **1969**, *91*, 6371.
134. Fletcher, J. R.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun*. **1970**, 687.
134. Dewar, M. J. S.; Jennings, W. B. *J. Am. Chem. Soc*. **1973**, *95*, 1562.
135. Mannschreck, A.; Koelle, U. *Tetrahedron Lett*. **1967**, *8*, 863.
136. Marullo, N. P.; Mayfield, C. B.; Wagener, E. M. *J. Am. Chem. Soc*. **1968**, *90*, 510.
137. Tolles, W. M.; Moore, D. W.; Thun, W. E. *J. Am. Chem. Soc*. **1966**, *88*, 3476.
138. El-Hiti, G. A. *Spectrosc. Lett*. **1999**, *32*, 671.
139. Atkinson, R. S.; Barker, E.; Price, C. J.; Russell, D. R. *J. Chem. Soc., Chem. Commun*. **1994**, 1159.

140. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem*. **1996**, *61*, 656.
141. Rathman, T. L.; Sleevi, M. C.; Krafft, M. E.; Wolfe, J. F. *J. Org. Chem*. **1980**, *45*, 2169.
142. Dai, X.; Virgil, S. *Tetrahedron Lett*. **1999**, *40*, 1245.
143. Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *Collect. Czech. Chem. Commun.* **1999**, *64*, 515.
144. Murray, T. P.; Hay, J. V.; Portlock, D. E.; Wolfe, J. F. *J. Org. Chem*. **1974**, *39*, 595.
145. Philipova, I.; Dobrikov, G.; Krumova, K.; Kaneti, J. *J. Heterocycl. Chem*. **2006**, *43*, 1057.
146. El-Hiti, G. A. *Synthesis*, **2004**, 363.
147. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2005**, 2951.
148. El-Hiti, G. A. *Monatsh. Chem.* **2004**, *135*, 323.
149. Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *J. Sulfur Chem.* **2005**, *26*, 121.
150. Smith, J. G.; Sheepy, J. M. *J. Heterocycl Chem*. **1975**, *12*, 231.
151. Briggs, T. F.; Winemiller, M. D.; Collum, D. B.; Parsons, R. L.; Davulcu, A. H.; Harris, G. D.; Fortunak, J. M.; Confalone, P. N. *J. Am. Chem. Soc*. **2004**, *126*, 5427.

Authors' Biographies

Professor Gamal A. El-Hiti

Gamal A. El-Hiti received his B.Sc. and M.Sc. degrees from Tanta University, Egypt in 1986 and 1990, respectively. He received his Ph.D. degree from Tanta University in 1996 including two years at Swansea University, UK. He first joined Keith Smith's research group in 1993 while enrolled for a PhD in Egypt. He was awarded a scholarship to allow him to spend two years in the UK to take advantage of the availability of advanced facilities. Keith and he were able to elaborate various quinazolinones into more complex derivatives and this formed the basis of his PhD thesis when he returned to Egypt to resume his job as a lecturer in 1996. As soon as his

university would permit it, Keith invited him back to the UK as a postdoctoral researcher and found support funding. Keith did the same on two more occasions and the latter has been continuous for the last 11 years. During these periods he has formed a very close working relationship with Keith's group and they have collaborated extensively. Together they have over 50 joint publications, including ones in all of the major areas of research in which Keith's group is involved and several reviews. They have recently started up a spin-out company to commercialise some of their innovations in the area of catalysis. He has acted as the Technical Director for the Company since August 2006. His research interests are primarily in the development of novel organic synthetic methods, especially ones that are "greener" than traditionally, and synthesis of compounds with interesting properties. Particular current research projects involve use of zeolites and solid-supported reagents and catalysts to gain selectivity in organic reactions; lithiation reactions, which they have used to devise novel heterocyclic ring syntheses and to introduce selectivity into aromatic and heterocyclic substitution reactions; heterocyclic chemistry and design and synthesis of novel compounds with interesting chemiluminescent or other photoactive properties. He is currently a Professor of Organic Chemistry since 2006 at Tanta University, Faculty of Science, Department of Chemistry, Egypt (on sabbatical leave to the UK).

Dr Amany S. Hegazy

Amany S. Hegazy received her B.Sc. degree in Chemistry from Tanta University, Egypt. She received her MPhil degree from Swansea University, UK in 2006 and her Ph.D. degree from Cardiff University, UK in 2009. She carried out her postgraduate studies under the supervision of Professor Keith Smith. Her research focused on the green synthetic methods of heterocycles and aromatics *via* use of organolithium reagents as intermediates.

Dr Mohammad H. Alotaibi

Mohammed Hayal Alotaibi was born in Saudi Arabia. He received his B.Sc. degree in Chemistry from King Saud University, Saudi Arabia. He received his Ph.D. degree from Cardiff University, UK in 2008 under the supervision of Professor Keith Smith. His research focused on the use of zeolites as catalysts in nitration of aromatic compounds. Currently, he is working in Forensic Laboratories in Riyadh, Saudi Arabia.

Dr Mansour D. Ajarim

Mansour D. Ajarm was born in Saudi Arabia. He received his B.Sc. degree in Pharmacy from King Saud University, Saudi Arabia. He received his Ph.D. degree from Cardiff University, UK in 2010 under the supervision of Professor Keith Smith. His research focused on the use of zeolites as catalysts in nitration of aromatic compounds. Currently, he is working in Forensic Laboratories in Riyadh, Saudi Arabia.

