Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9255–9303

TETRAHEDRON

Tetrahedron report number 658

Recent synthetic uses of functionalised aromatic and heteroaromatic organolithium reagents prepared by non-deprotonating methods

Carmen Nájera, José M. Sansano and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Received 18 September 2003

Contents

1. Introduction

The growth and development of organometallic chemistry in both organic and inorganic chemistry started 150 years ago.[1,2a] As part as this huge area, organolithium compounds have been considered as fundamental reagents due to their chemical behaviour[2] and have recently emerged as a valuable tool in the preparation of other organometallic compounds[2a,3] for the cross-coupling reactions catalysed by transition metal complexes.[2a,4] Functionalised organolithium compounds are attractive and very interesting intermediates for the construction of organic structures because in their reaction with electrophiles they are able to generate directly polyfunctionalised molecules.[2a,5] These compounds are mainly generated by direct deprotonation or by a halogen–lithium exchange, although tin–lithium, chalcogen–lithium and phosphorous–lithium exchanges are also known.[2a] In particular, aryl- and heteroaryllithium compounds, obtained by direct deprotonation have been

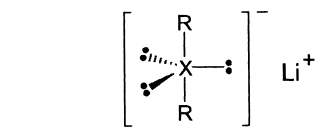
Keywords: organolithiums; aryllithiums; heteroaryllithiums; halogen–lithium exchange; oxygen–lithium exchange; phosphorous–lithium exchange; sulfur–lithium exchange; selenium–lithium exchange; tellurium–lithium exchange; deprotonations; addition reactions; transmetallation; cross-coupling reactions.

* Corresponding author. Tel.: +34-96-5903548; fax: +34-96-5903549; e-mail: yus@ua.es

doi:10.1016/j.tet.2003.09.065

sufficiently reviewed in the last few years,[2a,5a,6] but their preparation by non-deprotonating methods was treated in general articles on organolithium compounds and main group organometallic chemistry.[2a,5b–h] This review will cover the literature published between 1995[7] and 2002 dealing with the uses of functionalised aryl- and heteroaryllithiums generated by non-deprotonating methods.[2a,8]

Halogen–lithium exchange in arenes is faster than hydrogen–lithium exchange (direct metallation) and constitutes a strategy to functionalise aromatic compounds, giving structurally-challenging compounds in a regioselective manner. This method introduces a lithium atom into a determined non-activated position of the corresponding arene and also allows the preparation of arenes, which are not synthetically available by other routes such as, for example, electrophilic substitutions.[9] Since the discovery of the bromine–lithium exchange reaction simultaneously by Gilman and Wittig,[1,2a] until Beak's work,[10] many discussions and theories about the mechanism of the generation of alkyllithiums promoted by Bu^{t}Li, Bu^{s}Li and Bu^{n}Li have been maintained. Beak's proposal concerned the existence of an intermediate based on a trigonal bipyramid with apical ligands and equatorial lone electron pairs **1**.[11] Actually, the ate complex lithium diphenyliodate ($Ph_2I^-Li^+$), formed from iodobenzene and phenyllithium, has been characterised as an intermediate in THF/HMPA at low temperature.[11a,b] It has been confirmed that the formation of this halogen-ate intermediate **1** underwent a solvent acceleration by the solvent stabilisation of the transition state independent of the state of aggregation of the organolithium reagent.[11c]



X = Hal **1**

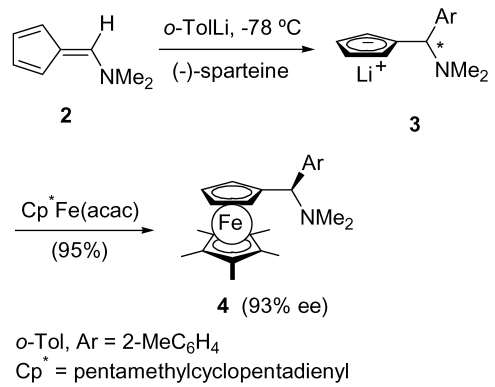
Regarding the lithium source, Bu^{t}Li, Bu^{n}Li and Bu^{s}Li are, in this order, the most frequently used reagents in the halogen–lithium exchange, but lithium metal is also a powerful reagent in arene-catalysed lithiations,[12] especially for the development of other heteroatom–lithium exchange processes, which will be described in due course. A comprehensive survey on the mechanism of the arene-catalysed lithiation involving the naphthalene radical anion and naphthalene dianion ruled out the generation of an 'ate' transition state intermediate **1** according to the reactivity profiles of alkyl and aryl chlorides. Dilithium naphthalene displayed an outer-sphere electron transfer mechanistic model with these acceptors.[13]

2. Functionalised aryllithium compounds

2.1. Carbon-bonded functionalised aryllithium compounds

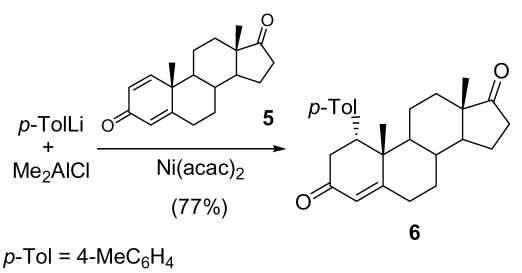
2.1.1. Alkyl, alkenyl and alkynyl substituents. In this section are included alkyl-substituted aryllithiums due to their important applications in organic synthesis (as potent nucleophiles and bases), although these substituents are not usually considered as functional groups. For instance, the syntheses of series of phosphoranes, oligosilanes, and especially the preparation of transition and main group metal complexes were accomplished by the more electropositive organolithium compounds. Several examples of the alkylated aryllithiums, generated previously by a halogen–lithium exchange, as well as their synthetic applications are shown in Table 1.

The preparation of enantiomerically enriched ferrocene derivatives was performed preparing the corresponding chiral ligand by an enantioselective addition of *p*-tolyllithium to 6-(dimethylamino)fulvene **2**. The reaction of the non-isolated organolithium compound **3** with Cp*-Fe(acac) afforded the complex **4** in very high chemical yield and optical purity (Scheme 1 and Table 1, entry 7).



Scheme 1.

The transmetallation of aryllithiums with Me_2AlCl or R_2SnCl_2 resulted in the formation of aryldimethylaluminium or diaryldialkyltin compounds, respectively. The aluminium reagents were employed in chemoselective conjugate additions to enones and steroidal dienones **5** in the presence of nickel(II) salts[33] to give **6** (Scheme 2). The diarylstannanes underwent reductive elimination (homocoupling reaction) mediated by Cu(II) salts, affording the biaryls in good chemical yields.[34]



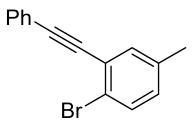
Scheme 2.

Alkylated aryllithiums, obtained by halogen–lithium exchange, were used for several structural studies concerning the dynamics of the exchange, relaxation and rotation of the carbon–lithium bond in monomeric species,[34] as well as in the synthesis and characterisation of the Lewis base-free σ-bonded aryllithiums.[35] More attractive, from the synthetic

Table 1. Synthesis of phosphoranes, oligosilanes and metal complexes mediated by alkylated aryllithiums

Entry	Aryllithium	Final compound	Ref.
1	2-MeC_6H_4Li	Spirophosphoranes	14
2	2-MeC_6H_4Li	Tricarbonylirontricarbonylmanganese complexes	15
3	2-MeC_6H_4Li	Tricarbonylirontricarbonylrhenium complexes	15b
4	2-MeC_6H_4Li	Titanium dinitrogen complexes	16
5	2-MeC_6H_4Li	Benzenetricarbonylmanganese(I) hexafluorophosphate	17
6	2-MeC_6H_4Li	Diironalkoxycarbene complexes	18
7	2-MeC_6H_4Li	Chiral ferrocenes	19
8	2-MeC_6H_4Li	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
9	2-MeC_6H_4Li	Alkoxycarbene manganese complexes	21
10	2-MeC_6H_4Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
11	2-MeC_6H_4Li	Diiron bridging alkoxycarbene complexes	23
12	2-MeC_6H_4Li	Tricarbonylirondicarbonyl(arylcarbonyl)iron complexes	24
13	3-MeC_6H_4Li	Spirophosphoranes	14
14	3-MeC_6H_4Li	Ricarbonylirontricarbonylmanganese and rhenium complexes	15b
15	3-MeC_6H_4Li	Titanium dinitrogen complexes	16
16	3-MeC_6H_4Li	Diironalkoxycarbene complexes	18
17	3-MeC_6H_4Li	Furanyl-coordinated alkoxy(amino)carbeneiron and acyliron complexes	25
18	3-MeC_6H_4Li	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
19	3-MeC_6H_4Li	Alkoxycarbene manganese complexes	21
20	3-MeC_6H_4Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
21	3-MeC_6H_4Li	Diiron bridging alkoxycarbene complexes	23
22	4-MeC_6H_4Li	Yttrium and lanthanide biphenyldiide complexes	26
23	4-MeC_6H_4Li	Hexacoordinated antimony-ate complexes	27
24	4-MeC_6H_4Li	Spirophosphoranes	14
25	4-MeC_6H_4Li	Bis(imidoaryl)molybdenum complexes	28
26	4-MeC_6H_4Li	Tricarbonylirontricarbonylmanganese and rhenium complexes	15b
27	4-MeC_6H_4Li	Titanium dinitrogen complexes	16
28	4-MeC_6H_4Li	Diironalkoxycarbene complexes	18
29	4-MeC_6H_4Li	Furanyl-coordinated alkoxy(amino)carbeneiron and acyliron complexes	25
30	4-MeC_6H_4Li	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
31	4-MeC_6H_4Li	[η^5-(Diarylhydroxymethyl)cyclopentadienyl]cobalt complexes	29
32	4-MeC_6H_4Li	Alkoxycarbene manganese complexes	21
33	4-MeC_6H_4Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
34	4-MeC_6H_4Li	Diiron bridging alkoxycarbene complexes	23
35	4-MeC_6H_4Li	Tricarbonylirondicarbonyl(arylcarbonyl)iron complexes	24
36	2,3-$Me_2C_6H_3Li$	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
37	2,3-$Pri_2C_6H_3Li$	Bis(imidoaryl)molybdenum complexes	28
38	2,4,6-$Me_3C_6H_2Li$	Spirophosphoranes	14
39	2,4,6-$Me_3C_6H_2Li$	[Bis or tris(trimethylsilyl)methyl]silanes	30
40	2,4,6-$Et_3C_6H_2Li$	Spirophosphoranes	14
41	2,4,6-$Pri_3C_6H_2Li$	Spirophosphoranes	14
42	2,4,6-$Pri_3C_6H_2Li$	[Bis or tris(trimethylsilyl)methyl]silanes	30
43	2,4,6-$Pri_3C_6H_2Li$	Azadigermiridines	31
44	2,4,6-$Pri_3C_6H_2Li$	Fluorosilylphosphidoiron and nickel complexes	32
45	2-But-3,4,5-Me_3C_6HLi	[Bis or tris(trimethylsilyl)methyl]silanes	30

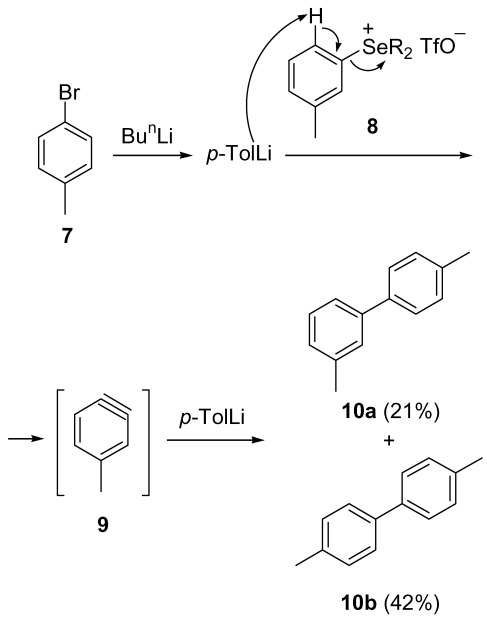
point of view, was the preparation of biaryls by oxidative coupling of organolithium compounds induced by oxovanadium(V) complexes[36] and by a reaction with selenonium salts **8**.[37] In the first example, a possible degradation of the organovanadium(V) to the organovanadium(IV) species formed the biaryl, which was facilitated by the high electron density of the aromatic ring, whilst, in the second example, an aryne **9** was generated as an intermediate, followed by the addition of another equivalent of *p*-tolyllithium (Scheme 3). When the alkynylarene **11** was used in this reaction as a precursor of the corresponding organolithium compound, instead of 4-bromotoluene (**7**), a 1:1 mixture of the 1,3- and 1,4-biaryls **10a** and **10b** was obtained. *o*-Tolyllithium was employed as the nucleophile in a ligand exchange at the iodine atom of vinyliodonium triflates, achieving new unsymmetrical diaryliodonium salts in good yield.[38] The same property of this aryllithium was exploited in a study of migratory aptitudes in rearrangement–displacement reactions of aryl groups in dimethoxysilanes.[39]



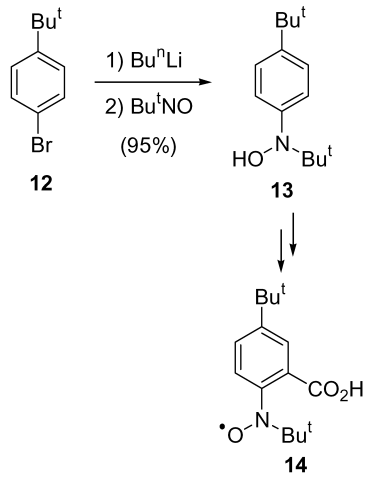
11

The synthesis of a water-soluble aromatic carboxylate nitroxide, which is required for such different applications as NMR spectroscopy, pharmacology and organic transformations, could be carried out by the reaction of an aryllithium (obtained from the bromide **12**) and 2-methyl-2-nitrosopropane (Scheme 4). Three more steps, including a hetero-Cope rearrangement of the compound **13**, were needed for obtaining the desired free radical **14**.[40]

In the search of light-emitting polymers, the synthesis of polyfluorenes with polyphenylene dendron side chains



Scheme 3.

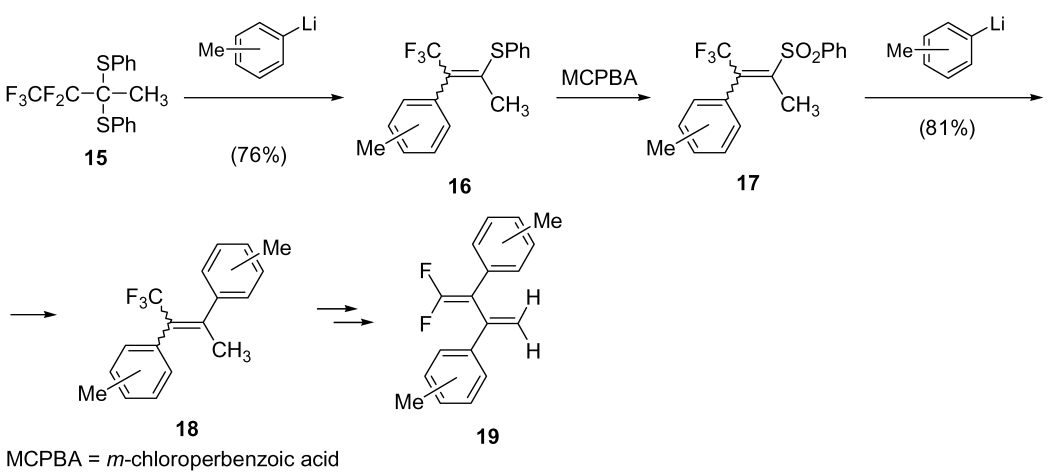


Scheme 4.

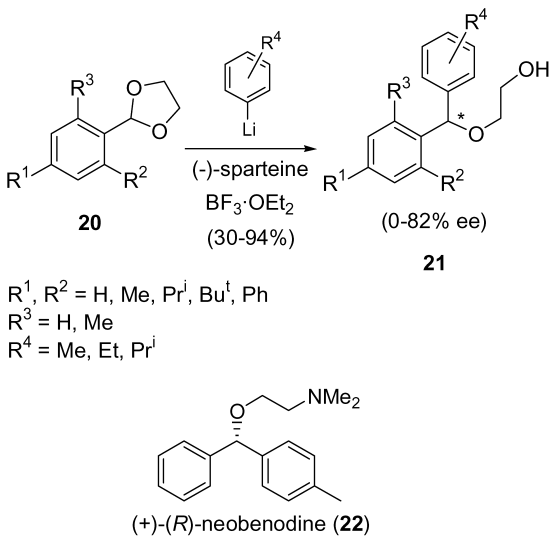
started with the addition reactions of several aryllithiums onto aromatic methyl esters.[41] Double addition of an aryllithium, obtained from halogen–lithium exchange, was required in the preparation of the interesting 2,3-diaryl-1,1-difluoro-1,3-butadienes **19**.[42] Firstly, the aryllithium attacked the sulfur atom of the compound **15**, providing a carbanion, which then quickly underwent a β-defluorination reaction to give the intermediate β-fluoro-β-trifluoromethylvinyl sulfide. These transient compounds were so reactive that they suffered an addition–elimination reaction with a second equivalent of the aryllithium reagent, giving the alkene **16**. In the second step, compound **17** (an excellent Michael-type acceptor obtained by oxidation of the sulfide **16**) again underwent an α-addition reaction and generation of the α-anion with respect to the trifluoromethyl group, instead of reacting with the aryllithium reagent at the expected β-position to the sulfonyl group. The final elimination of lithium benzenesulfinate afforded the butenes **18**, which were used as precursors of the butadienes **19** (Scheme 5).[42]

The synthesis of trialkylsilylated benzyl mercaptans and benzenethiols has revealed that the trialkylsilyl substituent, introduced by the reaction of a trialkylsilyl chloride with the corresponding aryl bromide in the presence of *n*-butyllithium, had a remarkable effect in reducing the foul smell of the parent compounds.[43] Other silylated arenes were studied as electrophiles in cross-coupling reactions and the Mizoroki–Heck reaction catalysed by palladium complexes.[44]

The combination of an aryllithium compound with a stoichiometric amount of a chiral base [(−)-sparteine] and an achiral Lewis acid (BF_3·OEt_2) generated the alcohols **21** from **20** in up to 82% enantiomeric excess. These chiral products are constituents of several biologically-active compounds such as (+)-(*R*)-neobenodine (**22**) (Scheme 6).[45] The mechanism of this S_N2-type reaction remains unclear, but, presumably, a nucleophilic attack of the base-associated organolithium reagent to a BF_3-activated acetal can occur, it not being possible to rule out the involvement of chiral ion-pair intermediates.



Scheme 5.



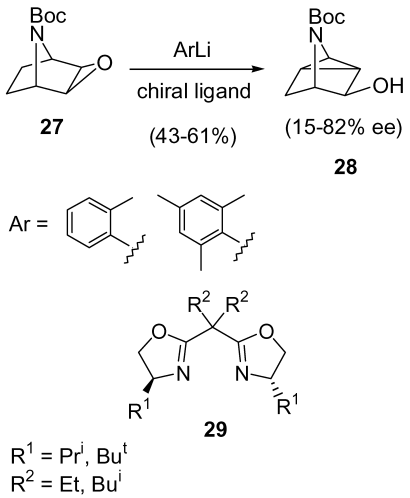
Scheme 6.

Various 1-arylnaphthalenes were accessible via a simple two-step process involving aryllithiums, which reacted with alkenylbenzocyclobutenones furnishing the expanded dihydronaphthalenes, which were readily dehydrated by known procedures.[46] When 1,5-dichloroanthraquinones were employed, the aryllithium reagent gave a double 1,2-addition to both carbonyl groups, affording the dihydroxyanthracenes, which were transformed into rubicenes after reduction and an intramolecular cyclisation reaction.[47]

Chiral and non-chiral triarylcarbenium ions have been tested in allylations of aldehydes[48] and in aromatic Mukaiyama aldol additions.[49] In the latter example, the chiral triarylcarbenium ion **24**, generated by the reaction of compound **26** with 4-Bu^{t}C$_6$H$_4$Li, induced a modest enantioselectivity in the reaction of benzaldehyde and the silyl ketene acetal **23** to obtain the final product **25** (Scheme 7).[49]

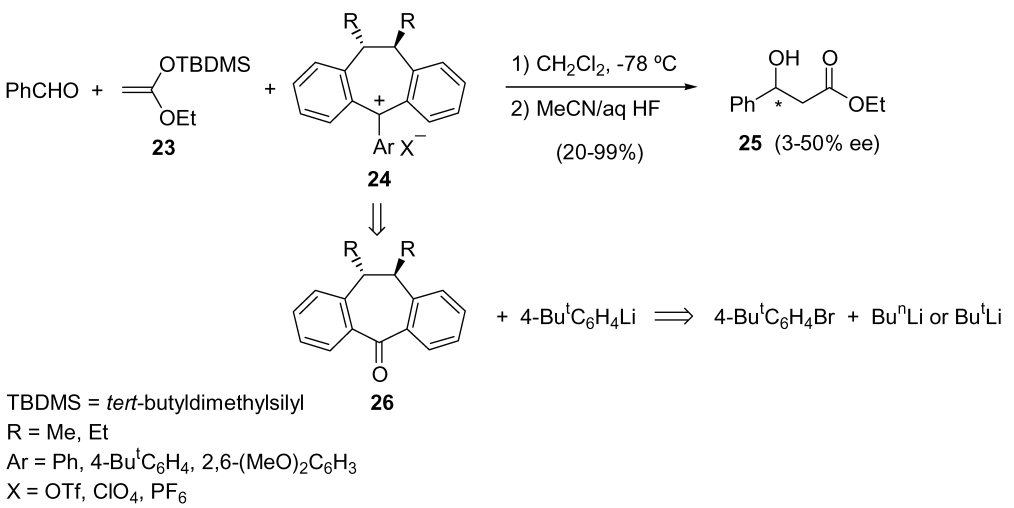
Dinitrogen tetroxide was found to be an excellent electrophile in the nitration of aryllithiums, and *p*-tolyllithium [obtained as described previously (see Scheme 3)] afforded *p*-nitrotoluene in 86% yield.[50] The reaction was much cleaner when N_2O_4 was deposited onto the surface of a frozen solution of the aryllithium in 1,2-dimethoxyethane (DME). Other electrophiles, such as 2,3-alkylidenedioxybenzoic acid esters, reacted with *o*-tolyllithium to give the biphenyls in good chemical yield (see below, Scheme 45),[50] but the most interesting application will be shown later (see the alkoxycarbonyllithium section, Scheme 45).

The enantioselective deprotonation of the epoxide **27** with aryllithiums to give the azanortricyclanol **28**, used in a radical rearrangement approach to the potent non-opioid analgesic epibatidine derivatives, was studied with (−)-sparteine and with bisoxazolines **29** as the chiral ligands (Scheme 8). In general, the better optical yields were achieved with the ligands **29**, although the chemical yields were slightly higher using (−)-sparteine.[51]

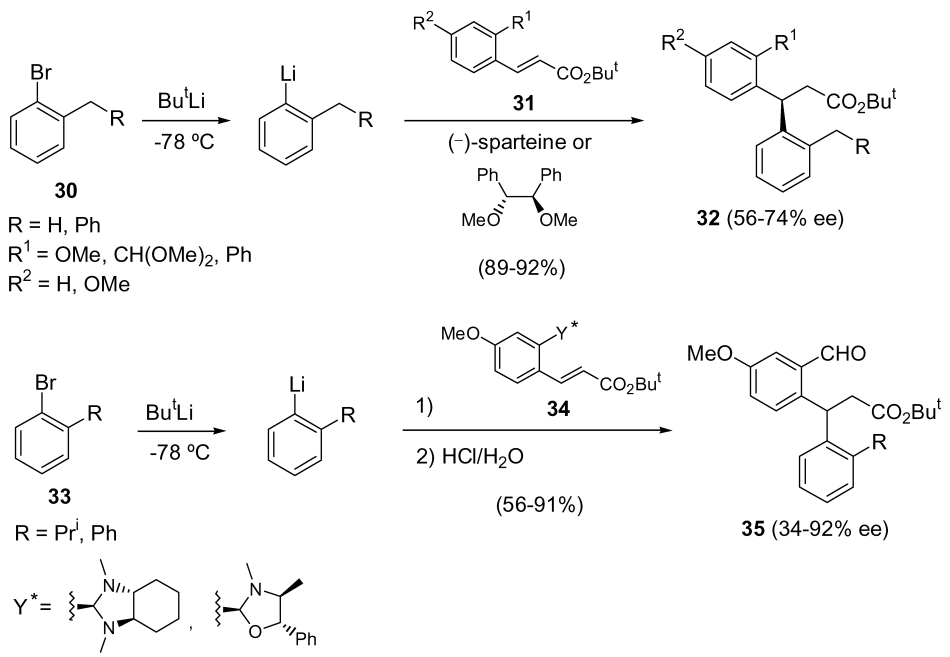


Scheme 8.

Aryllithium-chiral additive complexes were readily generated in non-polar aprotic solvents via a halogen–lithium exchange reaction from the corresponding aryl bromides **30** and **33** in the presence of a series of chiral additives. The optimal enantioselectivities were obtained in the reactions of aryllithium reagents with the α,β-unsaturated *tert*-butyl



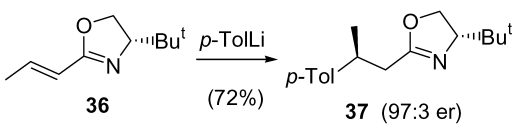
Scheme 7.



Scheme 9.

esters **31**, using (−)-sparteine or the chiral 1,2-dimethoxy-1,2-diphenylethane as the chiral ligands, the products **32** being obtained (Scheme 9).[52] A different approach to the compounds **35**, starting from the compound **33**, was achieved using a chiral oxazolidine or imidazolidine group directly bonded to the aromatic ring, as in compound **34** (Scheme 9). The levels of stereoselectivity observed in this process were dependent on the structure of the Michael-type acceptor and the solvent effects.[53]

A diastereoselective Michael-type addition reaction of *p*-tolyllithium onto the α,β-unsaturated compound **36** (prepared from crotonic acid and *tert*-leucinol) took place to give the compound **37** (Scheme 10), a precursor of (+)-α-curcumene, which is a constituent of a large number of essential oils detected in the rhizomes of *Curcuma aromatica* Salisb.[54]

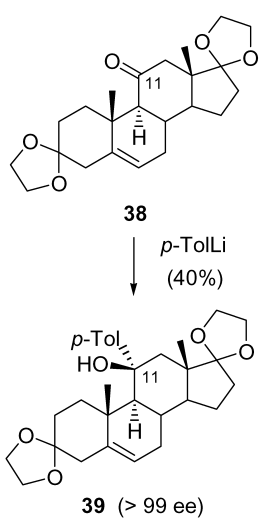


Scheme 10.

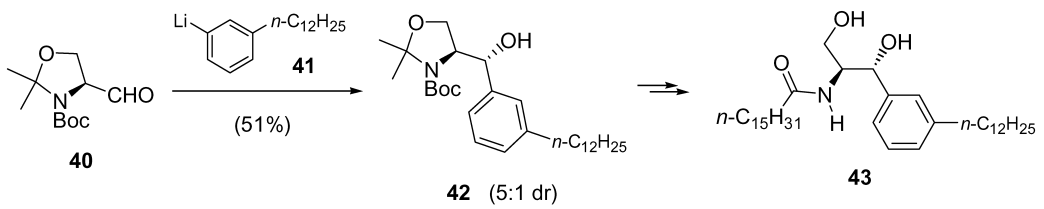
Alkyl-substituted aryl- and heteroaryllithiums were treated with SO_2(g) to obtain the arylsulfinic acid salts in very good yields. In this case, this was the first step for the general synthesis of arylsulfonylhydrazides, which could also be transformed, under reductive reaction conditions, to deliver the desired sulfonamides.[55]

Several methyl-, dimethyl- and trimethylaryllithiums were used in the preparation of arylhydroxymethane[3]orthocyclo[5]-(1,8)-naphthalenophanes that rearranged in acidic media to benzoazulenes or to other different polycyclic systems,[56a] as well as in the elaboration of 1,2-acetoxy-1,2-bis(aryl)ethenes upon addition to highly-hindered 1,2-diaryl ketones.[56b]

Disiloxane-protected 2-deoxyribonolactone is an efficient precursor to 1,2-dideoxy-1β-aryl-D-ribofuranoses by a highly-diastereoselective addition of several tolyllithiums to the lactone moiety.[57] These ribofuranoses have been studied as potential universal bases and for using as nucleoside replacements in the design of novel base pairs. Other attractive structural variations, currently undertaken on steroids, were challenging in terms of chemical methodologies, *p*-tolyllithium reacting with estrone benzyl ether at −78°C in a mixture of toluene/THF in the presence of boron trifluoride etherate.[58] More recently, the same research group described the addition of *p*-tolyllithium to an 11-oxosteroid **38**, furnishing the protected 11α-aryl-11β-hydroxyandrostendione **39** in overall acceptable yields, considering the low reactivity of the 11-oxosteroids (Scheme 11). The structure **39** can be considered as a key intermediate in a short route to progesterone antagonists.[59]



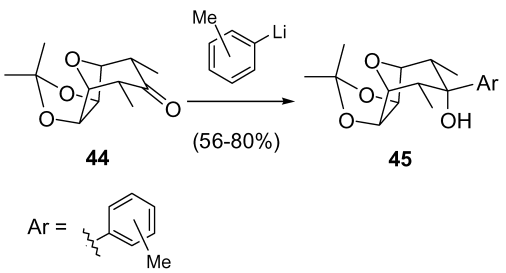
Scheme 11.



Scheme 12.

Ceramides are important signalling molecules implicated in a myriad of physiological events and are one of the major lipid components of the human skin. The ceramide analogue **43** was synthesised by a diastereoselective addition of the organolithium compound **41** to Garner's aldehyde **40**. The major compound **42** was successively transformed into the corresponding ceramide derivative in a two-step sequence[60] (Scheme 12).

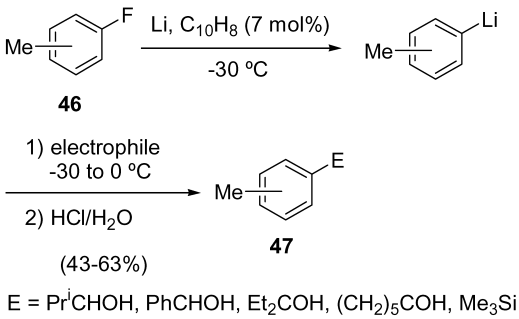
The addition of tolyllithiums to the oxabicyclo[3.2.1]octan-3-one **44** resulted in the formation of the benzylic alcohols **45** in good yields (Scheme 13). The effect of these compounds **45** on the growth of *Sorghum bicolor* was evaluated, the *p*-methylphenyl derivative being one of the most active and causing 100% inhibition of the development of its aerial parts and roots of the weeds and crops.[61]



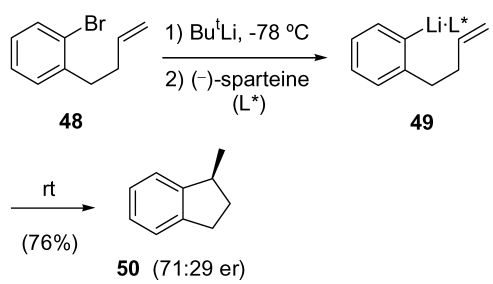
Scheme 13.

Aryl iodides, bromides and chlorides are the most frequently used starting materials, which are prone to undergo halogen–lithium exchange, although other starting materials such as phenyl triflate can also give this reaction, but they do not undergo such a clean interchange with lithium powder and substoichiometric amounts of naphthalene (4 mol%); this mixture, in the presence of boron trifluoride, reacted with benzaldehyde affording only a 17% yield of diphenylmethanol.[62] On the other hand, the fluoroarenes **46** afforded the corresponding aryllithium intermediates with lithium powder and a catalytic amount (7 mol%) of naphthalene in THF at −30°C. The resulting organolithiums reacted with different electrophiles, under Barbier-type reaction conditions, to give the expected products **47** in moderate to good yields[63] (Scheme 14).

Aryllithiums bearing an alkenyl substituent have been used in carbocyclisations. The intramolecular substitution reaction of geminal dibromoalkenes proceeds to afford indenes and 1,2-dihydronaphthalenes in very good yields via the in situ-generated lithium alkylidene carbenoids.[64] The asymmetric version of the carbocyclisation has been applied to the compound **48**, employing (−)-sparteine as the chiral ligand and obtaining methylindan **50** in good yield and moderate enantioselectivity,[65] the intermediate **49** being probably involved in the process (Scheme 15).

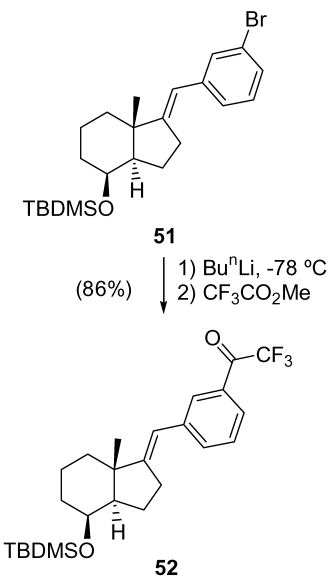


Scheme 14.



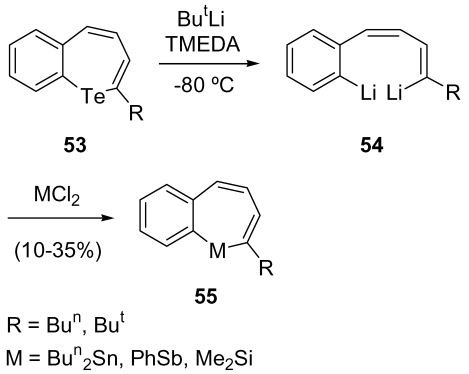
Scheme 15.

In the first synthesis of a diazirine-bearing photoactivatable calcitriol analogue, a concise synthesis including a bromine–lithium exchange in the compound **51** and further reaction with methyl trifluoroacetate gave the product **52** in good chemical yield[66] (Scheme 16).



Scheme 16.

The sophisticated tellurepines **53** were lithiated with *tert*-butyllithium (direct tellurium–lithium exchange) in the presence of TMEDA, affording an organolithium intermediate **54**, which was allowed to react with a series of metallic salts (MCl_2) in order to obtain in low yield the 1-benzostannepines, 1-benzostibepines, and 1-benzosilepines **55**[67] (Scheme 17).



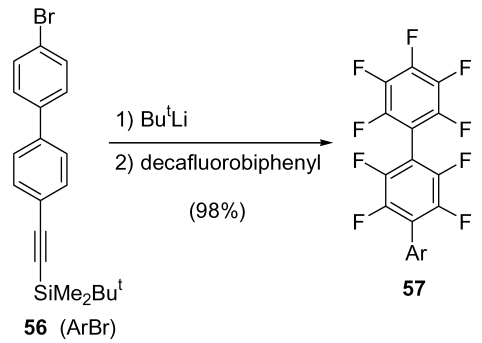
Scheme 17.

Alkynylphenyllithiums were prepared by bromine–lithium exchange and immediately used in the Negishi reaction catalysed by palladium(0) upon transmetallation with zinc bromide. This process provided a rapid route to novel cyclophanes and macrocycles, inserting arene, alkene and alkyne units.[68]

Polyaryllithiums have been used, apart from the synthesis of sulfonamides (see Ref. 55), in the generation of new organometallic complexes, but to a lesser extent than the functionalised aryllithiums (see Table 1). The most relevant examples in this area are lised in Table 2.

Selenium–lithium and tellurium–lithium exchanges have been studied in polyaryllithiums by dynamic NMR (DNMR). The very fast intramolecular selenium–lithium replacement did not proceed appreciably through the observable ate complexes. The authors proposed that, in this reaction, the separated ion pairs (SIP)/strong contact ion pairs (CIP) interconversion is slower than the selenium–lithium exchange rate.[73]

Linear oligophenylenediynes containing 6, 9 and 12 phenylene rings were synthesised in high yield using a nucleophilic aromatic substitution (S_NAr) of perfluoroarenes by alkynyl-substituted biaryllithium reagents as the key carbon–carbon bond-forming reaction. These polyaryllithiums were prepared from compound **57**, which was generated in situ by a halogen–lithium exchange from **56** using Bu^{t}Li[74] (Scheme 18).

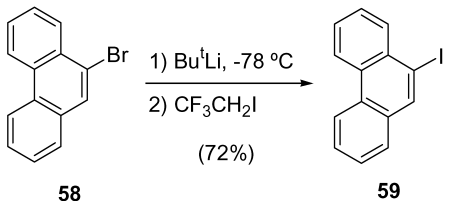


Scheme 18.

The 1- and 2-naphthyllithiums have been used in the reactions described above such as in the addition onto acetals,[45,50] in the synthesis of hindered arylnaphthalenes,[46] in stereoselective Michael-type addition reactions[53] and in the synthesis of 1-β-aryl-D-ribofuranose derivatives.[57] 7-Substituted dinaphtho[2,1-*b*;1′,2′-*d*]siloles and germoles, the first isolated examples of optically active binaphthoheteroles, have been prepared from 2,2′-dibromo-1,1′-binaphthyl and *tert*-butyllithium at −78°C through the corresponding 2,2′-dilithio-1,1′-binaphthyl intermediate.[75]

Monoditerpene chiral oligofluorenes[76] and 9,9-diphenylfluorene-capped oligothiophenes[77] were prepared by using the sequence aryl bromide→aryllithium→boronic acid→Suzuki-Miyaura cross-coupling product. In the latter example, the resulting oligothiophenes exhibited an intriguing reversible redox behaviour.[77]

A simple preparation of iodoarenes has been reported employing 2,2,2-trifluoro-1-iodoethane as the electrophile, and 9-bromophenanthrene **58** was transformed into the corresponding iodide **59** in 72% yield[78] (Scheme 19).



Scheme 19.

Table 2. Synthesis of metal complexes mediated by the addition of polyaryllithiums

Entry	Polyaryllithium	Final compound	Ref.
1	2-Biphenyllithium	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
2	4-Biphenyllithium	Yttrium and lanthanide biphenyldiide complexes	26
3	2,6-(Dipp)$_2$-C$_6$H$_3$Li[a]	Monomeric organolithium species	69
4	2,6-(Tripp)$_2$-C$_6$H$_3$Li[b]	Monomeric organolithium species	69
5	2,6-(Diphenyl)phenyllithium	Gallium complexes	70
6	1-Naphthyllithium	Metalloporphyrins	71
7	1-Naphthyllithium	Chiral metallocenes	19
8	1-Naphthyllithium	Ruthenium- and osmium-carbyne complexes	72
9	2-Naphthyllithium	Ruthenium- and osmium-carbyne complexes	72

[a] Dipp=2,6-disopropylphenyl.
[b] Tripp=2,4,6-triisopropylphenyl.

Table 3. Synthetic uses of polystyryllithium

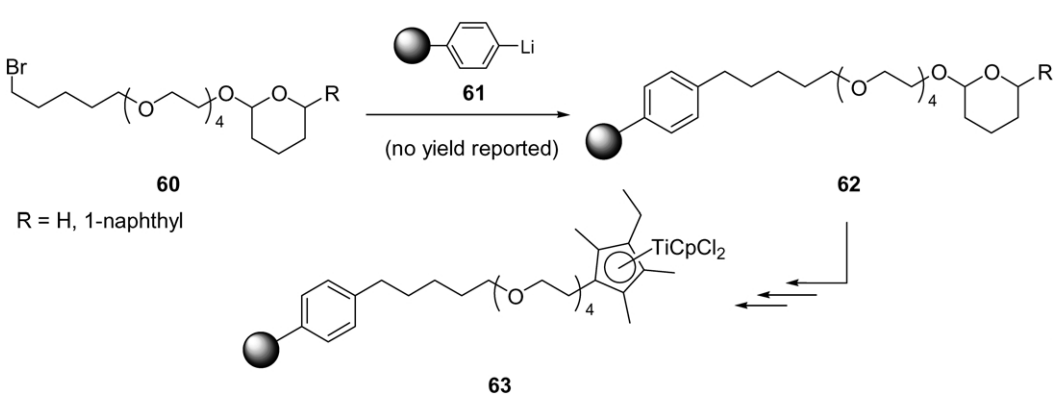
Entry	Application	Ref.
1	Synthesis of metallocene catalysts	79
2	Synthesis of polystyrenesulfonic acids	80
3	Synthesis of polymer-supported organozinc and/or organocopper reagents[a]	81
4	Synthesis of polymers incorporating 9,10-anthracenylidene chromophores	82
5	Synthesis of tetramethylpolysulfones and polyphenyl sulfones[b]	83
6	Synthesis of high molecular weight cyclic and multicyclic polystyrenes	84
7	Synthesis of block and grafted copolymers	85
8	Influence of dialkylphenoxyaluminium on the reactivity of polystyryllithium	86
9	Star branched polymers	87
10	Synthesis of poly(isoprene-*graft*-styrene) with polyfunctional branch points	88
11	Synthesis of diene-functionalised macromonomers	89
12	Influence of lithium chloride on the anionic propagation mechanism	90
13	Mechanism of coupling reactions of polystyryllithium with dihalomethanes	91
14	Synthesis of comb-like branched polystyrenes and graft copolymers	92
15	Functionalisation of polystyryllithium	93
16	Synthesis of arborescent graft polystyrenes	94
17	Synthesis of functionalised polystyrenes with D-glucose and/or D-galactose units	95
18	Reactions of polystyryllithium with 9,10-bis(halomethyl)anthracene	96
19	Synthesis of macrocyclic polystyrene	97
20	Synthesis of polystyrene with dendritic branching	98
21	Synthesis of poly(*m*-halomethyl)styrenes	99
22	Amine functionalisation of polystyryllithium	100
23	Synthesis of functionalised polystyrenes with (chloromethyl)phenyl groups	101
24	Synthesis of soluble graft-like complexes	102
25	Synthesis of star branched polymers	103
26	Influence of di-*n*- and di-*s*-butylmagnesium on the reactivity of polystyryllithiums	104
27	Anionic polymerisation of secondary aminostyrene	105
28	Synthesis of a diphenylene bearing aromatic tertiary amine groups	106
29	Aggregation in lithium-based anionic polymerisation	107
30	Microstructure effect in the reactivity of polystyryllithium	108
31	A new system for living anionic polymerisation	109
32	Chain functionalisation with a benzamide derivative	110
33	Reaction of polystyryllithium with propylene oxide	111

[a] Via organozinc reagents generated by lithium–zinc transmetallation with $ZnHal_2$.
[b] Polybisphenolic rings underwent halogen–lithium exchange.

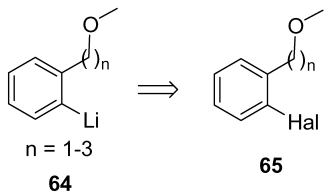
One of the most important reactions for the functionalisation of cross-linked polystyrene is the bromine–lithium exchange from bromopolystyrene and a number of functionalised polymers have been prepared from the lithiated polystyrene, some of these being shown in Table 3.

As a typical example of all of these applications, the reaction of polystyryllithium **61** with a polyoxygenated primary alkyl bromide **60** yielded a link **62** ready for anchoring a metallocene unit **63**[79] (Scheme 20).

2.1.2. Oxygen-containing alkyl substituents. Ether chelation by the oxygen in molecules of the type **64** is intermediate in strength (for n=1, 2) compared to the strong chelation exhibited by the analogous amines, competing with the interaction with THF molecules. It has been demonstrated by variable-temperature ^{6}Li and ^{13}C NMR spectroscopy that there is a reliable qualitative correlation between the strength of the chelation and the strength of the aggregation.[112] These chelation and aggregation effects modulate the reactivity of the organolithium compounds **64**,



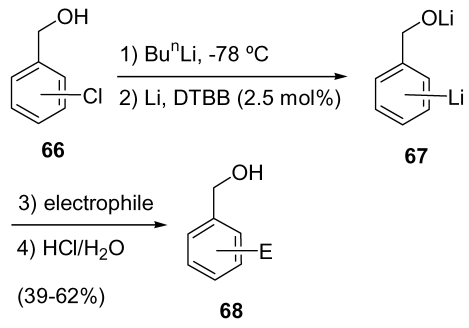
Scheme 20.



Scheme 21.

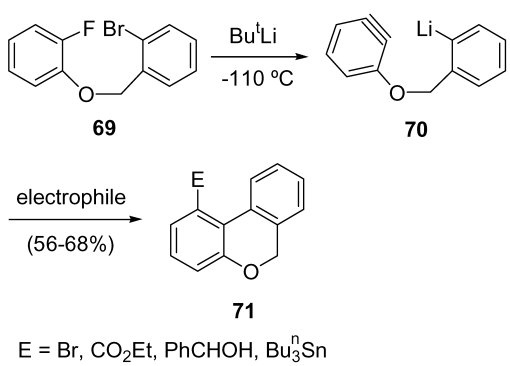
which were prepared from **65** by halogen–lithium exchange (Scheme 21). In addition, the lithioarenes **64** have been used for the generation of polymer-bound radicals, which were the subject of kinetic measurements of intramolecular hydrogen transfer reactions.[113]

4,4′-Di-*tert*-butylbiphenyl (DTBB)-catalysed lithiation of chlorinated benzylic alcohols **66** afforded the dianions **67**, which were ready to react with several electrophiles (Scheme 22), this transformation allowing the preparation of the functionalised aromatic molecules **68** in a one-pot process.[114] Very similar reactions involving halogenated arylalkyl methyl esters were carried out performing the reductive cleavage at the benzylic and aromatic positions with an excess of lithium metal and a catalytic amount of naphthalene (5 mol%), leading to the formation of complex reaction mixtures.[115]



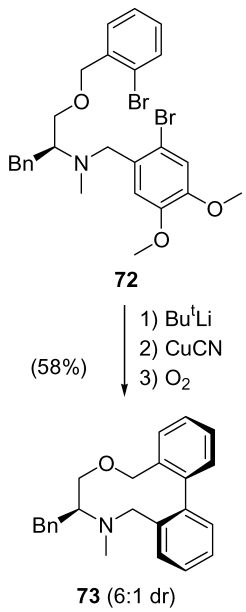
Scheme 22.

The synthesis of the functionalised benzofused heterocyclic derivatives **71** was developed by a route the key step of which involved the generation, from compound **69**, of a benzyne-tethered aryllithium compound **70** that underwent an intramolecular anionic cyclisation (Scheme 23). It is noteworthy that this simple and straightforward synthesis of functionalised heterocycles allows access to some compounds that are otherwise more difficult or tedious to prepare.[116]



Scheme 23.

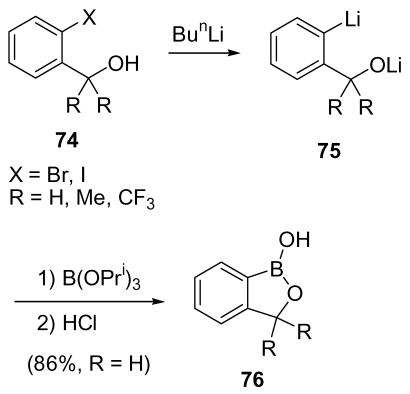
The tetrahydropyranyl derivative of 4-bromobenzyl alcohol was the precursor of the organolithium intermediate employed in the preparation of tetraphenylporphyrins substituted with methylchalcogeno groups.[117] The benzyl ether **72**, with another type of functionalised chain, was designed in order to prepare organocuprates from the corresponding aryllithiums. The oxidative coupling of the corresponding cuprates afforded medium ring species **73** utilised in the preparation of new polyfunctionalised polymers[118] (Scheme 24).



Scheme 24.

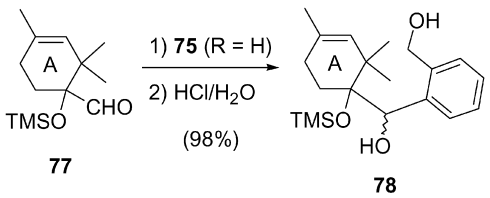
The Negishi cross-coupling reaction between sterically-hindered vinyl iodides and organozinc reagents was examined. In this case, the organolithium reagents, obtained by a lithium–halogen exchange, were transformed into their corresponding organozinc compounds by transmetallation, which were employed in the synthesis of vitamin D analogues.[119] Benzoboroxoles **76** are novel organoboron heterocycles prepared, in very good yield, from the readily available *o*-bromobenzyl alcohols **74** via dilithiation, followed by the reaction of intermediate **75** with triisopropyl borate[120] (Scheme 25). Their potential synthetic utility as boronic acid was very promising, especially in transition metal-catalysed or non-catalysed cross-coupling reactions.

Aryllithiums have also been exploited in the preparation of chiral and homochiral ligands, as has occurred in the case of hindered phosphanes or their derivatives. Dibenzo[*b*,*f*]phosphepin-5-oxides,[121] fluorenyldiphenylphosphanes[122a] and chiral triarylphosphanes[122b] are three representative examples where a bromine–lithium exchange was used to incorporate the phosphorous atom as the electrophilic fragment.



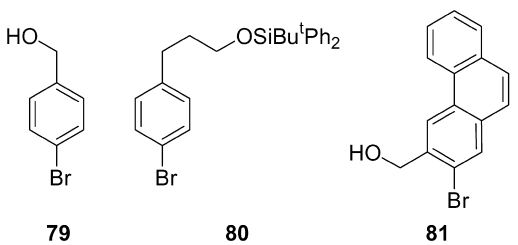
Scheme 25.

The reaction of the taxane ring A precursor **77** with the aryllithium reagent **75** (R=H) afforded a separable 1.7:1.0 epimeric mixture of products **78** in excellent yield[123] (Scheme 26). The taxane ring B was built in nine steps from the compound (*S*)-**78** in 53% overall yield.

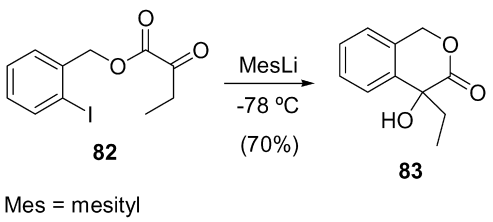


Scheme 26.

The brominated compounds **79** and **80** were used for introducing the aryl-substituted framework in molecules exhibiting high affinity for σ_1 receptors[124] and in branched hexasaccharides through a solid-phase synthesis,[125] respectively. The functionalised phenanthrene **81** was chosen as an intermediate in the synthesis of phenanthro[2,3-*c*]furan, a heterocycle fifteen-fold more reactive than isobenzofuran, which was prepared in several steps, beginning with a bromine–lithium exchange from compound **81**, followed by addition to DMF.[126]



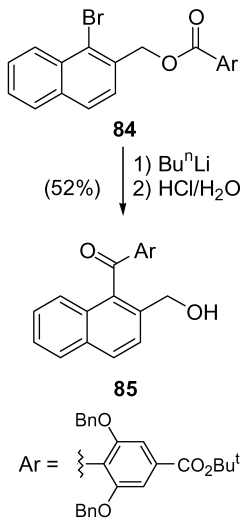
Mesityllithium was found to be an excellent selective lithiating agent to prepare chemoselectively aryllithium compounds possessing alkoxycarbonyl groups. The iodooxalate **82** reacted with mesityllithium (also prepared by a bromine–lithium exchange), giving the corresponding organolithium intermediate, which cyclised yielding the benzolactone **83** (Scheme 27). The use of other organolithium compounds such as Bu^{n}Li and Bu^{t}Li gave the lactone **83** in very low yields.[127]



Mes = mesityl

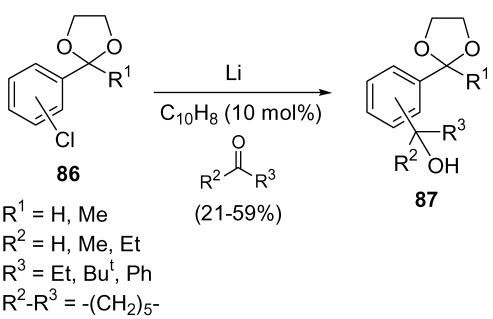
Scheme 27.

In the synthesis of balanol derivatives (inhibitors of protein kinase C) bearing modified benzophenone subunits, the bromonaphthalene **84** was lithiated with Bu^{n}Li and the resulting organolithium reacted intramolecularly with the ester group[128] (Scheme 28). The result of this reaction was a regioselective migration of an acyl group from an alkyl chain in **84** to the aromatic α-position in **85**.



Scheme 28.

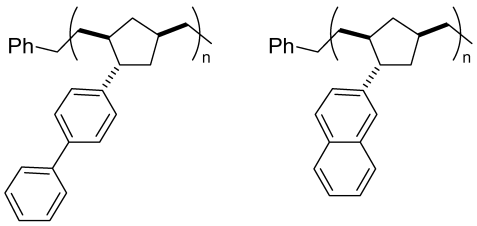
Cyclic or acyclic acetals have frequently been employed in main group organometallic chemistry as an effective protecting group. The chlorophenyl-2,3-dioxolanes **86** were allowed to react with lithium powder and a catalytic amount of naphthalene (10 mol%) at −78°C, generating the corresponding organolithiums. The final functionalisation of the aromatic ring was achieved by reaction with aldehydes and ketones to give the compounds **87** in modest yields[129a] (Scheme 29), the reaction being performed under typical Barbier-type conditions in order to avoid decomposition of the organolithium intermediate. It is worthy of note



R^1 = H, Me
R^2 = H, Me, Et
R^3 = Et, Bu^t, Ph
R^2-R^3 = -(CH$_2$)$_5$-

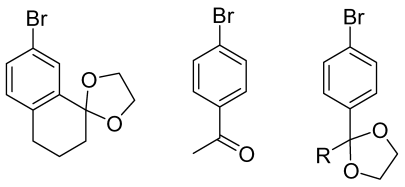
Scheme 29.

that the process did not work as expected when DTBB was used as the electron-carrier agent because a reductive opening of the heterocycle partially occurred.[129a] More recently, higher yields of the products **87** (substituted at the *para* position) were achieved employing the polymer-supported biphenyls **88a** and 2-naphthyls **88b** (ROMP gel-supported arenes) as electron carriers in 10 or 20 mol% amounts at −78°C.[129b]



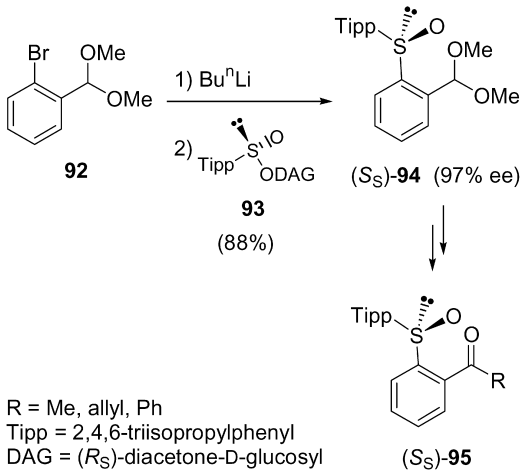
88a **88b**

2-(Haloaryl)-1,3-dioxolanes, such as compound **89**, were used in the synthesis of rigid-spacer chelators in supramolecular chemistry,[130] whilst the compound **91** (R=Me) and its precursor **90** were employed in a general straightforward synthesis of rubicenes.[47] The compound **91** (R=H) was the starting material in the preparation of *p*-styryldiphenylphosphane, which was copolymerised with divinylbenzene and styrene for the preparation of polymer-supported phosphonium bromides, useful as catalysts in the protection and deprotection of alcohols and alkyl vinyl ethers.[131]



89 **90** **91**

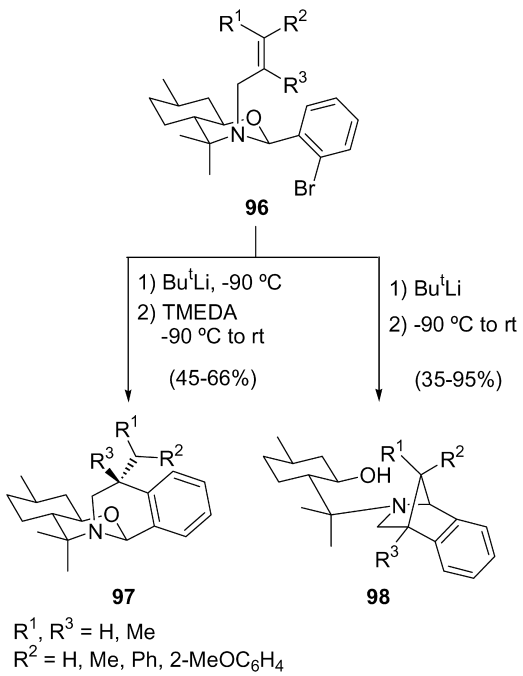
A highly stereoselective 1,4-asymmetric reaction of 2-(arylsulfinyl)benzaldehydes and 2-(arylsulfinyl)phenyl ketones **95** with Grignard reagents was studied. The preparation of the chiral compounds **95** was achieved by halogen–lithium exchange from the compound **92**, followed by reaction with the optically pure glucosyl benzenesulfinate **93** from −78 to −30°C (Scheme 30).



Scheme 30.

When using *p*-tolylmagnesium bromide in THF and the formyl sulfoxide derived from **94**, the potent antihistaminic (*R*)-neobenodine **22** was obtained.[132] In addition, the bromoarene **92** was conveniently elaborated in the reported synthesis of novel spiropiperidines, investigating their affinity for σ_1- and σ_2-receptors by means of radioligand binding assays.[133] The *p*-bromo isomer of compound **92** was selected as the starting material in the synthesis of optically active polymers employing repetitive Sakurai–Hosomi allylation reactions.[134,135]

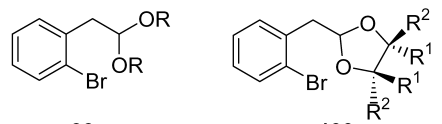
Aryllithiums, prepared by a bromine–lithium exchange from the enantiomerically pure perhydro-1,3-benzoxazines **96**, participated in an intramolecular 6-*exo*-*trig*-carbolithiation reaction with unactivated double bonds attached to the heterocyclic nitrogen atom. Whereas the related carbocyclisation allowed the preparation of the enantiopure 4-substituted tetrahydroisoquinolines **97**, a domino process favoured when no TMEDA was used (or by extending the reaction time and triggered by a deprotonation at the benzylic position) constituted an unprecedented stereoselective synthesis of the enantiopure 7-substituted 2-azabenzonorbornane derivatives **98**[136] (Scheme 31).



Scheme 31.

The acetals **99** and **100** are oxygen-containing alkyl-substituted brominated aromatic compounds, which were transformed into their corresponding coordinatively-stabilised organolithiums with *n*-butyllithium. The compound **99** (R=Me) was used in different processes, such as in the synthesis of spiropiperidines as described previously,[133] for the development of chiral salicylaldehydes, which are derivatives of Kagan's ether,[137] and in the elaboration of the C-ring taxane skeleton. The organolithium derived from compound **99** (R=Et) reacted with the aldehyde **101** to give a 3.4:1 mixture of the diastereoisomers **102a** and **102b** (Scheme 32). The C-aromatic taxane ring system was finally accomplished by an oxonium ene cyclisation reaction as the

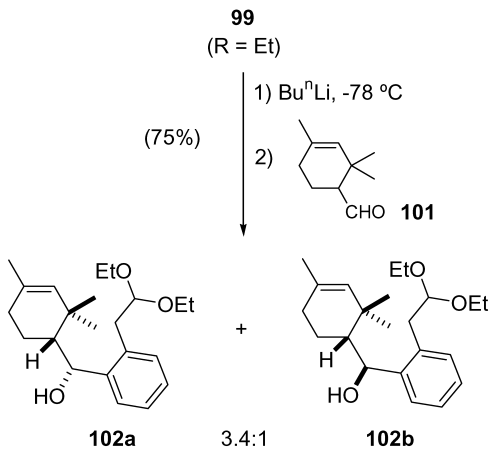
key step.[138]



99
R = Me, Et

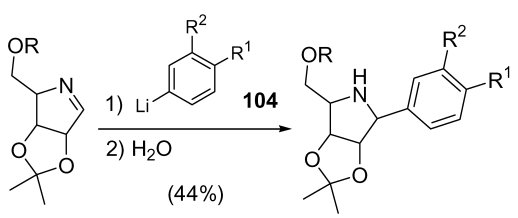
100
R^1 = H, Me, CH_2OMe, $C(Me)_2OMe$
R^2 = H, Me

Several chiral bromoarenes **100** were investigated as precursors of organolithium reagents able to control the diastereoselectivity in the addition to acylimines. Further transformation of the resulting major diastereomers furnished dihydroisoquinolines and *N*-methyl-D-aspartate antagonist tetrahydroisoquinolines in good yield.[139]



Scheme 32.

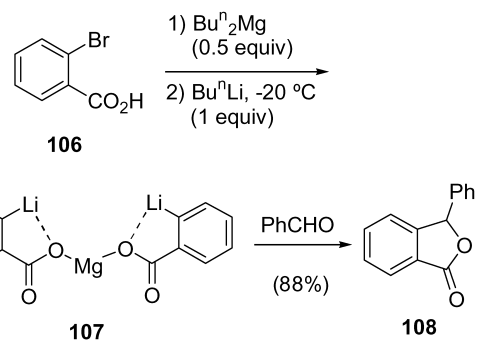
Alkoxycarbonyl groups bonded to the aromatic ring were chemoselectively prepared from mesityllithium as described above (see Scheme 27) for the synthesis of a camptothecin precursor.[127] An iodine–lithium–deuterium exchange sequence was also designed for obtaining pure samples of 4-deuteriobenzoic acid in a survey of possible reactions of 1,4-aryl diradicals with amino acid residues in proteins.[140] A large number of transition state inhibitors of *N*-riboside hydrolases and transferases bearing an alkoxycarbonyl aromatic moiety (as for example **105**) have been obtained by the addition of the aryllithium **104** onto the cyclic imines **103** as the key step (Scheme 33). These imines were easily prepared from the protected 1,4-dideoxy-1,4-imino-D-ribitol.[141]



R = *tert*-butyldimethylsilyl
R^1 = CO_2Li, R^2 = H

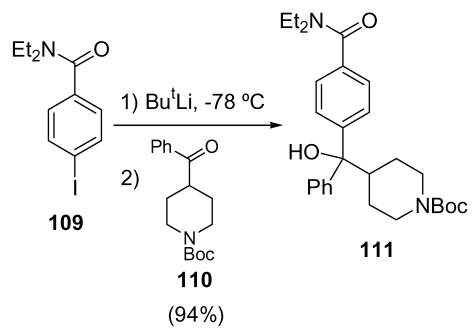
Scheme 33.

The formation of stable magnesium intermediates allowed a non-cryogenic metallation of aryl bromides bearing proton-donating groups, the stabilised species **107** (generated from bromoarene **106**) reacting smoothly with several carbonyl compounds affording the 3-substituted phthalides, e.g. compound **108**, in good yields (Scheme 34). This methodology was expanded to other bromides bearing proton-donating groups such as hydroxymethyl and ethylaminocarbonyl in high conversions, the more reactive aromatic esters, however, being unsuitable functional groups for this transformation.[142a] In spite of this known reactivity, *p*-bromobenzoic acid *tert*-butyl ester was lithiated and immediately transformed into the corresponding organozinc reagent, which was employed as a building block for certain vitamin D analogues.[119] *o*-Bromobenzoic acid ethyl ester was transformed into the corresponding boronic ester and used in the synthesis of antibacterial and antitumour agents, particularly the kinamycins and lomaiviticin A.[142b]



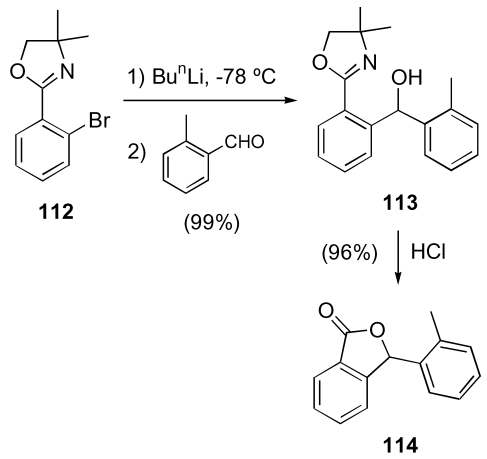
Scheme 34.

The diarylmethylpiperidine **111** has been prepared by iodine–lithium exchange from the benzamide **109** and further reaction with the ketone **110**[143] (Scheme 35). Other related aromatic amides were used, after halogen–lithium exchange, in different processes such as the synthesis of nitroarenes upon reaction with dinitrogen tetroxide,[50] in studies concerning the competition of deprotonation, in tin- or halogen–lithium exchange,[144] and in a synthetic approach to 2,3-dihydro-1*H*-isoindol-1-ones.[145]



Scheme 35.

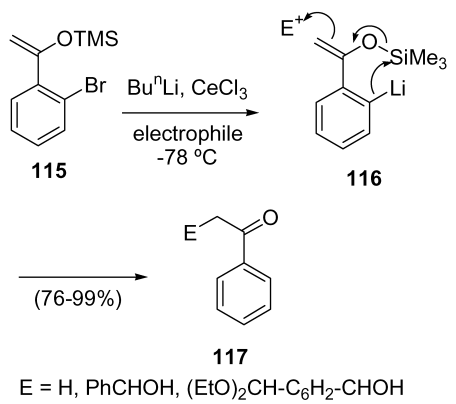
The reaction of *o*-tolualdehyde with the organolithium reagent derived from 2-(2-bromophenyl)-4,4-dimethyl-1,3-oxazole (**112**) afforded the benzydryl derivative **113** in excellent yield (Scheme 36). The 1,3-oxazole was a masked ester group, which was further transformed into the 3-*o*-tolylphthalide **114**, employed in the preparation of



Scheme 36.

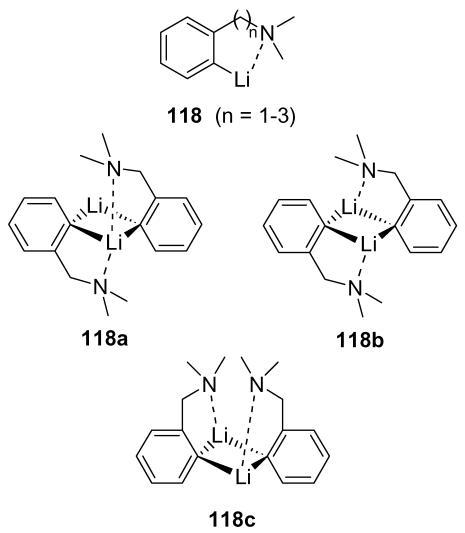
spirocyclic intermediates for the synthesis of dibenzodithiocinium derivatives.[146]

The silyl enol ether **115** was the substrate in a versatile retro-[1,4]-Brook rearrangement-enolate addition domino process. As a consequence of the regioselective lithiation in the *ortho* position, the directed migration of the trimethylsilyl group from the oxygen atom to the aromatic ring occurred efficiently in the intermediate **116**. The resulting enolate was allowed to react with different electrophiles, obtaining the silylated benzophenones **117** in very good yields[147] (Scheme 37).

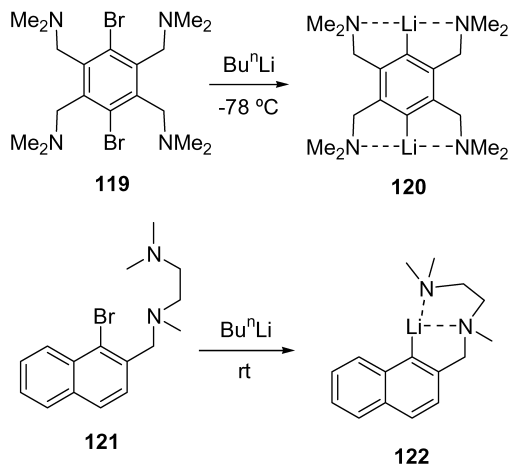


Scheme 37.

2.1.3. Nitrogen-containing alkyl substituents. As described above for oxygen-containing alkyl substituents, the parent amines **118** (generated by tin- or halogen–lithium exchange) also formed strong five-ring chelates, but not six- and seven-ring amine chelates.[113] These amine-chelated aryllithium reagents were the subject of in-depth structure and dynamics studies using multinuclear NMR experiments. The intramolecular chelation was not disrupted by cosolvents as TMEDA or HMPA, and at very low temperatures (−120°C) three robust isomers of the corresponding dimers **118a**, **118b** or **118c** were detected by ^{6}Li and ^{15}N NMR spectroscopy. Dynamic NMR studies also provided the rates and activation energies for the interconversion of these three isomers.[148]

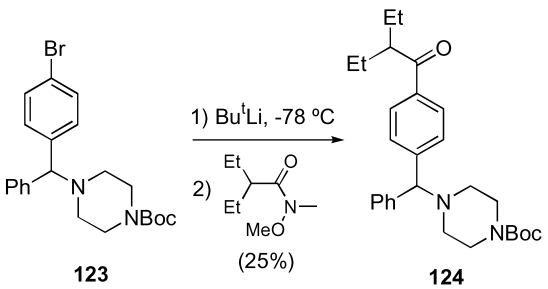


The strongly-chelated organolithiums **120** and **122**, prepared from arenes **119** and **121** by a bromine–lithium exchange (Scheme 38) were used, respectively, for the synthesis of stabilised 1,4-phenylene-bridged homo- and heterodinuclear palladium and platinum organometallic complexes[149] and to obtain well-defined 2:1 and 2:2 copper–copper bromide aggregates, which afforded selectively the biaryls in moderate yields.[150]



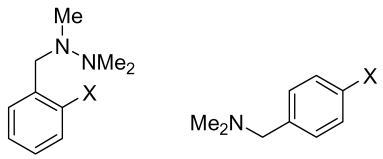
Scheme 38.

Functionalised nitrogen-containing heterocycles were also prepared in good yield (as depicted in Scheme 23) using fluorinated anilines and involving benzynes as intermediates.[116] The diarylmethylpiperazine **124**, a precursor of opioid receptor agonists, was accessed by a different approach, compared to the analogous piperidines shown in Scheme 35. In Scheme 39 the carbonyl group was incorporated by the reaction of the corresponding organolithium compound (generated from bromoarene **123**) with an *N*-methoxy-*N*-methylamide (Weinreb amide), the yield being unfortunately poor,[143] whilst the carbonyl moiety belongs to the organolithium framework in the reaction illustrated in Scheme 35.



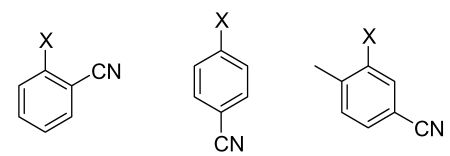
Scheme 39.

A Parham reaction of chiral *N*-(iodobenzyl)pyridones furnished very interesting condensed chiral isoindolines, which served as model for the synthesis of indolizidine 209D.[145b] Silicon compounds intramolecularly coordinated by hydrazine groups[151] and dendritic carbosilanes containing silicon-bonded mono- and bis(amino)aryllithium end groups[152] could be obtained from the compounds **125a** and **126a**, respectively. In the first case, the coordinating ability of the lithiated intermediate **125b** was used to stabilise silyl cations by the formation of pentacoordinated siliconium ions.[151] Secondly, the organolithium **126b** was involved in the first published multilithiated dendrimer systems with stable C–Li bonds, that could be used to introduce various metals via lithiation–transmetallation sequences.[152]



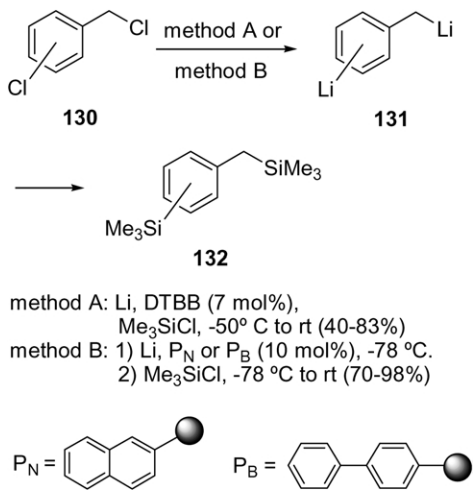
125a (X = Br) **126a** (X = Br)
125b (X = Li) **126b** (X = Li)

Halobenzonitriles are considered as reactive nitrogen-functionalised alkyl substituents susceptible to undergo interesting synthetic transformations. In this way, compound **127a** was employed through compound **127b** in the preparation of biaryls in good yield by a homocoupling reaction mediated by oxovanadium(V) compounds.[36] The nitriles **128a** and **129a** were precursors of organozinc and organoborane compounds, respectively, used for different purposes.[36] The reagent **128b** allowed the synthesis of building blocks for the preparation of vitamin D analogues[119] and the reaction of **129b** with trimethyl borate constituted the first step in the synthesis of a receptor heparin possessing a novel boronic acid-containing amino acid, with good affinity and selectivity.[153]



127a (X = Br) **128a** (X = Br) **129a** (X = Br)
127b (X = Li) **128b** (X = Li) **129b** (X = Li)

2.1.4. Other functionalised alkyl substituents. The in situ generation of *ortho*-, *meta*- and *para*-lithiobenzyllithium **131**, from the starting materials **130**, and successive trapping by an electrophile under Barbier-type reaction conditions[154] (or not)[155,156] afforded diols or disilylated



Scheme 40.

compounds **132** in good yields[154–156] (Scheme 40). These lithio-functionalised lithioarenes could be prepared by a double chlorine–lithium exchange using lithium metal and a catalytic amount of DTBB at −50°C[154] (Method A) or a catalytic amount of polymer-supported naphthalene or biphenyl as electron carriers[155,156] (Method B) (Scheme 40). Naphthalene (P_N) or biphenyl (P_B) supported polymers were prepared by radical polymerisation of 2-vinylnaphthalene or 4-vinylbiphenyl, respectively, with styrene and divinylbenzene. In general, Method B gave better results for the compounds **132** when trimethylsilyl chloride was selected as the electrophile.

Fluoro-substituted 4-(trifluoromethyl)phenyllithium participated in the preparation and characterisation of new organometallic compounds (Table 4). It was also added to xanthone, fluorenone, benzophenone and dibenzosuberone for the preparation of racemic triarylcarbenium ions (similar to **23**, Scheme 7) used in allylation reactions.[48] A (trifluoromethyl)aryl bromide was used in the regioselective synthesis of indenes[64] and in the stereoselective organozinc addition reactions to 1,2-dihydropyrans for the assembly of complex pyran structures.[158]

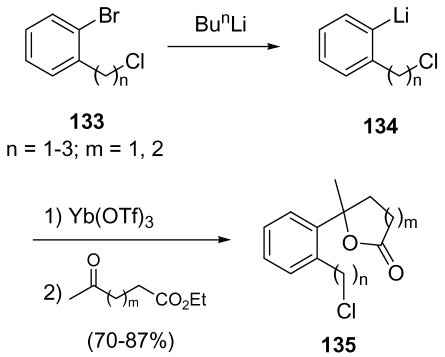
A protocol of annulation reactions of various dihalides **133** with keto esters could be carried out to provide an entry to eight- and nine-membered ring carbocycles **135**. In this process, where an aryl bromide and a tethered alkyl chloride are present (**133**), a selective halogen–metal exchange

Table 4. Applications of 4-$CF_3C_6H_4Li$ in the synthesis of new organometallic complexes

Entry	Final compound	Ref.
1	Tricarbonylirontricarbonylmanganese complexes	15b
2	Tricarbonylirontricarbonylrhenium complexes	15b
3	Alkoxycarbene manganese complexes	21
4	Diiron bridging alkoxycarbene complexes	23
5	Tricarbonylirondicarbonyl(arylcarbonyl)iron complexes	24
6	Furanyl-coordinated alkoxy(amino)carbeneiron and acyliron complexes	25
7	Hexaaryltellurium complexes	157
8	Organozinc reagents[a]	158

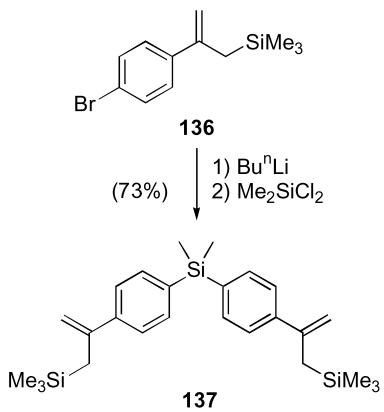
[a] This method allowed the synthesis of complex pyran structures by addition to 1,2-dihydropyrans.

reaction between the Csp^2-hybridised bromide and *n*-butyllithium initiated the reaction. Transmetallation of **134** to give an organo-ytterbium reagent generated species that underwent selective carbonyl addition to the ketone group of the keto ester, creating a lactone **135** in good yields[159a] (Scheme 41).



Scheme 41.

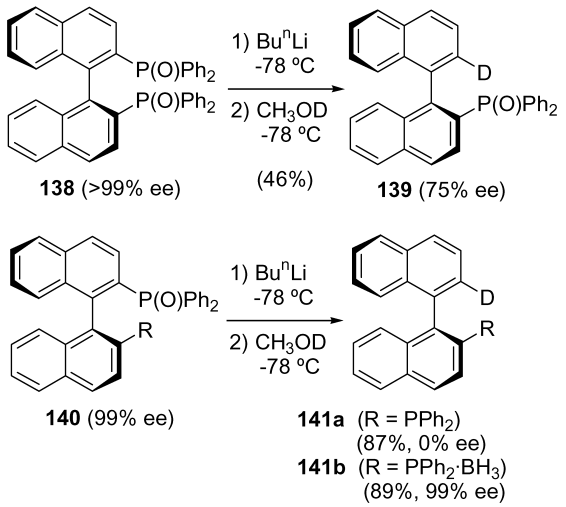
The bisallylsilane **137**, obtained from allylsilane **136** as depicted in Scheme 42, was one of the monomers introduced in an asymmetric polymer synthesis (by repetitive Sakurai–Hosomi allylation reactions) with different dialdehydes.[134,135] The radical-induced formation of some siloles and diazasiloles started with a bromine–lithium exchange and reaction with iodine to afford a *o*-(trialkylsilyl)methyliodobenzene in very good yield.[159b]



Scheme 42.

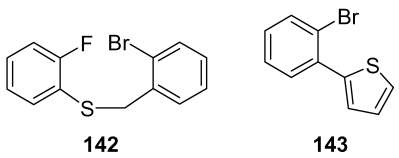
The known carbon–phosphorous bond cleavage in triphenylphosphane oxide mediated by alkyllithiums was applied to the selective lithiation of the phosphane oxide derivatives **138**. The phosphorous–lithium exchange in **138** afforded, after quenching with deuterated methanol, compound **139** in moderate yield. The retention or loss of the enantiomeric purity during the lithiation step was dependent on the substituents at the 2-position in **138** and **140**. The racemisation was very fast with the diphenylphosphino group (see compound **141a**), while the enantiomeric excess was retained with its borane complex **141b**[160] (Scheme 43).

Alkyl substituents bearing a sulfur atom such as in the compounds **142** and **143** were used in the synthesis of functionalised heterocycles involving a benzyne intermedi-



Scheme 43.

ate[116] (see Scheme 23) and for the preparation of novel chelated iron complexes,[25] respectively.



2.2. Oxygen-bonded functionalised aryllithium compounds

Oxygen-bonded functionalised aryllithiums were the subject of numerous contributions which have appeared in the literature, the most important impact of these organolithium compounds being their applications in the preparation of natural products or synthetic biologically-active molecules. On the other hand, many organometallic complexes have been obtained by the reaction of these functionalised aryllithium reagents, some examples being included in Table 5.

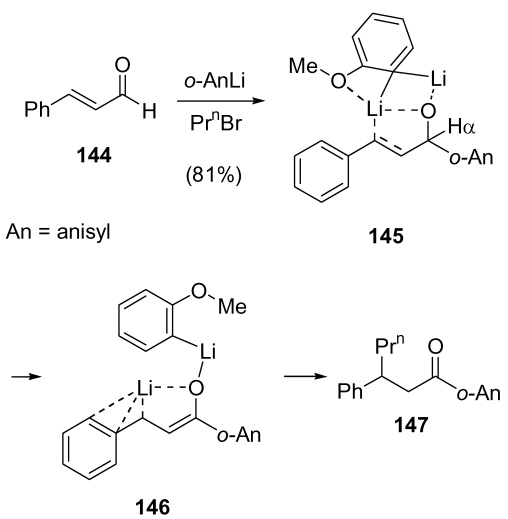
A domino reaction between (*E*)-cinnamaldehyde (**144**) and *o*-anisyllithium affording β-substituted dihydrochalcones **147** was studied by NMR spectroscopy. Trapping of the intermediate **145** with electrophiles, and theoretical calculations of transition states were consistent with a mechanism involving an electron transfer from dimeric aryllithium to the aldehyde **144**. This stage, followed by a further attack of the second aryllithium equivalent to the α-hydrogen in **145**, afforded the intermediate **146**[162] precursor of the final product **147** (Scheme 44).

Aryllithiums gave asymmetric nucleophilic substitution on acetals[45] (see Scheme 6) and nucleophilic aromatic substitution in 2,3-alkylidenedioxybenzoic esters **148**. In this transformation, the asymmetric version was also assayed, affording biaryls **149** in good chemical yield and enantioselectivity[50] (Scheme 45).

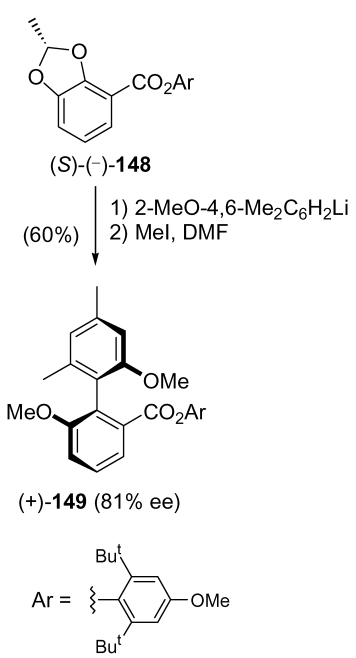
A convenient convergent synthesis of 6-substituted phenanthridines was performed by the addition of aryllithiums to

Table 5. Applications of alkoxyaryllithiums in the synthesis of new organometallic complexes

Entry	Aryllithium	Final compound	Ref.
1	2-MeOC$_6$H$_4$Li	Benzenetricarbonylmanganese(I) hexafluorophosphate	17
2	2-MeOC$_6$H$_4$Li	Chiral ferrocenes	19
3	2-MeOC$_6$H$_4$Li	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
4	2-MeOC$_6$H$_4$Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
5	2-MeOC$_6$H$_4$Li	Chiral platinum complexes	161
6	3-MeOC$_6$H$_4$Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
7	4-MeOC$_6$H$_4$Li	Alkoxycarbenemanganese complexes	21
8	4-MeOC$_6$H$_4$Li	(Tricarbonyliron)dicarbonyl[ethoxy(aryl)carbene]iron complexes	22
9	4-MeOC$_6$H$_4$Li	Diiron bridging alkoxycarbene complexes	23
10	4-MeOC$_6$H$_4$Li	Tricarbonyliron dicarbonyl(arylcarbonyl)iron complexes	24
11	4-MeOC$_6$H$_4$Li	Furanyl-coordinated alkoxy(amino)carbeneiron and acyliron complexes	25
12	2,4-(MeO)$_2$C$_6$H$_3$Li	1,1′-Bis(η^5-cyclopentadienyl)-1-zircona-3-phosphaindenes	20
13	2,5-(MeO)$_2$C$_6$H$_3$Li	Zinc-*meso*-linked porphyrin-quinone diads and triads	71



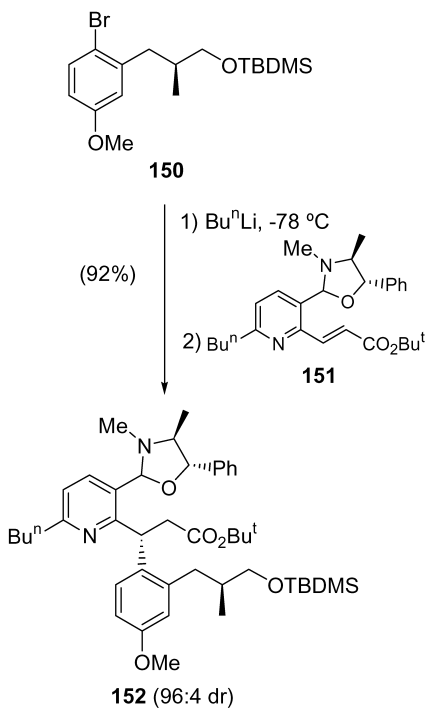
Scheme 44.



Scheme 45.

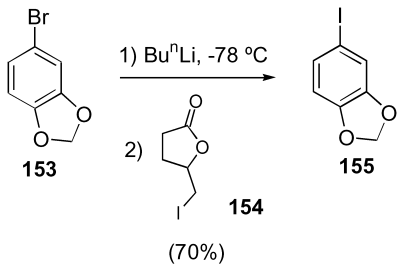
nitriles, the anionic ring closure taking place in good chemical yield.[163] In Scheme 33 (R=TBDMS, R^1=OSiPh$_2$Bu^t, R^2=H) *p*-anisyllithium was used in the synthesis of inhibitors of *N*-riboside hydrolases and transferases upon addition to cyclic imines.[141] Other addition reactions to multiple bonds exhibited by organolithium compounds were the Michael-type addition reactions,[52,53] which are described and illustrated in Scheme 9. In addition, this sequence was applied to the asymmetric synthesis of an endothelin receptor antagonist, one of its key steps being an asymmetric conjugated addition, obtaining the optimal diastereoselectivity for compound **152** using the mixture chiral aryl bromide **150**/Bu^{n}Li and the *N*,*O*-acetal **151**[164] (Scheme 46).

There are two procedures for the synthesis of aryl iodides from oxygen-bonded aryllithiums, one of which is the method already described involving 2,2,2-trifluoro-1-iodoethane as the electrophile[78] (see Scheme 19). The



Scheme 46.

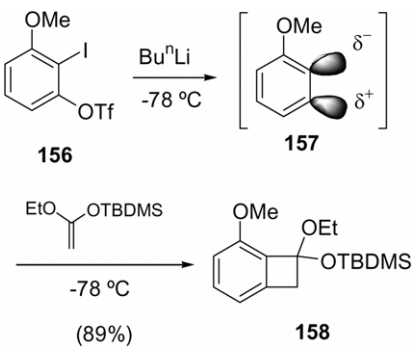
second preparation employed the organolithium derived from **153** and the iodolactone **154** as the iodine electrophilic source, affording iodoarenes, such as compound **155**, in moderate to good yields[165] (Scheme 47).



Scheme 47.

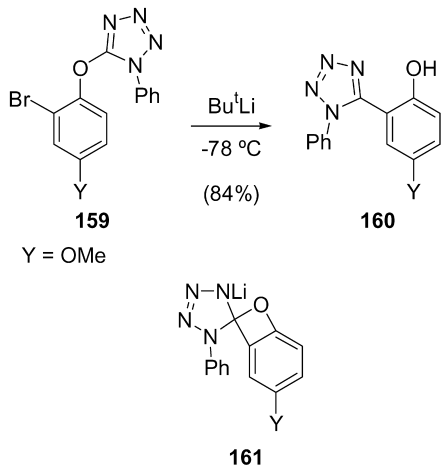
In previous sections, several reactions in which alkoxyaryllithiums participated were described, such as the study of the effect of the silanol substituents in the Heck–Mizoroki type and cross-coupling reactions,[44] the synthesis of benzyl mercaptan derivatives having only a faint smell[43] and the asymmetric rearrangement of *N*-Boc-7-azanorbornene oxide[51] (see Scheme 8).

The halogen–lithium exchange of the *o*-haloaryl triflate **156** quickly generated the aryne **157**, which reacted with the co-existing ketene silyl acetals to give the [2+2] cycloadduct **158** in high yield. The polarisation of the aryne intermediate species **157**, induced by an adjacent alkoxy group, directed the regioselectivity of the cycloaddition (Scheme 48). The subsequent acetal cleavage under acidic conditions gave the corresponding benzocyclobutenone in high yield.[166,167] This compound was transformed into a hindered 1-arylnaphthalene by ring expansion mediated by another equivalent of an alkoxyaryllithium.[46] Aryne intermediates were also proposed as fleeting species in a method developed for the efficient preparation of *o*-trialkylsilylaryl triflates from readily available *o*-bromophenols, naphthols and phenanthrols. The transformation was extremely simple, requiring only an aqueous work-up and one purification step, and being of wide applicability to the synthesis of precursors of substituted and polycyclic arynes.[168]



Scheme 48.

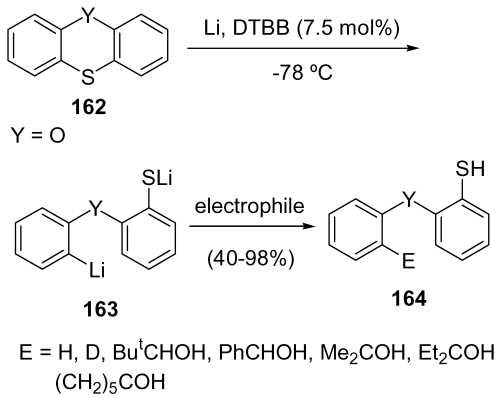
The *ortho*-directing group properties of the (aryloxy)tetrazole functionality and its rapid anionic rearrangement to provide 5-(hydroxyaryl)-1-phenyl-1*H*-tetrazoles **160** were studied with compounds **159**, the reaction proceeding, presumably, through the four-membered intermediate **161**[169] (Scheme 49).



Scheme 49.

Alkoxyaryllithiums were employed in the synthesis of racemic and non-racemic triarylcarbenium ions, as described previously for the compounds **23** (see Scheme 7), and applied to the allylation of aldehydes[48] and the Mukaiyama aldol reaction.[49] Lithiated alkoxynaphthalenes were selected as precursors of structures ready to undergo dearomatising annelation from five-membered rings to naphthalenes, which share structural features of the active lignan phyllotoxin.[170]

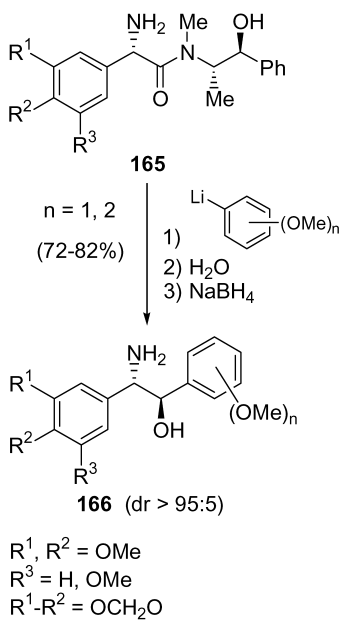
Alkoxyfluoroarenes show the same chemical behaviour as their analogous alkylfluoroarenes **46** (see Scheme 14) in the fluorine–lithium exchange reaction and in further reactions with electrophiles.[63] Nevertheless, higher yields of functionalised thiophenols **164** were obtained in the sulfur–lithium exchange and the subsequent reaction with electrophiles when phenoxathiin **162** (Y=O) was employed as the starting material (Scheme 50). The aryllithium **163** was generated by DTBB-catalysed lithiation at −78°C with lithium metal, some of the resulting compounds **164** being cyclised to afford the homologous seven-membered dibenzoheterocycles in high yields.[171]



Scheme 50.

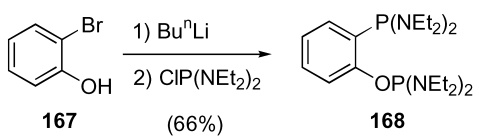
The asymmetric synthesis of chiral ligands is a very important area in organic synthesis, many aryllithiums being incorporated into the synthetic routes for these compounds, in order to improve both the enantiomeric purity and the chemical yield. The 1,2-diaryl-2-aminoethanols were prepared by a diastereoselective addition reaction

of several oxygen-substituted aryllithiums onto the amide **165**, derived from (+)-pseudoephedrine, giving rise to sensitive α-aminoketone intermediates, which were reduced in situ to their corresponding aminoalcohols **166**[172] (Scheme 51).



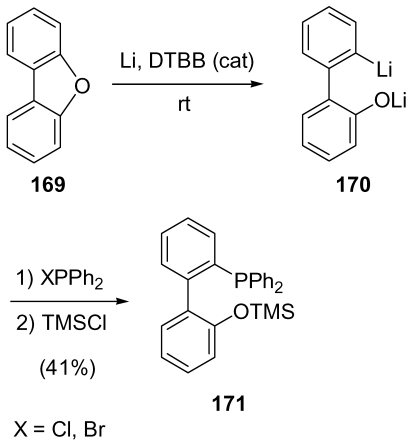
Scheme 51.

Chiral phosphane ligands, where the phosphorous atom was introduced by a previous bromine–lithium exchange, were tested in asymmetric allylations.[122b] In a similar way, a mixed chiral bidentate phosphonite-phosphite ligand was accessible in three simple steps, starting from *o*-bromophenol **167** (Scheme 52), and the compound **168** was finally treated with dry HCl, followed by treatment with (*R*)-binaphthol, yielding the new chiral ligand with good conversion.[173]



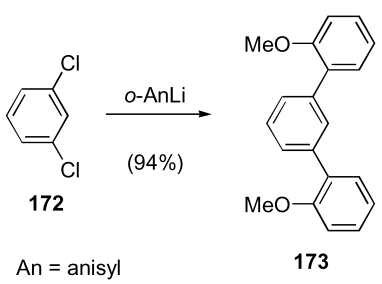
Scheme 52.

(+)-Pseudoephedrine could be used as a chiral auxiliary to form enantiomerically pure phosphane–borane adducts with different substitution patterns. In this case, 3,4-dimethoxyphenyllithium transformed stereospecifically the newly-formed P–O bond into a P–C(sp^2) linkage, with retention of configuration at the phosphorous atom.[174] A facile synthesis of phosphanyl ligands was developed by an oxygen–lithium exchange in dibenzo- and dinaphthofuran using an excess of lithium and DTBB in a substoichiometric amount. The dilithium intermediate **170**, generated from **169**, reacted chemoselectively with the phosphorous atom at the C(sp^2), rather than with the oxygen atom[175] furnishing the product **171** in moderate yield (Scheme 53). Comparative screening tests of phosphanylnaphthols and phosphanylbiphenols in rhodium-catalysed reactions under homogeneous conditions demonstrated catalytic activity in hydroformylation reactions.



Scheme 53.

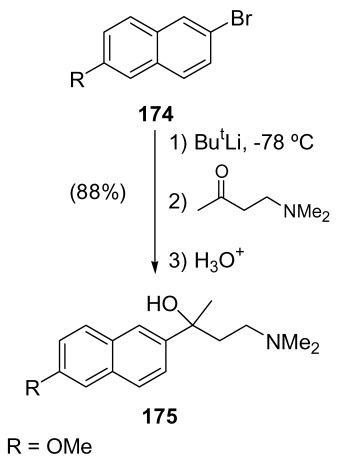
Diaryliodonium triflates,[38] (5*S*)-aryl-2-pyrrolidone derivatives[176] and masked *o*-benzoquinones[177] were obtained by the intermediacy of an alkoxyaryllithium. In the last application, a one-pot synthesis of several silyl bicyclic and oxatricyclic alkenes by inter- and intramolecular Diels–Alder reactions was described. In addition, 2,3-diaryl-1,1-difluoro-1,3-butadienes[42] (see Scheme 5), 2- and 3-pyridinyl(aryl)methanones,[178] rubicenes[47] and *m*-terphenyls such as **173** were also prepared from the same type of organolithium intermediates.[179] An excess of *o*-anisyllithium reacted with 1,3-dichlorobenzene (**172**) at room temperature, giving an excellent yield of the product **173**[179] (Scheme 54). Although in classic studies benzynes were proposed as intermediates, the absence of regioisomers in this reaction supported the displacement of the chlorine atom by a conventional addition–elimination mechanism.



Scheme 54.

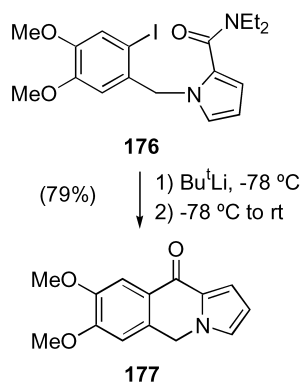
Racemic mixtures and enantiomers of (dialkylamino)alkylnaphthalenes **175** were found to be interesting novel analgesic agents, with potencies similar, or superior, to that of morphine. The synthesis of the products **175** was based on a bromine–lithium exchange from the compound **174** and reaction with 4-(dimethylamino)-2-butanone[180] (Scheme 55).

Perfluoromonomers, prepared by the halogen–lithium exchange methodology, were the precursors of polymers used as versatile coatings or liquid crystalline materials and other compounds with interesting physical properties.[181] Analogously, the synthesis of dumbbell-shaped bis-(pyrazolino[60]fulleren)-oligophenylenevinylene derivatives has received special attention in artificial photosynthesis and for electronic applications.[182]



Scheme 55.

The intramolecular cyclisation employing an aryllithium generated by halogen–lithium exchange is known as Parham cyclisation and allows the preparation of many carbocycles and heterocycles.[5b,8b] For example, the aryllithium generated by metallation of *N*-(*o*-iodobenzyl)pyrrole **176** underwent intramolecular cyclisation to give the pyrrolo[1,2-*b*]isoquinoline **177** in good yield[183] (Scheme 56). In addition, functionalised benzodihydrofurans were synthesised from 2-chloroethyl dibromoaryl or triiodoaryl ethers in higher chemical yields.[184]



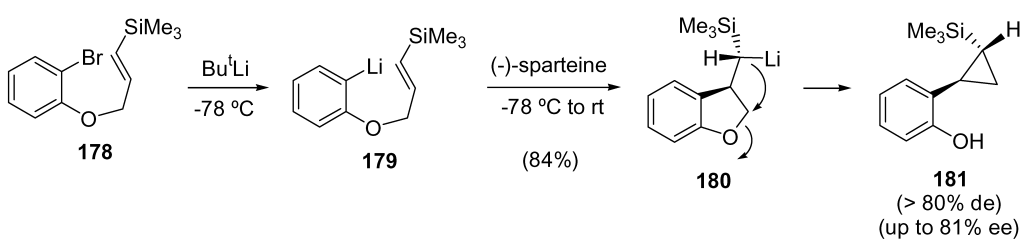
Scheme 56.

A domino sequence involving a carbolithiation-γ-elimination of the allyl 2-lithioaryl ether **179** (generated by bromine–lithium exchange from the compound **178**) for the synthesis of the new chiral cyclopropane derivative **181** (through the intermediate **180**) was optimised using (−)-sparteine as the chiral ligand.[185a] The racemic version of this reaction required the presence of TMEDA for achieving good yields of the cyclopropane **181** (Scheme 57). A similar Parham reaction with 2-iodophenyl propargyl ethers was also completed in good yield in the preparation of the very useful polyfused heterocycles.[185b] In the absence of chelating agents, these reactions suffered a domino anion translocation-Wittig rearrangement affording the corresponding allylic or benzylic alcohol.[186] Two other intramolecular reactions already described in this review involving alkylidene-lithium carbenoids[64] and hydrazinocarbonylaryllithiums[145] gave benzocondensed carbo- or heterocycles, respectively, in good yields.

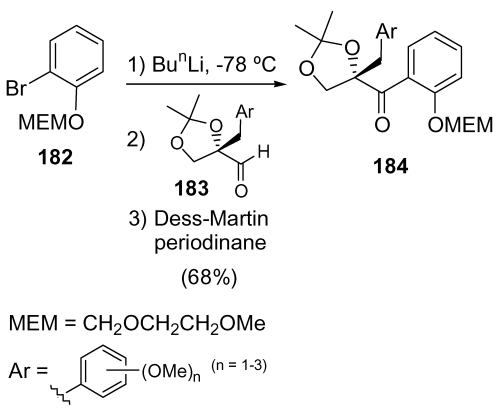
The lithium–metal transmetallation reaction from alkoxyaryllithiums occurred with metals that are more electronegative than lithium. Borates and boronic acids were prepared for the Suzuki–Miyaura couplings in (a) the synthesis of dendritic iron porphyrins with a tethered axial ligand used as mimics for heme-monooxygenases,[187] (b) for a study of their thermal properties and their applications as flame retardants,[188] (c) in the synthesis of chiral chromium complexes of biaryl analogues of actinoidic acid,[189] (d) in the synthesis and properties of a quaternaphthalenehexol (QUANOL),[190] (e) for the creation of hypervalent pentacoordinated anthracene-boron compounds,[191] (f) for the elaboration of polymer glasses with appended oligophenyl paddles[192] and (g) in the synthesis of oligo(hetero)arylene building blocks with bi- and terpyridine units.[193] The transmetallation of alkoxyaryllithiums with Me_2AlCl was very useful in the nickel-catalysed 1,4-addition of aryl groups to enones[33] (see Scheme 2). In addition, the transfer of an aryl group to di-*n*-butyltin dichloride[34] or to vanadium complexes[36] was performed in the generation of biaryls. The organozinc compounds, prepared by transmetallation, were applied to the synthesis of complex pyran structures in good yields.[158]

Numerous applications of oxygen-functionalised aryllithiums were focussed on the synthesis of natural products and non-natural biologically-active molecules. The simple aryllithium, derived from the brominated starting material **182**, which was used in the synthesis of eucomols, reacted with the chiral aldehydes **183** to give, after oxidation, the compound **184** in good overall yield[194] (Scheme 58).

The aryllithium **185** was used in the elaboration of analogues of paclitaxel through the opening of the cyclic carbonate in structure **186**[195] to give the compounds **187** (Scheme 59) and in the addition reaction to the aldehyde **188** to give the compound **189**, used in the preparation of mumbaistatin analogues, which are potent glucose-6-phosphate translocase inhibitors[196] (Scheme 59). On the other hand, silyloxylactones and the reagent **185** were allowed to react at very low temperatures to form an



Scheme 57.



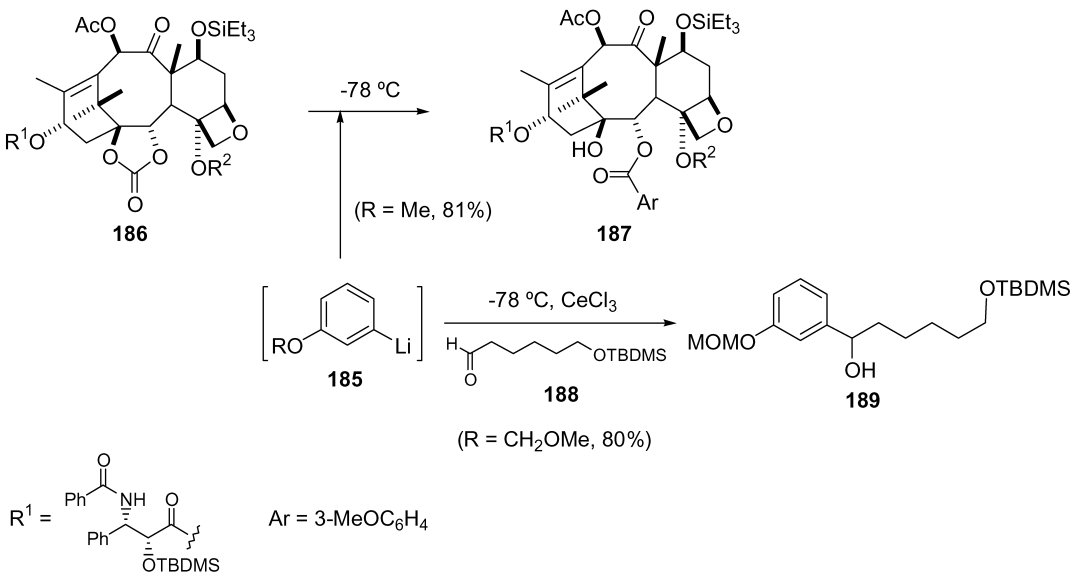
Scheme 58.

intermediate of a non-natural β-*C*-nucleoside 5′-triphosphate bearing an aromatic nucleobase with phenolic groups.[197]

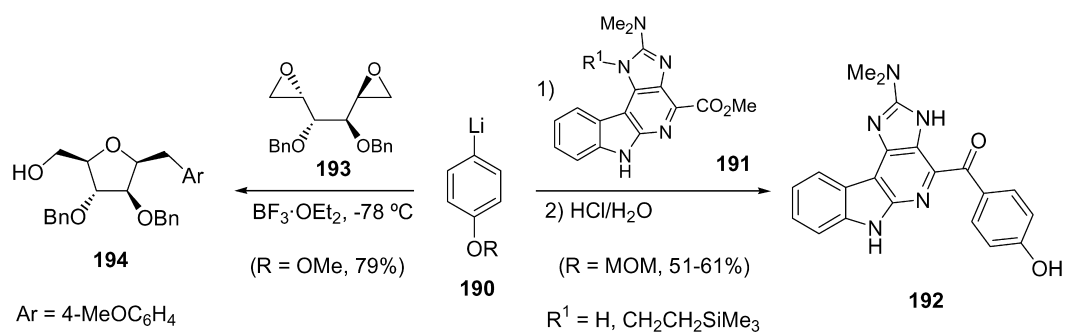
A short asymmetric synthesis of (+)-xanthorrhizol[54] (see Scheme 10), the addition reactions to estrone benzyl ether[58] and to 11-oxo-steroids[59] (see Scheme 11), and the preparation of oxacyclooctenones with herbicidal activity[61] were accomplished by the high nucleophilic character of the organolithiums **190**. Grossularines-2[198] (with interesting antitumour properties) and ATP mimics[199] (inhibitors of fibroblast growth factor receptor tyrosine kinase) were finally obtained through a synthetic route including nucleophilic addition of the intermediate **190** to the ester **191**[198] and the chiral epoxide **193**,[199] furnishing the products **192** and **194**, respectively (Scheme 60). In the generation of the compounds **194**, it was observed that a higher yield was obtained when the organolithium compound **190** was originated by a tin–lithium exchange rather than by a bromine–lithium exchange.[199]

2,4-Disubstituted arenes of the type **195** were successively employed in the regioselective prenylation of resorcinol derivatives (like compound **196**),[200] in the structure revision of medermycin, lactoquinomycin A and related glycosylated naphthoquinones (through compound **197**),[201] and in obtaining of potential precursors to DNA intercalators such as benzo-substituted phthalazines (with the dialdehyde **198**)[202] (Scheme 61).

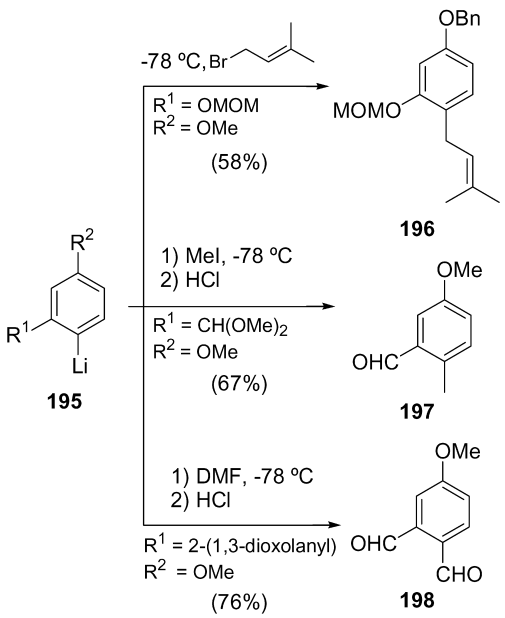
The aryl bromides **199** and **200** underwent halogen–lithium exchange and the corresponding organolithiums were added to a 6-methyldihydropyran[203] and to a taxoid aliphatic aldehyde,[204] respectively, in good yields. The addition reaction to dihydropyran followed by a ring opening afforded a 1,5-dicarbonyl compound that was the precursor of α-herbertenol, an isocuparane sesquiterpene with



Scheme 59.

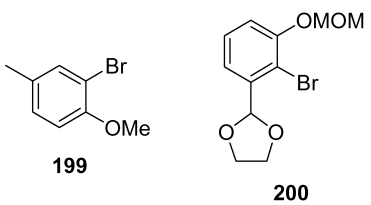


Scheme 60.



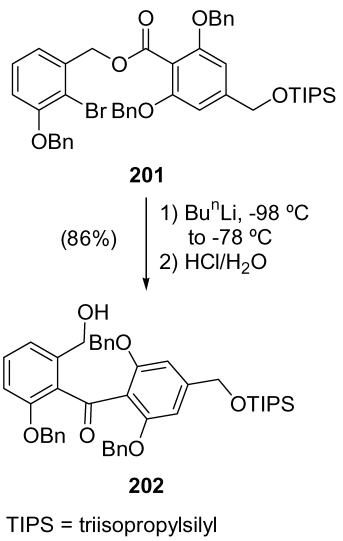
Scheme 61.

antifungal activity.[203]



The aryl bromide **201** reacted with *n*-butyllithium at −98°C to form the benzophenone derivative **202** that constituted a part of the structure of balanol, a potent protein kinase C inhibitor isolated from the fungus *Verticillium balanoides* (Scheme 62). The organolithium intermediate reacted intramolecularly with the ester functionality giving, as result, a migration of the aroyl group from the oxygen atom to the Csp^2 atom.[205]

The route **203→205** using **204** constituted a part of the synthesis of the marine sesquiterpene quinone (+)-puupehenone, a promising new antituberculosis agent[206] (Scheme 63). In another reaction, the addition of the organolithium **203** to the chiral aryloxirane **206** furnished the product **207** in good yield, which is the immediate precursor of natural combretastatin, a very interesting agent with antimitotic and antileukemic activity.[207] The lactol **209** was generated by the addition of the same type of intermediate **203** to the lactone **208** in good chemical yield during the total synthesis of (±)-ottelione B (Scheme 63), which exhibited a remarkable broad-ranging biological activity.[208]

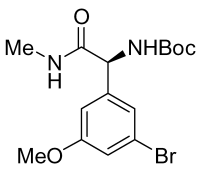


Scheme 62.

Bromine–lithium exchange from 4-bromo-1,2-methylenedioxybenzene (**153**), mediated by *n*-butyllithium, afforded the corresponding organolithium intermediate that reacted with the lactone **210** giving the lactol **211** quantitatively[209] (Scheme 64). The compound **211** is a common precursor of alkaloids such as (±)-crinine, (±)-6-epicrinine, (−)-amabiline and (−)-augustamine, all of which possess a wide range of biological activity.[209] Nevertheless, when the aryl bromide **153** was lithiated and employed in an aziridine ring-opening reaction (in the synthesis of narciclasine and several deoxypancratistatins) the results were very disappointing.[210]

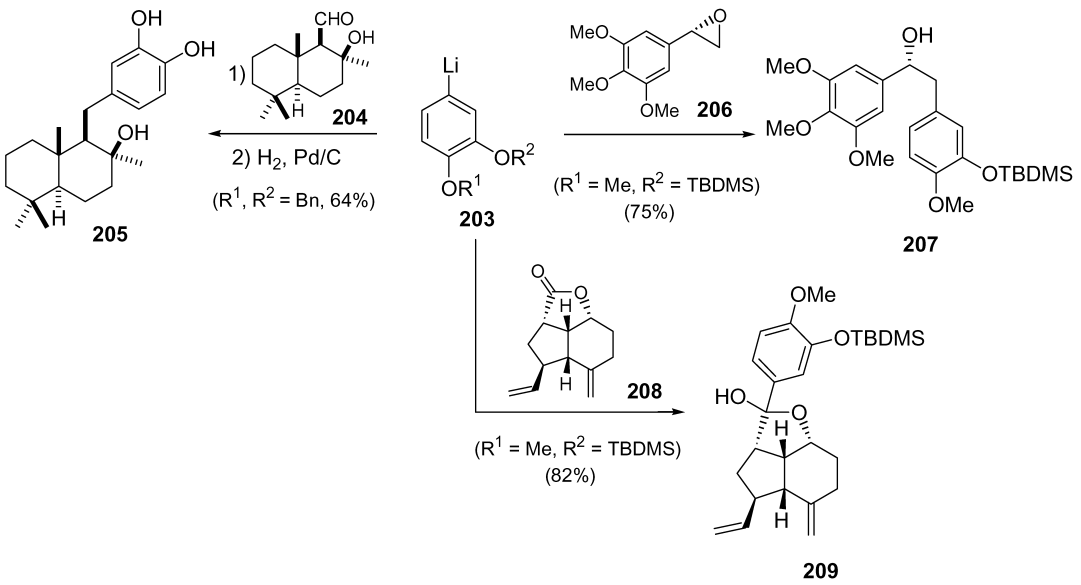
The synthesis of a selective endothelin A receptor antagonist (a useful agent for the treatment of hypertension, heart failure and renal diseases) included an asymmetric conjugate addition of the aryllithium **212** to the chiral alkene **213** and a chemoselective addition of the organolithium reagent **216** to the diester **215**, giving the compound **214** and the ketone **217**, respectively, in very good yields[211,212] (Scheme 65).

Teicoplanin is a member of the large family of glycopeptide antibiotics that includes the potent drug vancomycin. The protected bromoarylglycine derivative **218** was transformed into its boronic acid via a halogen–lithium–boron exchange sequence in 80% overall yield, and was then used to incorporate an arene moiety in the natural product by a Suzuki–Miyaura reaction.[213]

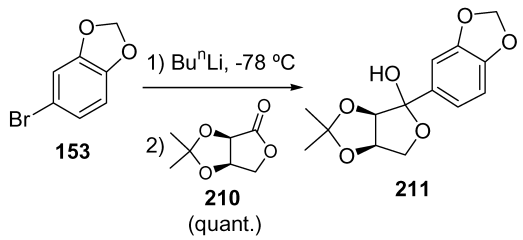


Trisubstituted aryllithiums bearing at least one alkoxy group have been exploited in the synthesis of biologically active compounds. The addition of the organolithium **219** to propylene oxide afforded the arene **220**, which was used in the first stages of the synthetic route to the free radical scavenger (±)-neocarazostatin B[214] (R=Bn) and the potent neuronal substance (±)-carquinostatin A[215] (R=Me) (Scheme 66). The chiral isocyanate **221** was the appropriate electrophile in the construction of the skeleton of the antitumour alkaloid (+)-pancratistatin (through compound **222**),[216] whilst an epimeric compound **221** was suitable in the synthesis of the antitumour agent (+)-narciclasin[216] (Scheme 66).

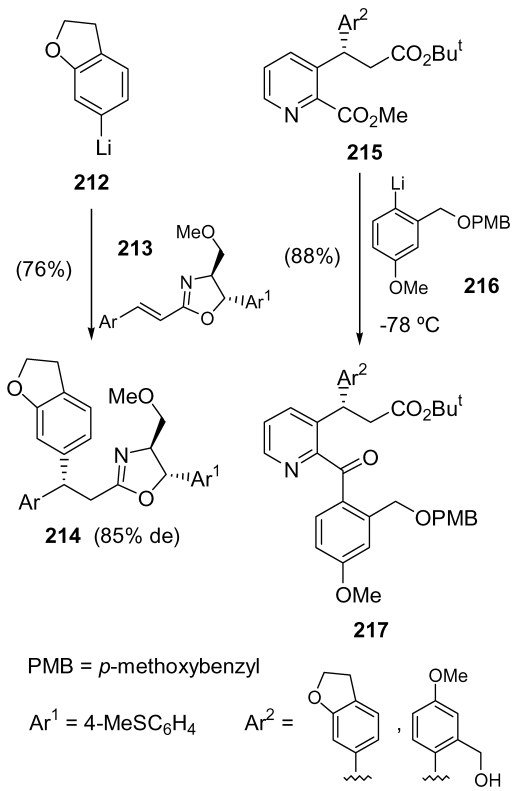
The benzofuran parts of the compounds ailanthoidol, XH-14 and obovaten (neolignans with a variety of biological



Scheme 63.



Scheme 64.



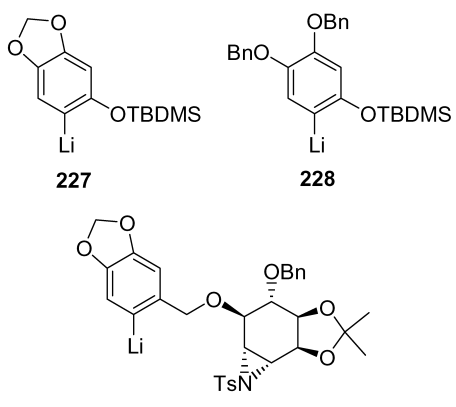
Scheme 65.

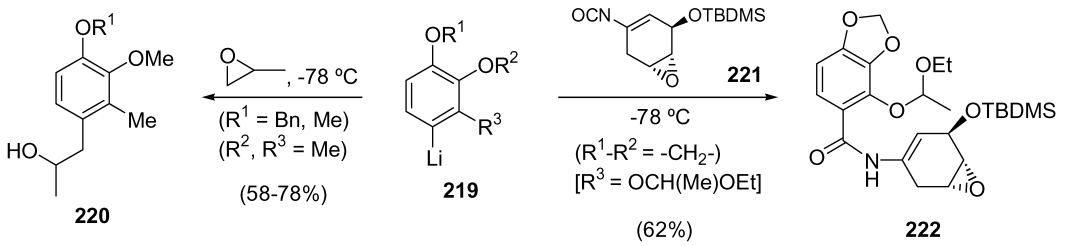
activities), were prepared from vanillin, which was transformed into the bromide **223** in a three-step sequence.

The treatment of **223** with *n*-butyllithium, followed by the addition to substituted benzaldehydes, resulted in the formation of the carbinols **224** in good yields[217,218] (Scheme 67). Benzaldehyde, acetaldehyde and formaldehyde were suitable electrophiles in the addition of a substituted organolithium compound bearing an acetal moiety during the synthesis of analgesic 2-benzopyran, isoquinoline and cinnoline derivatives,[219] respectively.

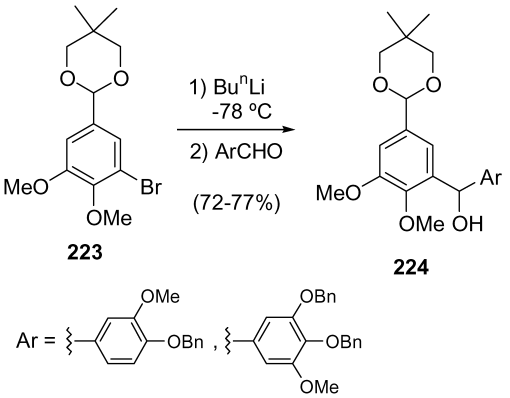
The conversion of the alkoxy-substituted benzyl alcohol **225** to the corresponding phthalide **226** has been performed by carbonation of its corresponding functionalised organolithium compound generated via bromine–lithium exchange (Scheme 68), this method being applied as the key step in the synthesis of different phthalideisoquinoline alkaloids.[220]

The alkylithium compounds **227** and **228**, obtained from the corresponding bromides, were both employed in the synthesis of monoterpenic analogues of puupehenone and puupehedione, showing an antitumour activity four- to ten-fold higher than that for the natural products.[221] When the compounds **229** were generated in situ in a new synthetic approach to narciclasine and deoxypancratistatin derivatives, the results were satisfactory in comparison with the poorer data described previously.[210]

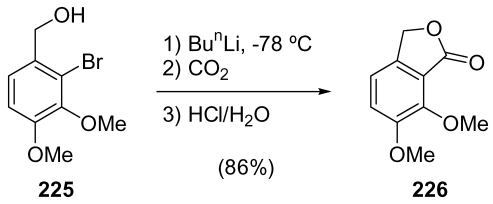




Scheme 66.

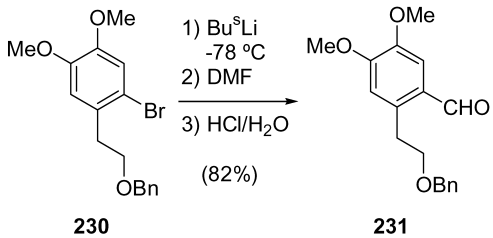


Scheme 67.



Scheme 68.

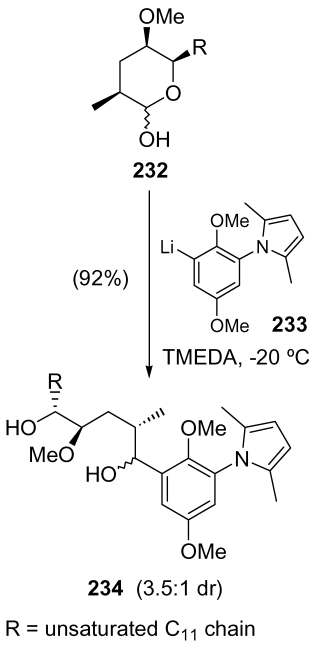
The bromide **230** was transformed into the corresponding aldehyde **231** in good yield, as depicted in Scheme 69. This step belongs to a concise asymmetric synthesis of the naturally-occurring (*S*)-(−)-xylopinine, a protoberberine-type alkaloid with antimicrobial, antileukemic, antitumour and antiinflammatory activities.[222]



Scheme 69.

The addition of the organolithium **233** to the chiral cyclic lactol **232** to give the compound **234** was one of the key steps in the formal total synthesis of (+)-macbecin, a representative ansamycin antibiotic that exhibited a wide spectrum of interesting biological activities[223] (Scheme 70).

Sterically-hindered 2,4,6-trisubstituted organolithiums were employed in the synthesis of balanol analogues in very good yields, this methodology also being applied to the building

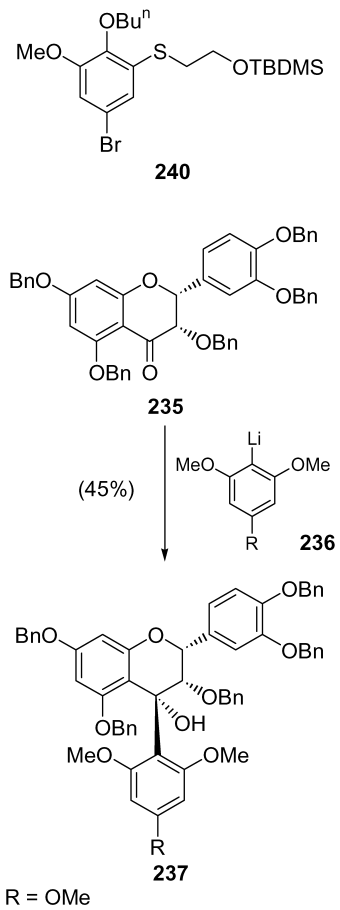


Scheme 70.

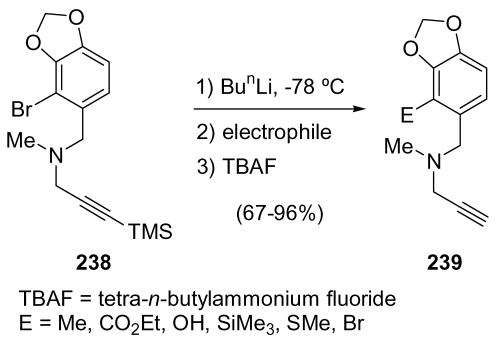
of modified benzophenone subunits, similar to the reaction showed in Scheme 28, and for the generation of sterically-congested boronic acids.[128] A very recent example using these organometallic compounds with the same objective, the synthesis of polysubstituted benzophenones, is the synthesis of (±)-geodin, the spirocoumaranone part of the compound Sch 202596, an antagonist of the galanin receptor subtype GalR1.[224]

The compound **237**, a direct precursor of epicatechin-4α,8-epicatechin, was generated by a diastereoselective addition of the reagent **236** to the ketone **235** in moderate yield[225] (Scheme 71). A similar functionalised organolithium **236** (with R=2-dioxolanyl) was used in the elaboration of the alkaloid ancistrocladidine, the key step of the process involving a bromine–lithium–tin–lead exchange sequence in very high chemical yield.[226]

The piperonylamine derivatives **239** are very simple structures exhibiting strong monoamine oxidase inhibition. The bromine–lithium exchange strategy from compound **238** was very convenient (compared to the direct deprotonation route), the terminal alkynes being protected with the trimethylsilyl group[227] (Scheme 72). 3,4,5-Trimethoxybromobenzene and the aryl bromide **240** were used in different stages of the synthesis of the platelet-activating factor antagonist MK-287 after bromine–lithium exchange followed by addition to a lactol and a lactone, respectively.[228]



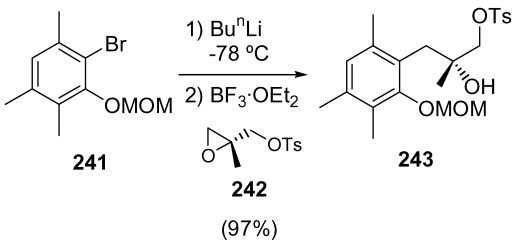
Scheme 71.



Scheme 72.

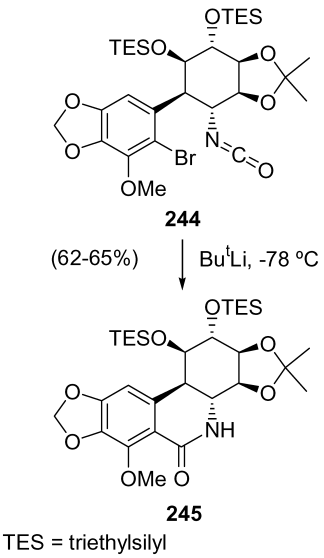
TAK-218, a compound used for the treatment of trauma in ischemic central nervous system injuries (due to its potent inhibitory activities on lipid peroxidation and dopamine release), was prepared by a chemoselective addition of the organolithium derived from the bromide **241** to the chiral tosylated oxirane **242** mediated by boron trifluoride etherate (Scheme 73), the resulting compound **243** being further treated in basic media to afford a new oxirane.[229]

The sensitive bromide **244** was lithiated and allowed to react intramolecularly with the isocyanate moiety to generate the arylamide **245**. The bromine–lithium exchange was faster than the direct addition of the *tert*-butyllithium to the



Scheme 73.

isocyanate group[230] (Scheme 74). This intramolecular version was an alternative synthesis to (+)-pancratistatin described in Scheme 66 (**219→222**), where the intermolecular coupling was achieved with a chiral isocyanate.

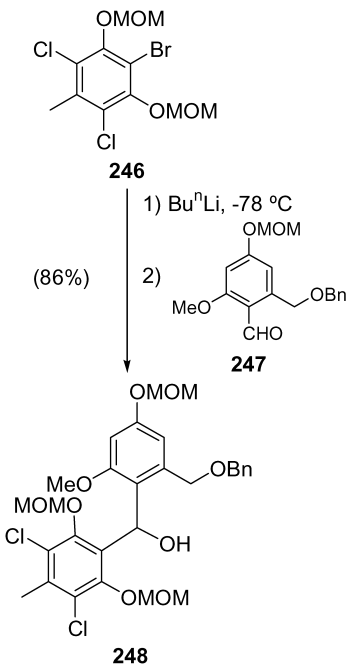


Scheme 74.

Fully-substituted aromatic organolithiums were employed for the preparation of sophisticated benzophenones, which are key intermediates in the synthesis of new cytotoxic antibiotics UPA0043 and UPA0044 having a *p*-quinone-methide structure,[231] as well as in the creation of (±)-geodin, the spirocoumaranone subunit of Sch 202596. This last compound, isolated from a fungal fermentation culture, is a promising agent for the treatment of feeding disorders involving overeating and obesity.[232] As observed, the bromine–lithium exchange was rather faster than the analogous chlorine–lithium exchange in **246**, the coupling with the aldehyde **247** taking place in very good yield, in spite of the steric hindrance of both species, giving the compound **248**[232] (Scheme 75).

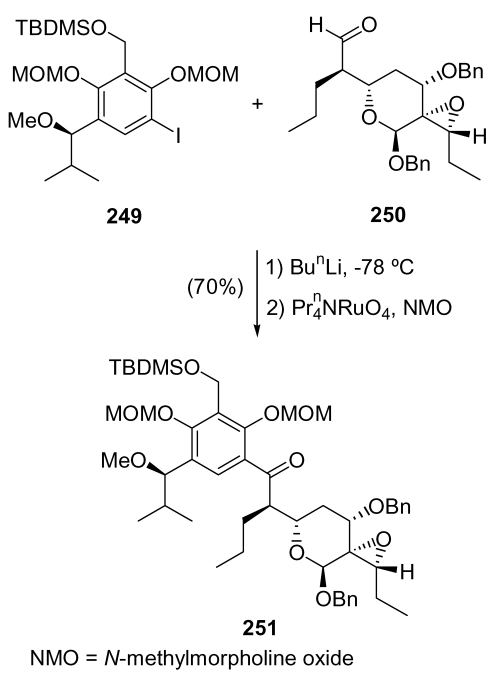
In the first total synthesis, and the establishment of the absolute structure, of the novel angiogenesis inhibitors luminacins C_1 and C_2, the polysubstituted aromatic moiety was anchored by an addition reaction of the organolithium derived from **249** to the chiral aldehyde **250** to afford a benzylic alcohol ready to be transformed into the corresponding ketone **251**[233] (Scheme 76).

The polysubstituted alkoxybromonaphthalenes **252** and **253** were both lithiated with *n*-butyllithium and treated with

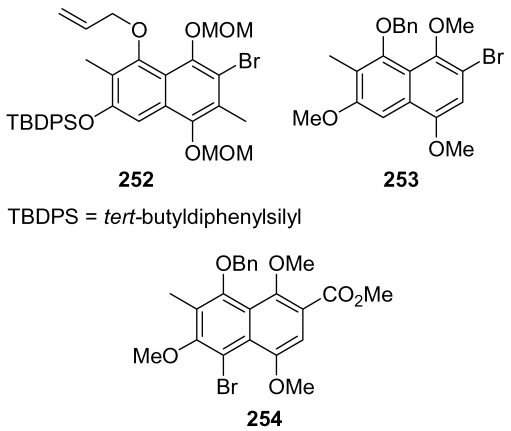


Scheme 75.

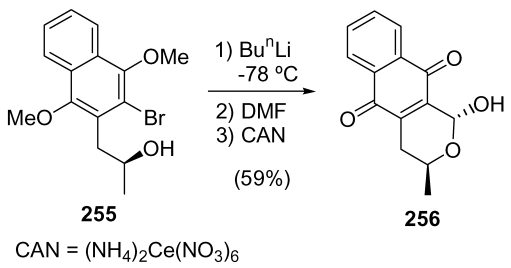
carbon dioxide to yield the corresponding naphthalenecarboxylic acids. These two molecules were employed in the synthesis of naphthoate precursors of damavaricin D[234] and of the nucleus of awamycin,[235] respectively. The bromoarene **254** was a crucial intermediate in the synthesis of the naphthoquinone framework of awamycin by reaction with *n*-butyllithium at −100°C followed by treatment with a chiral unsaturated aldehyde, yielding the expected ketone after oxidation with the Dess–Martin periodinane.[235]



Scheme 76.

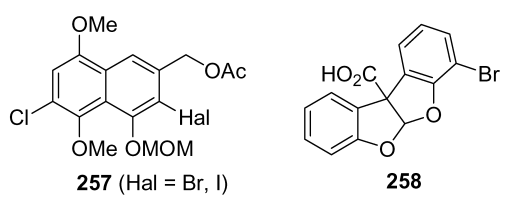


The product **256** and its enantiomer were found to be potent deoxy analogues of the 3C-protease inhibitor thysanone[236] (Scheme 77). The organolithium derived from compound **255** was formylated with DMF, the final oxidative demethylation to quinone **256** being accomplished with ceric ammonium nitrate (CAN). Another formylation reaction using ethyl formate instead of DMF was employed in an intermediate step of the synthesis of lactonamycin, which possesses antimicrobial activity against both methacilein- and vancomycin-resistant organisms.[237]

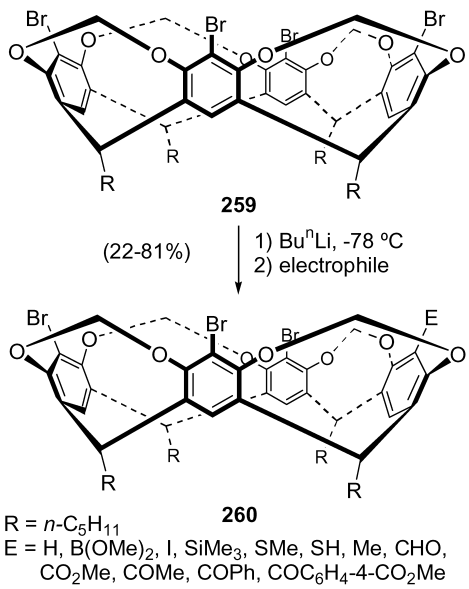


Scheme 77.

Espicufolin, a novel neuronal cell-protecting substance having a 1,8-dihydroxyanthraquinone skeleton, was prepared by an intramolecular acyl-transfer reaction of the 2-halogenonaphthalenes **257** triggered by a chemoselective bromine–lithium exchange (rather than a chlorine–lithium exchange) with *n*-butyllithium,[238] similar to the reaction shown in Scheme 62 for compound **201**. The dibenzo acetal **258** underwent a classical bromine–lithium–boron exchange in order to perform a Suzuki–Miyaura cross-coupling reaction with a bisheterocyclic triflate.[239–241]

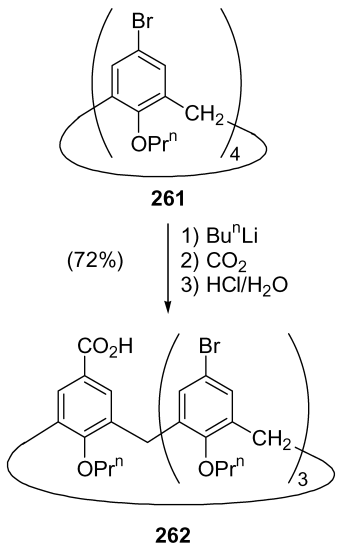


Selective bromine–lithium exchange from the bromide **259** afforded monolithiocavitand intermediates that reacted with a wide range of electrophiles to furnish several new cavitand bowl varieties **260**[242] (Scheme 78). This methodology was also useful for the simultaneous introduction of two groups at diametrically-opposed positions of the cavitand bowls.[243]



Scheme 78.

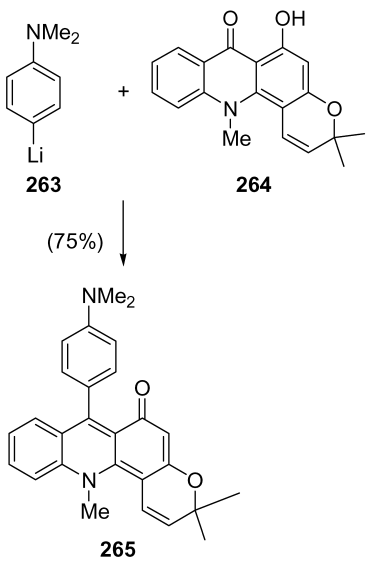
A similar selective bromine–lithium exchange has also been observed in the bromo-substituted calix[4]arene **261** with either *n*- or *tert*-butyllithium in THF[244] (Scheme 79). Other functionalisation or multifunctionalisation of these molecules, adding the exact amount of the alkyllithium reagent, was directed to obtaining of calix[4]arenes in the *cone* conformation.[245]



Scheme 79.

2.3. Nitrogen-bonded functionalised aryllithium compounds

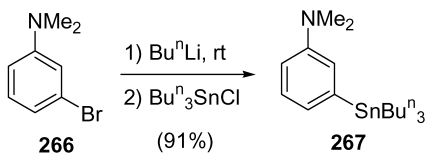
The incorporation of a nitrogenated-functionalised aryllithium is currently performed by a halogen–lithium exchange, after the convenient protection or total alkylation of the nitrogen atom. One of the most widely-used reagents is 4-(dimethylamino)phenyllithium (**263**), employed in the synthesis of water-soluble nickel(II) salen complexes[246] and in the preparation of derivatives such as quinone methides **265** (by reaction with the compound **264**), which are potent antitumour agents[247] (Scheme 80). Other examples where



Scheme 80.

participation of the aryllithium **263** was noticeable are the transmetallation with dimethylaluminium chloride in nickel-catalysed processes,[33] in the addition reaction to an 11-oxosteroid (see Scheme 11),[59] the synthesis of oxabicyclo[3.2.1]octen-3-one derivatives with herbicidal activity (see Scheme 13),[61] and the convergent synthesis of 6-substituted phenanthridines.[163]

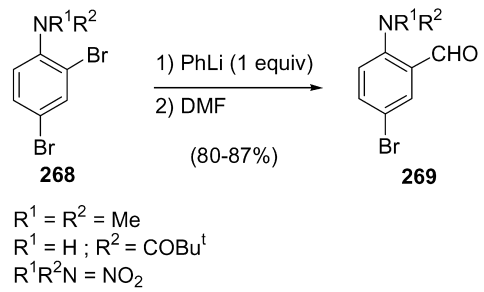
In the preparation of a chemically-powered molecular motor, a *m*-(dimethylamino)phenyl unit was introduced by a sequential bromine–lithium–tin exchange from the compound **266**, previous to the Stille cross-coupling reaction[248] (Scheme 81). This is a clear example of the utility and advantages of the halogen–lithium exchange reaction because it is the only way of accessing to compound **267**.



Scheme 81.

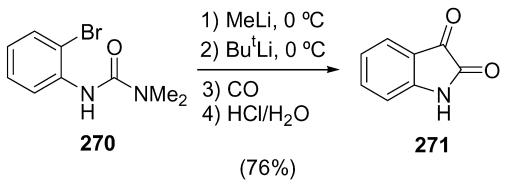
The observed speed of equilibration by halogen–metal exchange means that the outcome of the monolithiation of a dibromide is under thermodynamic control, so that when the brominated substituents are non-identical the result is always the most stable of the two possible organolithiums, as illustrated with the dibromides **268**. The bromine–lithium exchange in the compounds **268** generated the 2-lithioarene species, in which the amino or nitro groups are able to stabilise the lithium atom by intramolecular coordination affording the compound **269**[249] (Scheme 82). A different *N*-*tert*-butyl-*o*-bromoaniline was treated with *tert*-butyllithium and *tert*-butyl nitrite at −78°C, furnishing the precursor of a highly water-soluble stable free radical in 95% yield.[40]

Isatin **271** and substituted isatins could be formed in very good yields from *N*′-(2-bromophenyl)-*N*,*N*-dimethylurea



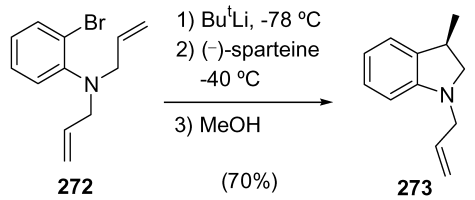
Scheme 82.

(**270**) via deprotonation and bromine–lithium exchange, followed by treatment with carbon monoxide. The presumed mechanism involved a carbonylation reaction affording an unstable acyllithium, which cyclised to give isatin **271**[250] (Scheme 83).



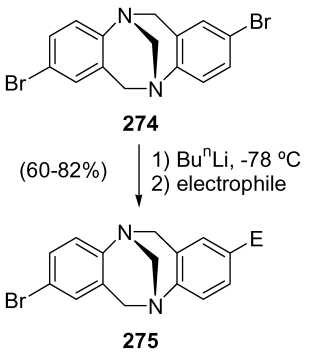
Scheme 83.

N,*N*-Diallyl-*o*-bromoanilines were used for the synthesis of indolines and indoles following a sequence consisting of a bromine–lithium exchange, 5-*exo*-*trig*-cyclisation and final quenching with electrophilic species.[251,252] The asymmetric version of this reaction starting from compound **272** was studied in the presence of (−)-sparteine (see also Scheme 15), obtaining very good results for the 1-allyl-3-methylindoline **273**[65] (Scheme 84). When the starting material **272** contained an allenyl group attached to the nitrogen atom, its cyclisation under the same reaction conditions was applied to the preparation of chiral polyfused heterocycles.[185b] In the treatment of 3-fluoro-*N*,*N*-diallylaniline under these conditions, however, the mechanism was totally different, due to the formation of an aryne intermediate before the cyclisation process, with no fluorine–lithium exchange being observed.[253] Other bis(diallylamino)phenyllithiums were used in the preparation of transition state inhibitors for *N*-riboside hydrolases and transferases by the addition to cyclic imines[141] (see Scheme 33).



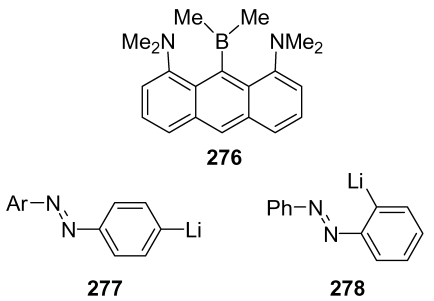
Scheme 84.

The dibromide **274** allowed a facile preparation of C_2-symmetric and -asymmetric 2,8-di- and monofunctionalised analogues of Tröger's base (**275**) in good yields. The method involving a single lithiation was also a simple way for the desymmetrisation of the skeleton giving, important synthetic building blocks, which were difficult to synthesise by other routes[254] (Scheme 85).



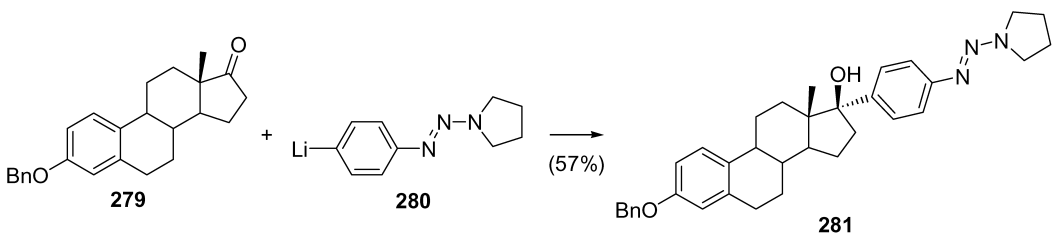
Scheme 85.

The sulfur–lithium exchange also occurred in the compound **162** (Y=NMe, Scheme 50) by a DTBB-catalysed lithiation at −78 or −90°C, this methodology being useful to introduce the *o*-amino functionality into an electrophile. The 9-borylanthracene **276**, generated from the corresponding bromide and *n*-butyllithium followed by electrophilic borylation, clearly has an unsymmetrical structure by coordination of only one dimethylamino group to the central boron atom, the energy difference between the symmetrical and unsymmetrical structures being very small, however, according to ^{1}H NMR measurements.[255] The lithioazobenzenes **277** and **278** were obtained from the bromo- or iodoazobenzenes and were applied to the synthesis of new azobenzene derivatives[256] and of azobenzenes bearing silyl, germyl and stannyl groups at the 2-position,[257] respectively.



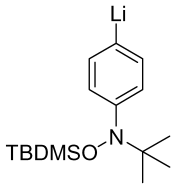
2,4-Diacyl analogues **187** of paclitaxel (see Scheme 59) were obtained by using *m*-azidophenyllithium in very good yield.[195] This protected amino group was taken as model for the synthesis of estradiol derivatives,[58,258] the organolithium **280** reacting with the protected estrone **279** to yield the compound **281** (Scheme 86), which serves to prepare the free amine by catalytic hydrogenation or the corresponding (4-iodophenyl)estradiol through a Sandmeyer-type reaction.[258]

The nitroxidebenzoic acid radical was elaborated in a three-step procedure involving the carbonation of the aryllithium **282**, its ferromagnetic properties being evaluated by low ESR spectroscopy.[259a] The synthesis of phenylnitroxide-substituted zinc(II) porphyrins also required the employment of the same organolithium compound **282** for the



Scheme 86.

generation of its boronic acid derivative and a subsequent Suzuki–Miyaura cross-coupling reaction.[259b]



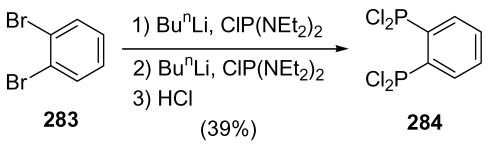
282

2.4. Halogen-bonded aryllithium compounds

Halo-substituted aryllithiums have been explored in the formation of new transition metal complexes, in studies of solvation and structural effects on the stability of ate-complexes, in mechanistic studies, etc. all of which have been discussed previously and are now summarised in Table 6.

In the reported arene-catalysed lithiation of fluoroarenes[63] (see Scheme 14), 1,4-difluorobenzene was treated with a lithium/naphthalene mixture using a two-fold excess of 3-pentanone to give a 31% yield of the monosubstitution product, together with a 37% yield of the defluorinated monocarbinol resulting from a second fluorine–lithium exchange followed by proton abstraction.[63] 4-Fluorophenyllithium was employed in the synthesis of several products such as molecules with herbicidal activity[61] (see Scheme 13), inhibitors for *N*-riboside hydrolases and transferases[141] (see Scheme 33), and complex pyran structures.[158] In addition, the fluoronaphthalene derivative **174** (Scheme 55, R=F) was also utilised in the generation of the analgesic agents **175**.[180] *o*-, *m*- and *p*-Chlorophenyllithium (derived from the corresponding aryl bromides) were employed for the same purpose[42,47,61,141,178] and maintained the same chemoselectivity, due to the faster bromine–lithium exchange occurring during the preparation of the related aryllithiums.

1,2-Dibromobenzene **283** was selected as a suitable material in a synthesis of isobenzofuran-1-ol derivatives in modest yields, presumably due to the formation of a benzyne intermediate in the presence of *n*-butyllithium at −100°C.[260] In spite of this undesirable side reaction, the bisphosphane **284** was obtained in 39% yield through a sequential bromine–lithium exchange, followed by reaction with the appropriate phosphorous-containing electrophile[261] (Scheme 87). This was the first step in the synthesis of chiral diphosphonites used in the asymmetric rhodium-catalysed conjugated addition of arylboronic acids. A homocoupling reaction of the intermediate organolithium at higher temperatures was described back in the 1950s[262] and, recently, it has been applied to the synthesis of silafluorenes.[262]



283 **284**

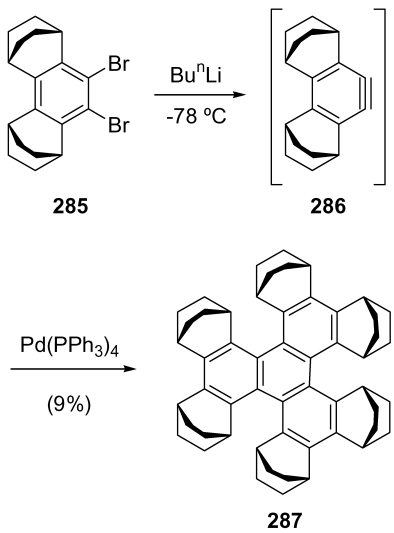
Scheme 87.

Another 1,2-dibromoarene **285** was treated with two equivalents of *n*-butyllithium to give the intermediate benzyne **286**, which hardly reacted with furan to yield the Diels–Alder adduct in 25% yield, or with itself in a cyclotrimerisation reaction catalysed by $Pd(PPh_3)_4$ in the absence of dienes to afford the triphenylene **287**[263,264] (Scheme 88). The last compound was also involved in the formation of a novel arenium ion from its radical cation after treatment with $SbCl_5$.[264]

In connection with the former reaction, comprehensive mechanistic work was carried out to explain the existence of aryne species as intermediates and to understand how to

Table 6. Synthetic utilities of haloaryllithiums

Entry	Aryllithium	Application	Ref.
1	$4\text{-}FC_6H_4Li$	Comparison between diarylferrocenylmethylium ion and its isolobal cobalt species	29
2	C_6F_5Li	Solvation and structural effects on stability of ate-complexes	11a
3	$3\text{-}ClC_6H_4Li$	Synthesis of diaryldimethyltin compounds	34
4	$4\text{-}ClC_6H_4Li$	Study of rearrangement-displacement of silanes	39
5	$4\text{-}ClC_6H_4Li$	Synthesis of acyliron and iron inner salt complexes	25
6	$4\text{-}ClC_6H_4Li$	Synthesis of diaryldimethyltin compounds	34
7	$4\text{-}ClC_6H_4Li$	Synthesis of diiron bridging alkoxycarbene complexes	23
8	$4\text{-}ClC_6H_4Li$	Synthesis of divinylbenzene-coordinated alkoxycarbene complexes	18
9	$4\text{-}BrC_6H_4Li$	Synthesis and characterisation of aryllithiums	35
10	$3,5\text{-}Br_2C_6H_3Li$	Synthesis of platinum-aryl complexes of chiral diphosphanes	161

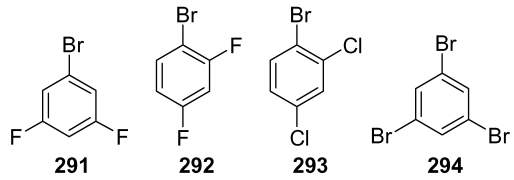


Scheme 88.

construct symmetrical and, eventually, unsymmetrical biaryls. In fact, this aryl–aryl coupling method could be modified by generating the aryne from a thermally-labile 2-haloaryllithium species in the presence of a more stable aryllithium compound. For example, when a solution of the compound **288** was treated with one equivalent of *n*-butyllithium and one equivalent of 1,2-dibromobenzene **283**, the product **290** was obtained in 79% yield[265] (Scheme 89), possibly involving the intermediate **289**.

3-Chlorobromobenzene was the starting material in the synthesis of piperidine analogues of 1-(3-chlorophenyl)piperazines, which are well-known serotonin ligands. The corresponding organolithium was treated with 1-methylpiperidin-4-one to provide the hydroxy derivatives in very good yield.[266] In macromolecules such as *p*-phenylene oligomers, containing perfluorinated segments[74] and oligofluorenes,[76] dibromoarenes appeared to be valuable starting materials for their preparation. 1,4- And 1,3-dibromobenzenes were employed in the synthesis of hyperbranched poly(carbosilarylenes) by a bromine–lithium exchange[267] and 1,4-dibromobenzene derivatives were used in the synthesis of transition state inhibitors for *N*-riboside hydrolases and transferases[141] and for the elaboration of phenanthroline macrocycles with *endo*- and *exo*-topic binding sites.[268] 9,10-Dibromoanthracene was sequentially lithiated and treated with different electrophiles, affording new anthracenes in very good yields, several of which have been employed in the synthesis and chemistry of 1*H*-cyclobuta[*de*]anthracenes.[269] A similar strategy was applied to the generation of Tröger's base derivatives starting from the compound **274**[254] (see Scheme 85).

A potent cyclooxygenase inhibitor was prepared by a Suzuki–Miyaura cross-coupling reaction between a vinyl bromide and a boronic acid derived from the trihalobenzene **291** through a bromine–lithium–boron exchange.[270] This approach gave slightly higher yields than the reaction of 4-lithiothioanisole with the same vinyl bromide.

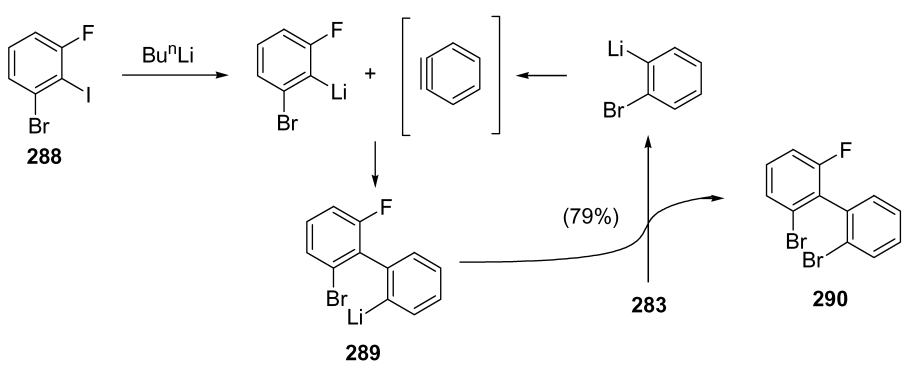


Bromine–lithium exchange in the compounds **292** and **293** generated the corresponding organolithiums, which were used in the synthesis of the analogues **187** of paclitaxel[195] (see Scheme 59). 1,3,5-Tribromobenzene **294** underwent a mono bromine–lithium exchange yielding an organolithium that reacted with a perfluoroalkyl ester, affording a useful ketone for the preparation of perfluoroalkylated materials.[271] The synthesis of non-polar dendrons carrying protected hydroxyalkyl groups in their periphery was accomplished by organolithiums derived from **294** and 1,4-dibromobenzene.[272]

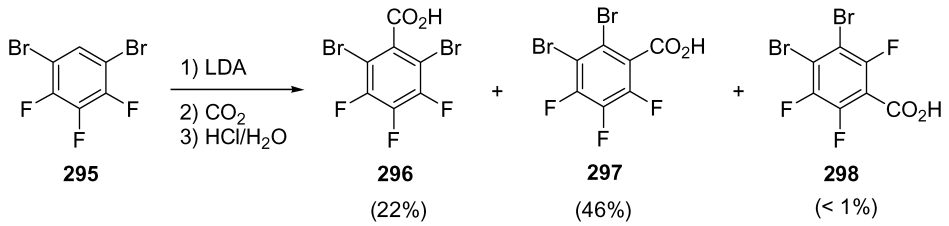
Extensive halogen scrambling and buttressing effects upon treatment of oligobromoarenes with bases have been encountered. Here, a proper halogen-lithium exchange did not occur, but halogen migration took place whenever the substrate contained three or more contiguous halogen atoms[273] (Scheme 90). Starting from the compound **295**, the structure of the base had a crucial effect in the final distribution of the products **296**–**298**. The fully-halogenated pentafluorobromobenzene was used in the preparation of triarylcarbenium chlorides in the catalysis of the allylation reaction which has already been described previously.[48]

2.5. Other heteroatom-bonded functionalised aryllithium compounds

Silicon-containing aryllithiums are not very common species in the literature. [4-(*tert*-Butyldimethylsilyl)]phenyllithium was employed in the characterisation of Lewis



Scheme 89.



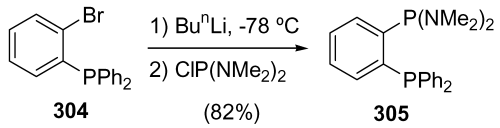
Scheme 90.

base-free σ-bonded lithium aryls.[35] The allylbromophenylsilanes **299** and **301** were transformed into the functionalised compounds **300** and **302**, respectively, which were used as silicon-based aromatic-transferring linkers to give polymers of the type **303** used for traceless solid-phase synthesis of aryl-, polyaryl- and heteroaryl-containing compounds[274] (Scheme 91).

Bromine–lithium exchange from the triarylphosphane **304** afforded the corresponding lithioarene that reacted with bis(dimethylamino)chlorophosphane giving 2-(diphenylphosphino)phenylphosphonous acid tetramethyldiamide **305** (Scheme 92). This compound was easily transformed into enantiomerically-enriched C_1-symmetric phosphinophosphonite and diphosphane ligands by reaction with chiral alcohols in good yields.[275]

2-Thioanisyllithium gave good yields of biaryls in the oxidative coupling promoted by vanadium complexes[36] and has also been used in a three-step route to benzothiophene derivatives.[276] *N*,*N*-Diethyl-*p*-bromophenylsulfonamide participated in a synthesis of new diarylmethylpiperazines with potent and selective non-peptidic δ opioid receptor agonist activity, in a similar process to the reaction shown in Scheme 35.[143]

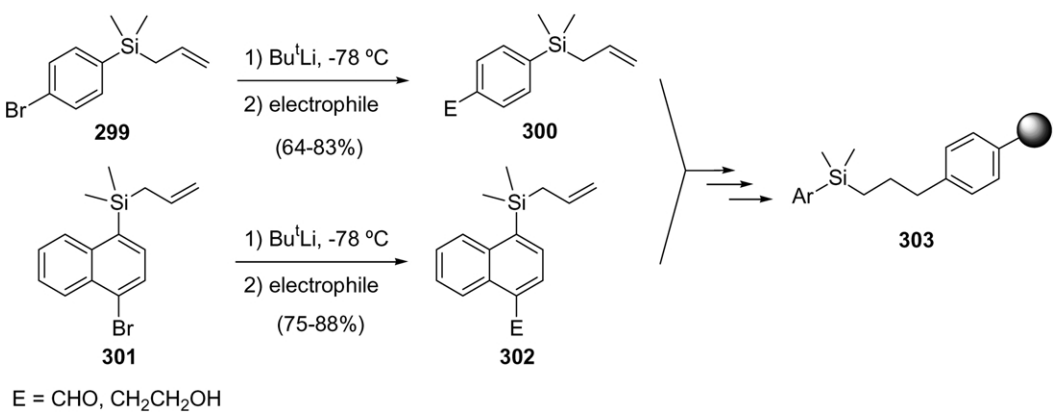
The lithiation of thianthrene (**306**) with lithium/DTBB (4 mol%) followed by reaction with carbonyl compounds at the same temperature furnished the intermediates **307**, which were lithiated with the remaining lithiation mixture and added to a second carbonyl compound, affording the diols **308** in good yields[277] (Scheme 93). As the conclusion of this work, thianthrene **306** was a source of the 1,2-benzene dianion synthon, and the intermediates **307** could be hydrolysed to the compounds **164** (Y=S, Scheme 50) or transformed into the corresponding dibenzoheterocycles by treatment of the compounds **308** under acidic conditions.



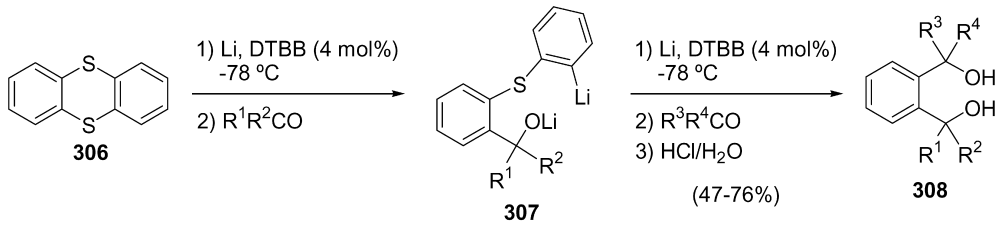
Scheme 92.

Potent cyclooxygenase-specific inhibitors were efficiently synthesised through compound **311**, prepared by using 4-thioanisyllithium **309** and compound **310** in a Michael-type addition-β-elimination process.[278] In the reaction of the same organolithium with the chiral amide-alkoxide **312**,[279] the compound **313** was obtained, giving a very low level (<1%) of the corresponding over-addition product (Scheme 94). In both synthetic routes, a Suzuki–Miyaura cross-coupling reaction with the boronic acid derived from 3,5-difluorobromobenzene (by bromine–lithium exchange) was carried out.

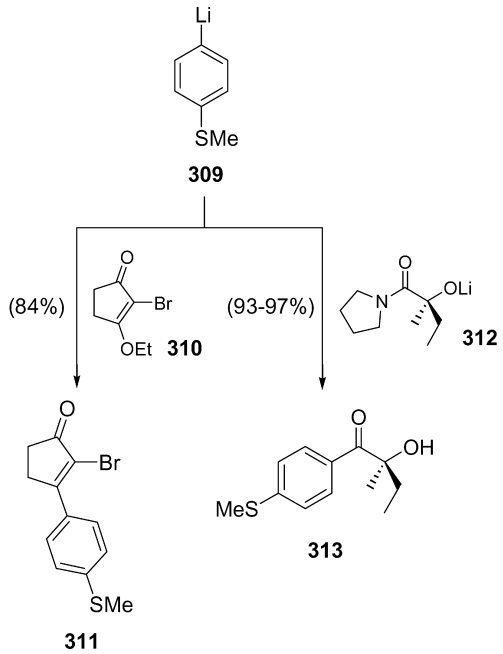
The bromine–lithium exchange of bromophenyl-*ortho*-carborane with *n*-butyllithium at 0°C was demonstrated to be faster than the direct deprotonation of the acidic C–H bond of the carborane cage. In this study, a facile proton exchange between the CH-carborane cluster and the phenyl anion produced the corresponding lithiated carborane.[280] The lithiated ferrocene **315** was achieved in several ways, one of them being the tin–lithium exchange occurring in compound **314**.[281] Another method consisted of a tellurium–lithium exchange from the compound **316**[282] and the third route was a sulfur–lithium exchange from the sulfoxide **317**[283] (Scheme 95). Perhaps the most important application of the last transformation was the straightforward asymmetric synthesis of enantiomerically enriched



Scheme 91.



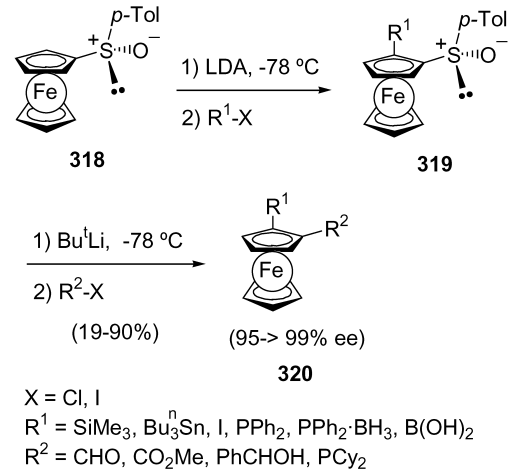
Scheme 93.



Scheme 94.

1,2-disubstituted ferrocenes **320** based on the previous synthesis of the chiral sulfoxides **318** as chiral auxiliaries followed by substitution of the sulfenyl group in the compounds **319**. Depending on the nature of the electrophile, bis(phosphanyl)ferrocenes[284] and other functionalised ferrocenes **320** were obtained in good yields[285] (Scheme 96).

Arene–chromium[286] and –osmium(II)[287] complexes were functionalised using a bromine–lithium exchange reaction

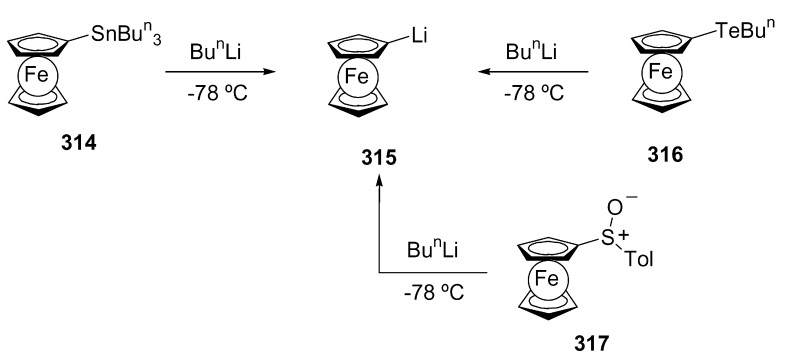


Scheme 96.

with *n*-butyllithium as the lithium source in good yields. In the first example, axially-chiral *N*,*N*-diethyl-2,6-disubstituted benzamides were prepared steroselectively as an optically active form.[286]

3. Heteroaryllithium compounds

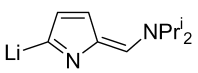
In this review, phenyllithium chemistry has not been covered as it does not contain any functionality. A heteroatom included in the aromatic ring was itself considered as a functionality, however, which directs the chemical behaviour of the whole heterocycle. For this reason, simple aromatic heterocycles will be considered in the next section.



Scheme 95.

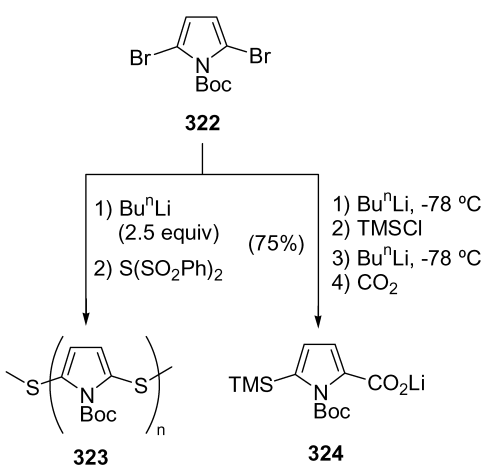
3.1. Five-membered heterocycles

3.1.1. One heteroatom nitrogenated heterocycles. The first known lithiated 1-azafulvene derivative **321** was generated by a bromine–lithium exchange from the corresponding bromide with *tert*-butyllithium. The organolithium **321** was a useful formal equivalent of 5-lithiopyrrole-2-carboxaldehyde since, after reaction with electrophilic reagents and subsequent hydrolysis, a wide variety of regiochemically-pure 5-substituted pyrrole-2-carboxaldehydes were formed.[288] Analogously, *N*-(triisopropylsilyl)-3-lithiopyrrole was generated with the same organolithium reagent at −78°C with the aim of preparing nitrodienylpyrroles by a condensation reaction with a nitrodienamine.[289]



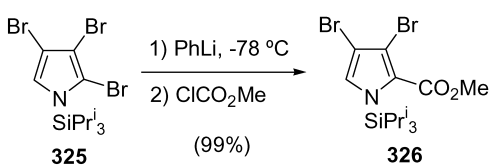
321

N-Boc-2,5-dibromopyrrole **322** was employed for the synthesis and characterisation of the pyrrole-sulfur oligomers and polymers **323** and their corresponding sulfoxides and sulfones by oxidation with *m*-chloroperbenzoic acid[290] (Scheme 97). In the total synthesis of the antitumour marine sponge alkaloid agelastatin A, the pyrrole ring A was introduced by condensation of the acyl chloride derived from the carboxylate **324** and a secondary amine. The compound **324** was prepared from the starting material **322** by a sequential bromine–lithium exchange as shown in Scheme 97.[291]



Scheme 97.

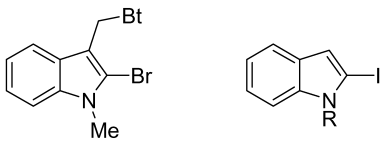
The *N*-protected tribromopyrrole **325** was treated with 1 equiv. of phenyllithium, giving the new stabilised 2-lithiopyrrole in a regiochemical manner (Scheme 98). The ester **326** (prepared by the reaction of the aforementioned intermediate with methyl chloroformate) was very useful in



Scheme 98.

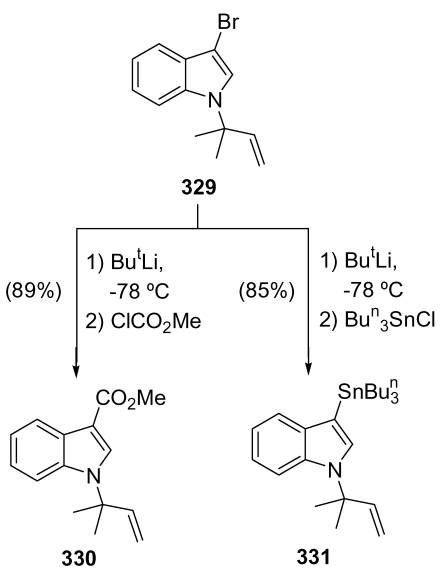
the convergent synthesis of several pyrrolic marine natural products, such as lamellarin O, lamellarin Q and lukianol A, and some more oxygenated congeners.[292]

The 3-substituted 2-bromoindole **327** underwent halogen–lithium exchange with *tert*-butyllithium and the resulting anion reacted with several heterocycle-3-carboxaldehydes for the synthesis of heterobicyclo[*b*]-fused carbazoles.[293] The synthetic application of the 1,2-dianion derived from 2-iodoindole **328** (R=H) by the addition of two equivalent of *n*-butyllithium at −70°C was studied. This dianion reacted predictably with an electrophile at the 2-position, but its treatment with very reactive electrophiles such as methyl iodide resulted in the formation of 1,2-dimethylated species, even when the electrophile was not used in excess.[294] The *N*-protected compounds derived from **328** (R=Me, allyl, Bn, SO_2Ph) were precursors of 2-indolylboronic acids employed in the synthesis of indolocarbazoles, the final annulation being promoted by palladium[295] or chromium-carbene complexes.[296]



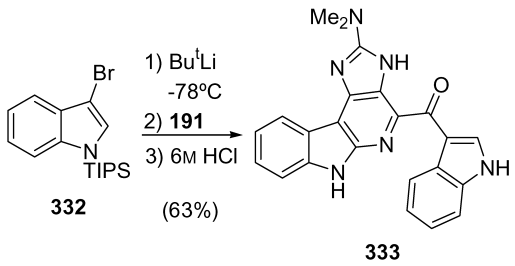
Bt = benzotriazole

3-Bromoindole **329** is an attractive molecule because it is an immediate precursor of antifungal indole alkaloids. The reaction of the resulting 3-lithioindole with methyl chloroformate afforded the *N*-reverse prenylated alkaloid **330** in good yield[297,298] (Scheme 99), which, by Sharpless asymmetric dihydroxylation, furnished another natural antifungal metabolite.[297,298] The organostannane **331** (easily prepared from the bromoindole **329**) participated in the Stille cross-coupling key step in the total synthesis of demethylasterriquinones A1 and B1, two bis-indolylquinones isolated from *Aspergillus terreus* with a wide range of medicinal activities.[299]



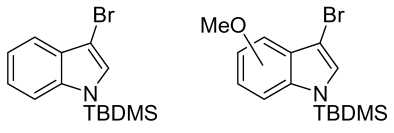
Scheme 99.

Grossularine-1 (**333**), an antitumour agent with a pyrido[2,3-*b*]indole structure, was obtained directly by the reaction of *N*-(triisopropylsilyl)-3-lithioindole and the fused heterocycle **191** (R^1=$CH_2CH_2SiMe_3$) (see Scheme 60) in 63% yield, after removing the silyl protecting group[198] (Scheme 100). The bromide **332** was also transformed into its corresponding boronic acid by a bromine–lithium–boron exchange and was allowed to react with vinyl bromides, obtaining β-(2*R*,3*S*)-methyltriptophans in very good yields.[300]

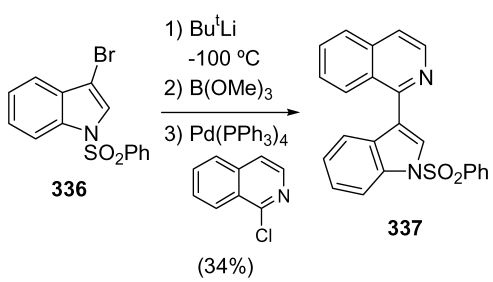


Scheme 100.

Another *N*-silyl-protected 3-bromoindole **334**[301] has been used in the synthesis of 3-[1-(aryl)aminomethyl]indoles. The corresponding organolithium (generated by reaction with *tert*-butyllithium) reacted with *N*-tosyl aldimines specifically at the 3-position, in spite of the directing ability of the *tert*-butyldimethylsilyl protecting group.[302] The generation of 4-, 5- and 6-methoxy-substituted 3-lithioindoles from the compounds **335** was applied to the preparation of 4-, 5- and 6-methoxy-3-substituted indoles in very good yields. On the other hand, 3-indolylzinc halides, prepared by lithium–zinc transmetallation, were employed as components in the Negishi cross-coupling reaction with halopyridines.[303] In particular, the corresponding 6-methoxy-substituted organolithium was used in the synthesis of topsentin, a marine alkaloid with antiviral and antitumour activities.[304]



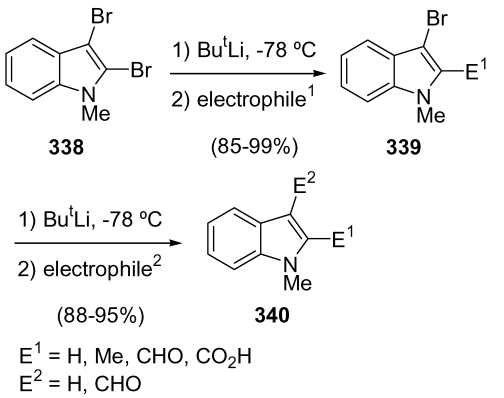
The *N*-phenylsulfonyl-3-bromoindole (**336**) was allowed to react with *tert*-butyllithium at −100°C, and was then transformed into the boronic acid by reaction with trimethyl borate. This compound underwent a Suzuki–Miyaura cross-coupling reaction with 1-chloroisoquinoline to afford the racemic atropoisomer **337** (Scheme 101), which was



Scheme 101.

phosphinylated at the 2-position of the indole ring, resolved, and used successfully as a ligand in palladium-catalysed asymmetric allylation reactions.[305]

The treatment of 2,3-dibromo-1-methylindole (**338**) with *tert*-butyllithium produced a clean monolithiation to give 3-bromo-2-lithioindole, that could be trapped with various electrophiles to afford the corresponding 3-bromo-2-substituted indoles **339**. A second bromine–lithium exchange and quenching with a second electrophile under the same reaction conditions produced the 2,3-disubstituted indoles **340** in very good yields[306] (Scheme 102).



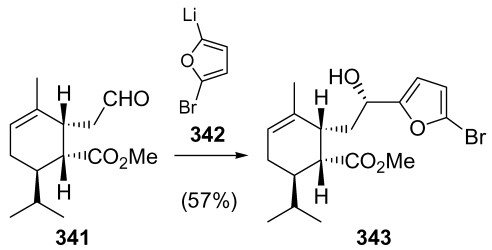
Scheme 102.

Indole arylation directed towards the synthesis of simplified Eastern subunits of chloropeptin and kistamycin was performed starting from 5-, 6- or 7-bromoindoles, which were transformed into the boronic acids through the corresponding organolithium intermediates. Other arylboronic acids were also prepared in order to perform the opposite approach involving bromoindoles in the Suzuki–Miyaura cross-coupling reaction.[307]

3.1.2. One heteroatom oxygenated heterocycles. Quantitative thermodynamic stability scales of organolithium compounds could be derived from measurements of the tin–lithium exchange equilibrium. In this study, 2-lithiofuran and 2-lithiobenzofuran were employed in the NMR experiments, showing that the charge was highly delocalised. The stability data from the tin–lithium exchange could easily be converted into 'effective pK' data, which were useful for predicting the acid–base behaviour of this type of organolithium species.[308]

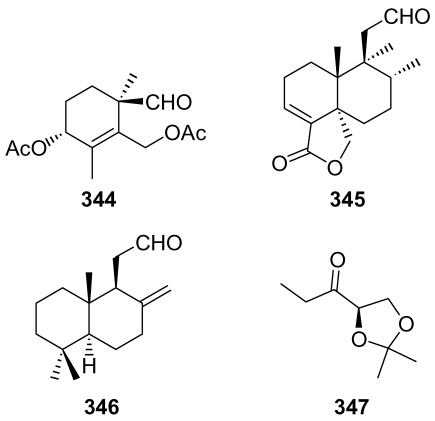
The total synthesis of eleuthesides incorporated the dihydrofuran unit using 2,5-dibromofuran, which was monolithiated by using *n*-butyllithium (to give the intermediate **342**) and allowed to react with the chiral aldehyde **341** with an excellent diastereoselectivity[309] to give the compound **343** in good yield (Scheme 103), the critical step being a remarkable Nozaki–Kishi reaction dealing with the remaining bromofuran.

The aldehydes **344**,[310] **345**[311] and **346**[312,313] and the ketone **347**[314] reacted with 3-furyllithium (**348**) (Scheme 104), obtained by a bromine–lithium exchange from 3-bromofuran promoted by an alkyllithium, to give the expected alcohols. The reaction between 3-furyllithium and the compound **344** took place in very good yield (85%) and



Scheme 103.

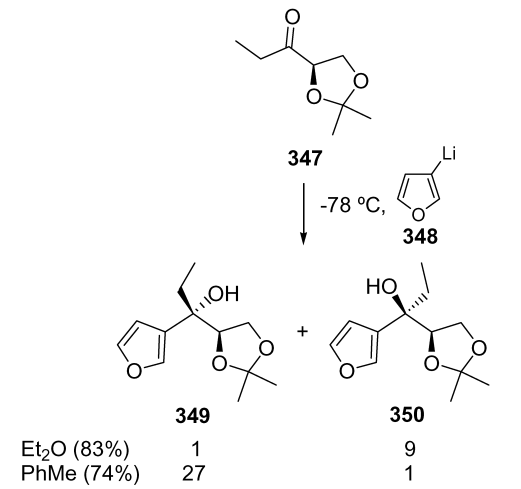
good diastereoselectivity (9.6:1), the resulting product being an intermediate in the synthesis of degraded limonoids [e.g. (±)-fraxinellonone, (±)-fraxinellone and (±)-isofraxinellone] considered as prototypes for insecticides.[310] The compound **345** reacted at the most reactive aldehyde group, rather than at the conjugated lactone moiety, affording a 1:1 diastereomeric mixture of alcohols in 68% overall yield, one of them being transformed, after acylation with acetic anhydride in pyridine, to tanabalin, which exhibited potent insect antifeedant activity against the pink bollworm, a severe cotton pest.[311] An identical diastereoselectivity was reported for the reaction of 3-furyllithium with the aldehyde **346** albeit with very different chemical yield. This low diastereoselectivity was not a drawback in the synthesis of (+)-coronarin E, because the last step required a β-elimination of water,[312] or in the synthesis of the terpene (+)-acuminolide, owing to the epimeric position generated by the related addition (91% yield) being further transformed into a carbonyl group.[313]



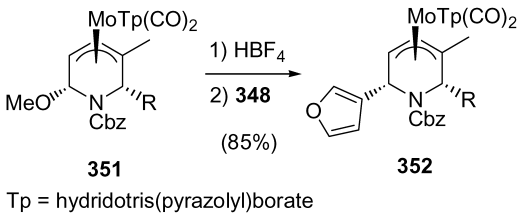
The chiral building blocks **349** and **350**, prepared from the chiral ketone **347** and 3-lithiofuran, were needed in the synthesis of the natural marine products plakortones, the absolute configuration of which is yet unknown. A change of solvents successfully controlled drastically the diastereomeric ratio of **349** and **350**, as depicted in Scheme 104.[314]

Enantiopure $TpMo(CO)_2$(pyridinyl) complexes were prepared using an efficient and scalable enzymatic kinetic resolution. The complex **351** could function as a chiral scaffold for the enantiocontrolled synthesis of substituted dihydropyridines **352** through the formation of a cyclic imine, followed by the addition of 3-furyllithium **348**[315] (Scheme 105).

One of the most significant challenges presented by complex *C*-arylglycoside antibiotics (e.g. kidamycin) lies in the design and development of a unified strategy for the synthesis of the major subgroups. 3-Lithiofuran **348** (or **355**)

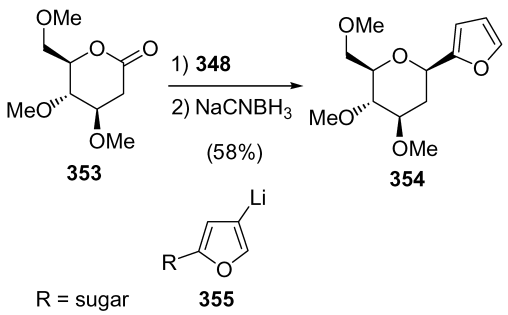


Scheme 104.



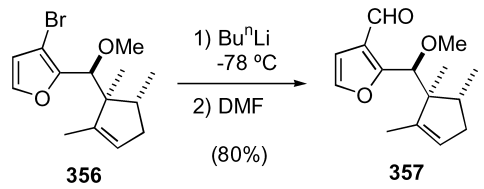
Scheme 105.

was employed in the reaction with the lactone **353** for the assembly of a furan ring in the compound **354**, that was needed later for the elaboration of a naphthyl fragment after an intramolecular Diels–Alder cycloaddition reaction[316] (Scheme 106).



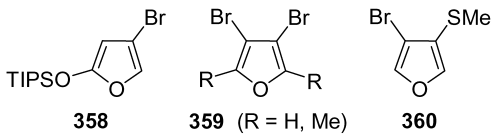
Scheme 106.

New 2,3-dithiosubstituted furans, synthesised by a bromine–lithium exchange followed by reaction with diaryl sulfides, were submitted to a sensitised photooxygenation to access phenyl thiomaleates.[317] The pinguisane-type sesquiterpene (±)-7-*O*-methyldehydropinguisenol bears a furan ring, which was introduced by an addition of 3-bromo-2-lithiofuran (generated by direct deprotonation) to a chiral ester, giving the corresponding ketone. The 3-bromofuran derivative **356** (obtained from the previously mentioned ketone by successive reduction and methylation reactions) was formylated at the 3-position in good yield (Scheme 107) to give the compound **357**, which was ready to undergo two more transformations before the final palladium-catalysed cycloisomerisation.[318]

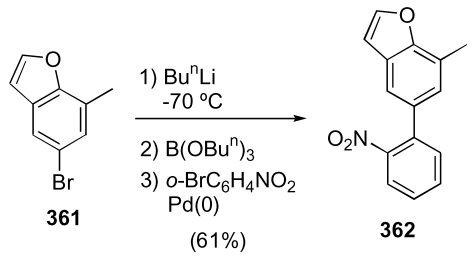


Scheme 107.

The bromides **358** (an intermediate in the synthesis of the decaline part of the insecticide azadirachtin),[319] **359** and **360** were transformed using a bromine–lithium exchange followed by reaction with electrophiles and employed for the synthesis of polysubstituted 3-thiofurans[320] and biheteroaryls.[34]

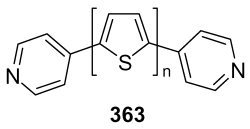


2-Benzofuryllithium was generated and transformed either to the corresponding organozinc compound and finally added to 1,2-dihydropyrans for the assembly of complex pyran structures,[158] or transformed into the corresponding boronic acid ready to undergo a Suzuki–Miyaura cross-coupling reaction in the creation of monoaryl- and biaryldihydroxytropolones, potent inhibitors of inositol monophosphatase.[321] Moreover, the boronic acid derived from the bromide **361** was utilised in a Suzuki–Miyaura cross-coupling reaction to give the compound **362** in good overall yield (Scheme 108), this compound being a direct precursor of furostifoline, a furo[3,2-*a*]carbazole alkaloid with a promising pharmacological potential.[322]

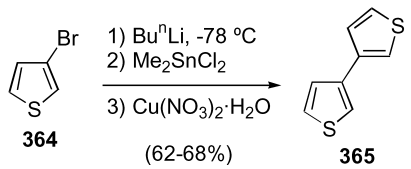


Scheme 108.

3.1.3. One heteroatom sulfurated heterocycles. The stereoselective addition of organozinc reagents derived from 2-lithiothiophene to 1,2-dihydropyrans for the assembly of complex pyran structures has already been mentioned in previous sections,[158] as well as in the synthesis diaryliodonium triflates.[38] Trisubstituted 2-bromothiophenes were employed to generate 2-lithiothiophenes that reacted either with DMF or formaldehyde, affording 2-formyl- or 2-hydroxymethylthiophene derivatives, respectively, in good yields.[323] The compounds **363** were promising new models for trans-membrane molecular conductors prepared by using bromine–lithium exchange, direct deprotonations and cross-coupling reactions mediated by palladium complexes.[324]

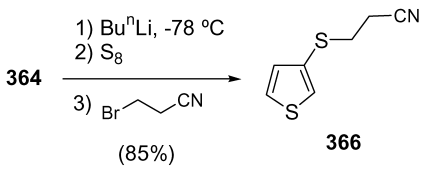


The bithiophene **365** was formed by the reaction of the in situ-generated 3-thienyllithium with dichlorodimethyltin followed by the Csp^2–Csp^2 coupling with Cu(NO$_3$)$_2$·H$_2$O in THF[34] (Scheme 109), the same process also being described for the corresponding 2-isomer. Both compounds **364** and its 2-isomer were also used in the synthesis of dihydroxytropolones (see Section 3.1.2).[321]



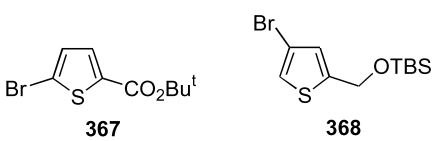
Scheme 109.

Elemental sulfur was used as an electrophile in the preparation of the intermediate **366**, able to create quaterthiophene-C$_{60}$ diads (Scheme 110)[325] that usually exhibit interesting photophysical properties. The substrate **364** was also transformed into its nitrated derivative by the generation of the corresponding organolithium and reaction with dinitrogen tetroxide.[50]

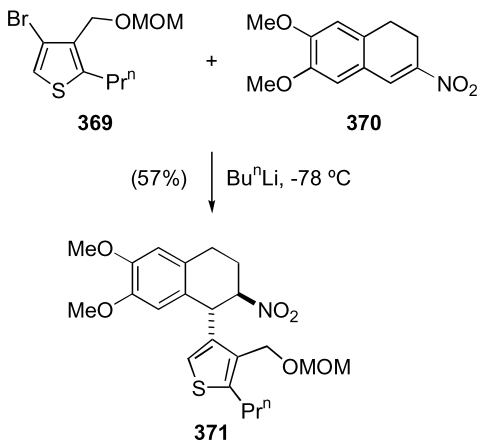


Scheme 110.

3-Thiopheneboronic acid, and more complex derivatives, were coupled with 2-bromopyridine in very good yield, affording the pyridine-substituted hydroxythiophenes, which are very interesting new materials with multiple applications.[326] A potent and selective small-molecule inhibitor of capsase-3 (cysteinyl aspartate-specific protease, which plays key roles in cytokine maturation and programmed cell death) incorporates a thiophene ring linker in the centre of the molecule. For its synthesis, the heterocycles **367** and **368** suffered bromine–lithium exchange (*n*-butyllithium, −78°C), followed by reaction with 1-formylpiperidine and ethyl chloroformate, respectively, in good yields.[327]

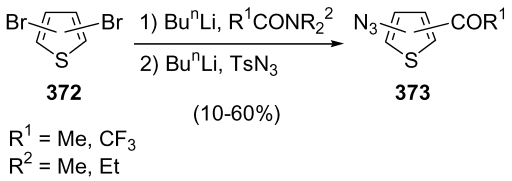


Dopamine D$_1$-selective agonists with the structure of hexahydrobenzo[*f*]thieno[*c*]quinolines were similarly prepared, one of the key steps involving the Michael-type addition of the lithiothiophene derived from the bromothiophene **369** to the nitroolefin **370**, affording the *trans*-isomer **371** as the major compound in good yield[328] (Scheme 111).



Scheme 111.

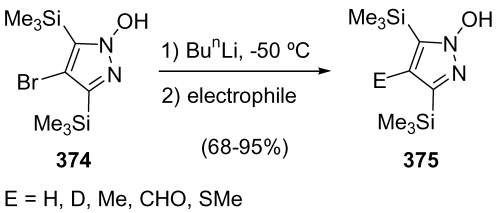
Lithiated thiophenes were also employed in the preparation of polymers entwined around copper centres[329] and polymers used as photochromic films.[330] In the last example, a boronic acid derived from a 2,4-dibromothiophene was the appropriate component in a Suzuki–Miyaura cross-coupling reaction, as well as in a double addition to perfluorocyclopentene, followed by a β-elimination of lithium fluoride, taking place in low chemical yield.[330] Starting from the 2,3-, 3,4- and 2,5-dibromothiophenes (**372**), the azidothiophenes were prepared in a one-pot procedure. Single halogen–lithium exchange and subsequent reaction of the generated bromothienyllithium with *N*,*N*-dimethylacetamide or *N*,*N*′-diethyltrifluoroacetamide resulted in the formation of intermediate heterocycles bearing a carbonyl group. After protection of the carbonyl fuctionality, a successive halogen–lithium exchange, followed by reaction with tosyl azide, then afforded the products **373** in moderate yields[331] (Scheme 112).



Scheme 112.

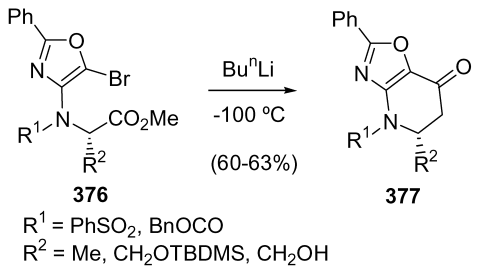
3.1.4. Heterocycles containing two or more heteroatoms.

A protocol for the introduction of electrophiles at the 4-position of 1-hydroxypyrazoles was developed. Treatment of the pyrazole **374** with an excess of *n*-butyllithium produced the expected bromine–lithium exchange giving a lithium intermediate, which, by reaction with electrophiles, afforded the 4-substituted pyrazoles **375** in good to excellent yields[332] (Scheme 113).



Scheme 113.

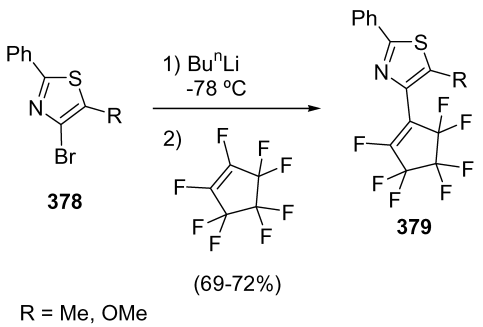
A novel strategy for the enantioselective synthesis of polyhydroxypiperidines, which could be considered as iminoglycitols or 2,6-dideoxyazasugars, started from α-benzenesulfonylamino esters, which served as a C_2N building block, while the 2-bromo-3-(bromomethyl)oxazoles and thiazoles contributed at a C_3-unit to the final piperidine ring. The oxazoles **376** were treated with *n*-butyllithium at −100°C to give the 5,6-dihydro[1,3]oxazolo[4,5-*c*]pyridin-7(4*H*)-ones **377** in good yields via an intramolecular addition of the generated organolithium onto the ester group[333] (Scheme 114).



Scheme 114.

The synthesis of isomeric bithiazoles by regioselective Stille and Negishi cross-coupling reactions was readily available from 2,4-dibromothiazole. The final compounds represent a very important class of natural products, which exhibit an intriguing and diversified spectrum of biological activities[334]

As described above for lithiothiophenes, several thiazoles **378** were lithiated and treated with perfluorocyclopentene, giving, after addition and β-elimination reactions, the thiazolylcyclopentenes **379** in good yields (Scheme 115). All of these final compounds **379** underwent a reversible photocyclisation reaction from the open- to the closed-ring structures.[335]

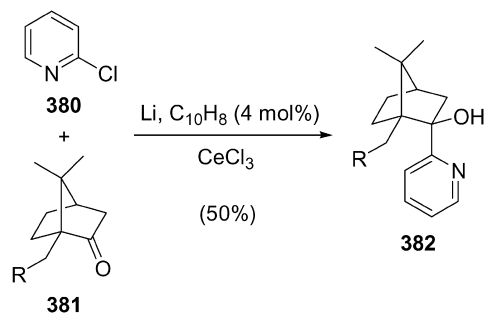


Scheme 115.

3.2. Six-membered heterocycles

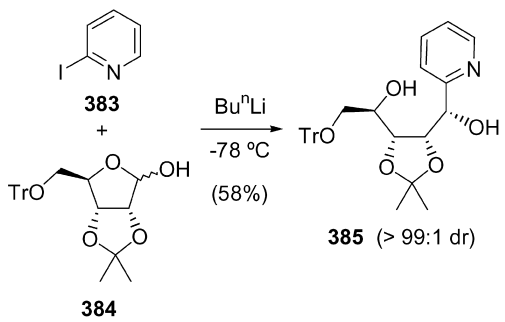
3.2.1. One heteroatom nitrogenated heterocycles.

The naphthalene-catalysed reductive lithiation of the 2-, 3- and 4-chloropyridines **380** in the presence of different electrophiles, such as the ketone **381**, yielded, after hydrolysis, the expected functionalised heterocycles, e.g. compound **382** (Scheme 116). In some particular examples, cerium trichloride was required for achieving better chemical results.[336]



Scheme 116.

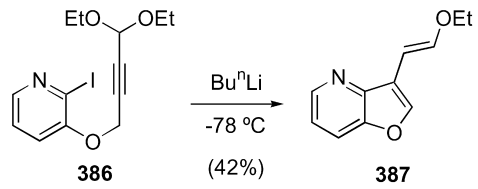
2-Bromo- or 2-chloropyridines underwent halogen–lithium exchange and the corresponding organolithium was used in different reactions, such as in the synthesis of 5-substituted 2,2′-bipyridines by a modified Negishi cross-coupling reaction,[337] in lithium–boron and lithium–tin exchanges involved in Suzuki–Miyaura and Stille cross coupling reactions,[338] in the preparation of 2,2′-bypyridyl diselenides and ditellurides,[339] and in the synthesis of other functionalised pyridines.[340] In the last case, 2- and 3-iodopyridines were used under Barbier-type conditions, with ultrasonic irradiation, affording good results for the new pyridines, even in the presence of ring substituents such as methylsulfanyl, methoxy or chloro groups.[340] 2-Iodopyridine **383** suffered iodine–lithium exchange and the resulting organolithium compound was diastereoselectively added to the ribofuranose derivative **384**, affording the compound **385**, a precursor of β-C-deoxynucleosides having a pyridine nucleus as the base moiety[341] (Scheme 117).



Scheme 117.

Alkoxy-substituted 2-iodopyridines were useful precursors in the synthesis of orelline and analogous toxins present in poisonous mushrooms. The 2,2′-bipyridine structure of the related natural products was accessed by iodine–lithium–zinc or iodine–lithium–tin exchange, followed by palladium-mediated cross-coupling reactions, in good overall yields.[342] The intramolecular reaction of the alkoxy-2-iodopyridine **386** with 3.3 equivalents of *n*-butyllithium gave access to the 3-vinylfuro[3,2-*b*]pyridine **387** through a 5-*exo*-*dig* heterocyclisation in modest yield, but with total *E*-selectivity (Scheme 118). This 3-vinyl heterocycle **387** is a very useful building block, particularly for alkaloid synthesis, because its dienic moiety could be engaged in Diels–Alder cycloaddition reactions.[185b]

Pyridyltellurium derivatives were prepared by the reaction



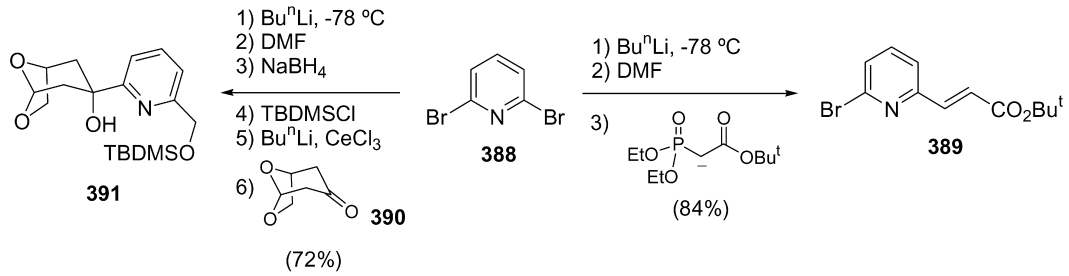
Scheme 118.

of halopyridines and lithium butanetellurolate, the tellurium–metal exchange being investigated using *n*-butyllithium to give 2-substituted pyridines after addition to different electrophiles.[343]

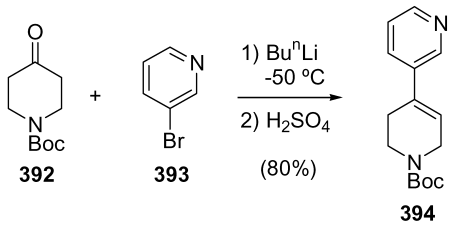
The selective monolithiation of 2,5-dibromopyridine either at the 2-position or at the 5-position has been reported. The inaccessible 2-lithio-5-bromopyridine was generated (up to 34:1 selectivity ratio) via a monolithiation reaction using *n*-butyllithium (1.2 equiv) in toluene at −78°C in a 0.017 M solution and trapped with several electrophiles.[344] In a recent publication, 6-halopyridine-3-boronic acids and esters were prepared by using *n*-butyllithium in ether and 2,5-dibromopyridine or other dihalopyridines.[345] These two transformations demonstrated the versatility of the dihalogenated substrates and the importance of factors such as concentration, solvent and temperature. More sophisticated 2,5-dibromopyridines, bearing two amino-protected groups, were transformed into their tri-*n*-butyltin derivatives, which were employed in the synthesis of polypyridines for a study of their optoelectronic properties.[346]

2,6-Dibromopyridine (**388**) was selected in many cases as the starting material in several total syntheses, including the preparation of ceramide analogues bearing a heteroaromatic nucleus[60] (see Scheme 12), the elaboration of serotonin ligands,[266] the preparation of L-739,010 (a 5-lipooxygenase inhibitor)[346] and the synthesis of β-pyridyl-β-amino acid derivatives.[347] In the latter example, the compound **389**, obtained from the corresponding pyridinecarboxaldehyde (Scheme 119), was further treated with chiral amides to produce enantiomerically-enriched β-amino acid derivatives in good yields.[347] The sequential double bromine–lithium exchange and functional group transformations were exploited from **388** in the synthesis of a precursor of L-739,010 **391**, where the second organolithium compound was diastereoselectively added to the cyclic ketone **390**[348] (Scheme 119).

3-Bromopyridine **393** was the starting material for the generation of 3-lithiopyridine, which was used in different reactions such as the synthesis of inhibitors of *N*-riboside hydrolases and transferases[141] (see Scheme 33), in the preparation of 3-pyridinyl(aryl)methanones,[178] the synthesis of vitamin D analogues,[119] the development of synthetic routes to achieve 3-functionalised pyridines[336,340,349] (see Scheme 116), and in the preparation of nitrogen-containing bis(heteroaryl)iodonium salts.[350] In a complex study on the structure–affinity relationships of the unique nicotinic ligand N^1,N^1-dimethyl-N^4-phenylpiperazinium iodide, it was possible to identify molecules such as the compound **394** (prepared from the compound **392** and the in situ-generated 3-lithiopyridine) with interesting affinities for $\alpha_4\beta_2$ receptors[351] (Scheme 120).

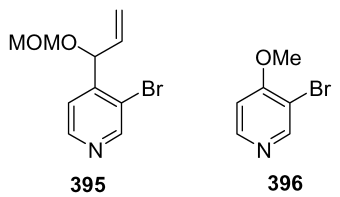


Scheme 119.



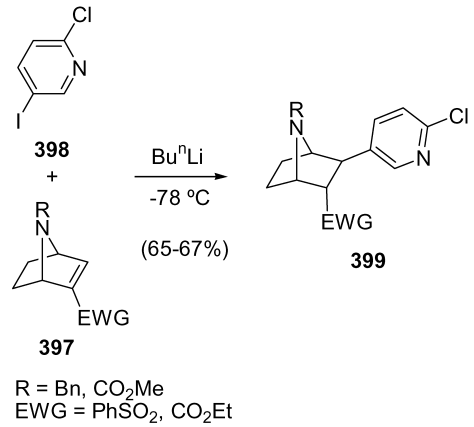
Scheme 120.

The lithium–zinc,[352] lithium–boron[349,353] and lithium–tin[354] transmetallations from 3-lithiopyridine were applied to palladium-catalysed cross-coupling reactions, obtaining mainly the 3-arylpyridines,[352] 3-substituted pyridines[352,349] and azacorannulenes and other heteroaromatic compounds.[355] The bromides **395** and **396** were both successfully treated with *n*-butyllithium at −78°C and DMF to afford the corresponding pyridinecarboxaldehydes in good yields. These compounds were the precursors of hexahydropyrrolo[3,2-*f*]pyrindine, an annulated nicotine analogue,[354] and toddaquinoline, a constituent of many Asian folk medicines,[356] respectively. In the last example, an intramolecular cyclisation of a lithioarene served to form the basic skeleton of the alkaloid.[356]



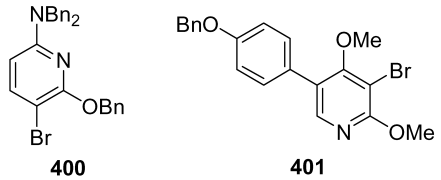
A set of dihalopyridines were selectively lithiated and transformed into the corresponding boronic acids and esters, this work again demonstrating that iodine–lithium exchange is faster than the analogous bromine–lithium exchange, and that iodides and bromides are more reactive than chlorides and fluorides. Finally, for 2,3-dibromopyridine, it was possible to isolate the corresponding 3-pyridylboronic acid in good yields.[357] As a consequence of this survey, 2-chloro-5-iodopyridine (**398**) was used in one of the last steps in the synthesis of the potent analgesic epibatidine (Scheme 121). The generated 5-lithiopyridine derivative reacted with the electrophilic alkene **397** to give the Michael-type adduct **399** in similar yields independently of the electron-withdrawing groups anchored to the molecule (phenylsulfonyl[358] or ethoxycarbonyl[359]groups).

The pyridine **400** was converted into its organolithium derivative and reacted with perbenzylated ribonolactone

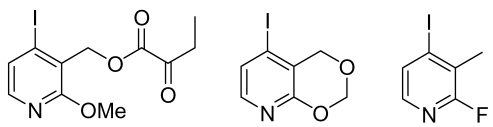


Scheme 121.

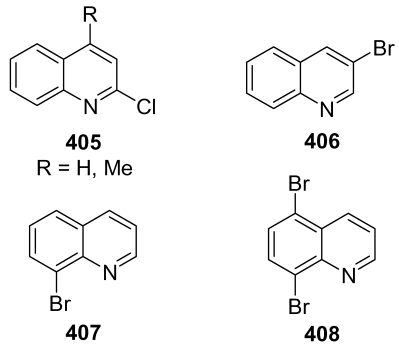
during the total synthesis of 1-deazacytidine, a C-nucleoside analogue of cytidine.[360] The organolithium derived from compound **401** reacted with a conjugated aldehyde to give the carbon skeleton of piridovericin, a protein tyrosine kinase inhibitor.[361]



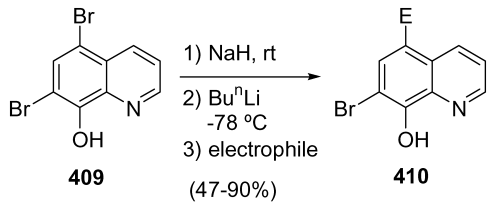
4-Pyridyllithium was nitrated by reaction with dinitrogen tetroxide[50] and was used to obtain bis(heteroaryl)iodonium salts.[350] Perhaps, the main application of this organolithium compound is the lithium–boron exchange, furnishing a wide variety of 4-pyridylboronic acids and esters,[362,363] one of them being a segment of the compound GR-55562, which could act as a partial agonist and neutral 5-HT$_{1B}$ antagonist by chemical modulation.[364] The functionalised 4-iodopyridine **402** (similar to **82**) was lithiated with methyllithium, whereupon an intramolecular 1,2-addition occurred, affording a camptothecin precursor in 57% yield (see Scheme 27). The condensed 1,3-dioxane **403** was prepared for the same purpose, but, in this case, *n*-butyllithium was the lithium source, the electrophile being a chiral ester derived from *trans*-2-(α-cumyl)cyclohexyl alcohol.[365] The organolithium derived from the fluoroiodopyridine **404** was used as building block in the synthesis of the mappicine ketone and (±)-mappicine, which possesses potent activity against herpes-viruses and human citomegalovirus.[366]



2-Functionalised quinolines were obtained upon treatment of the compounds **405** with lithium metal and substoichiometric amounts of naphthalene as the electron carrier, followed by reaction with electrophiles[336] (see Scheme 116). On the other hand, the compounds **406**–**408** were employed in the synthesis of bis(heteroaryl)iodonium salts after bromine–lithium exchange.[350]



The highly regioselective bromine–lithium exchange in 5,7-dibromo-8-hydroxyquinoline (**409**) took place after deprotonation of the phenolic proton and reaction with *n*-butyllithium. The resulting carbanion reacted with several electrophiles in good yields to give the 5-functionalised-7-bromo-8-hydroxyquinolines **410**[367] (Scheme 122). Another selective functionalisation, more sophisticated than that reported previously, occurred in electron-deficient heteroaromatic rings using bromine–tellurium–lithium exchange from 2-bromoquinolines and 1-bromoisoquinolines.[368]

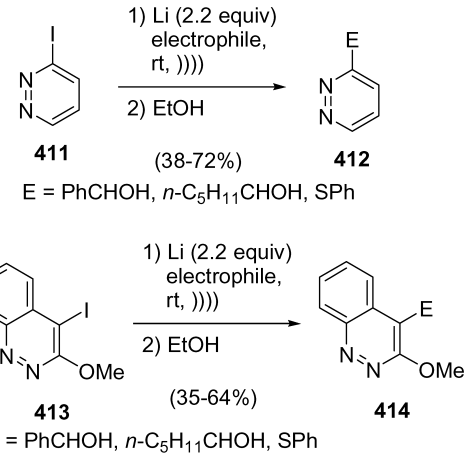


Scheme 122.

3.2.2. Heterocycles containing two or more heteroatoms.

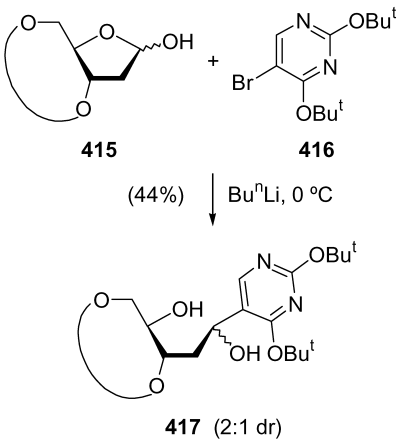
The pyridazines **411** and cinnoline **413** underwent a Barbier-type reaction with lithium metal under sonication, giving a very rapid and smooth functionalisation of these heterocycles obtaining compounds **412** and **414**, respectively[340] (Scheme 123). Analogously, substituted pyrimidines also reacted under the reaction conditions shown in Scheme 116[336] and Scheme 123.[340]

5-Lithiopyrimidines were generated by bromine–lithium exchange (e.g. from the compound **416**) and used in the



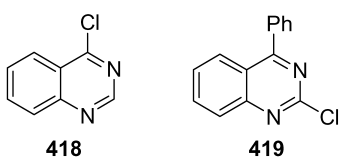
Scheme 123.

synthesis of monoaryl- and bisaryldihydroxytropolones,[321] as well as in the preparation of C-aza-2-deoxy-L-lyxonucleoside **417** by direct addition to the D-erythropentofuranose derivative **415** in moderate yield[369] (Scheme 124). The pyrimidine **416** was also used in the synthesis of various 5-(bromoaryl)-substituted and 5-(3′-aryl)uracils[370,371] in good to excellent yields, after a bromine–lithium–boron exchange and a final Suzuki–Miyaura cross-coupling reaction.



Scheme 124.

Benzocondensed pyrimidines such as the compounds **418** and **419** were suitable starting materials for the regioselective chlorine–tellurium–lithium exchange, their further functionalisation furnishing quinazolines in moderate yields.[368]

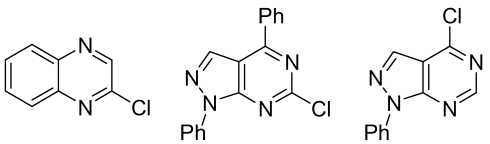


The pyrazines **420** and **421** were regioselectively transformed into their organolithium derivatives following the reaction conditions described in Scheme 116[336] and Scheme 123,[340] respectively, allowing the preparation of functionalised pyrazines in good yields.

420 R = H, Me

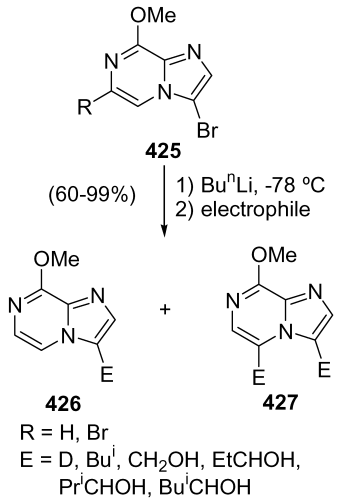
421 (X = H, Cl)

The quinoxaline **422** and pyrazolo[3,4-*d*]pyrimidines **423** and **424** were transformed into the corresponding organolithium intermediates by a chlorine–tellurium–lithium exchange in moderate yields.[368]



422 **423** **424**

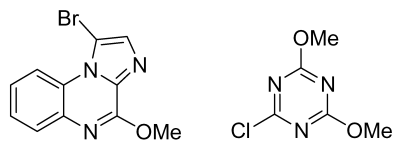
A not-so-regiospecific metallation occurred in the 3-bromoimidazo[1,2-*a*]pyrazine **425**, where two different species **426** and **427** were detected, in proportions depending on the nature of the electrophile. The products **426** were the major components in the final mixture, except when propanal and deuterium chloride were used as the electrophiles, in which case the molecules **427** were the most abundant species[372] (Scheme 125).



425 **426** **427**

Scheme 125.

The *n*-butyllithium-mediated halogen–metal exchange from the imidazo[1,2-*a*]quinoxaline **428**, followed by quenching with electrophiles, was studied. The reaction conditions were optimised and various C-1-substituted imidazo[1,2-*a*]quinoxalines were obtained in high yields.[373] Finally, just one example of the triazine **429** has been reported where the chlorine–lithium exchange was carried out using lithium metal/naphthalene (4 mol%) and the reaction with electrophiles achieved new triazines in modest to good yields.[336]



428 **429**

4. Conclusion

In spite of the known low chemoselectivity of lithium compounds, very reactive aromatic and heteroaromatic organolithiums have not a limited scope. They are easily prepared, the regioselectivity being very high when the halogen–lithium exchange was produced. All of these advantages, together with the fast transmetallation or exchange with other non-metallic species, provide a new synthetic tool for the generation of components in cross-coupling reactions catalysed by transition metal complexes. Many natural product syntheses incorporate an aryllithium as an intermediate step in their course, involving a wide range of Csp^2–Csp^2, Csp^2–Csp^3 and Csp^2–Csp bonds with high efficiency and good yields.

Acknowledgements

We thank the DGES of the Spanish Ministerio de Ciencia y Tecnología (BQU2001-0538 and BQU2001-0724-C-02-01) and Generalitat Valenciana (CTIDIB/2002/318 and CTIOIB/2002/320) for financial support.

References

1. Eisch, J. J. *Organometallics* **2002**, *21*, 5439–5469.
2. (a) Clayden, J. In *Selectivity for Synthesis*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon: Oxford, 2002. (b) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1990. (c) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; 2nd ed. Pergamon: New York, 1990.
3. (a) Massey, A. G. *Main Group Chemistry*. Willey: Chichester, 2000. (b) In *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon: Exeter, 1995.
4. (a) Li, J. J.; Gribble, G. W. *Palladium Heterocyclic Chemistry. A Guide for the Synthetic Chemist*; Pergamon: Amsterdam, 2000. (b) Chauder, B.; Green, L.; Snieckus, V. *Pure Appl. Chem.* **1999**, *8*, 1521–1529. (c) Diederich, F.; Stang, P. J. *Metal Catalyzed Cross-Coupling Reactions*; Wiley: Chichester, 1997.
5. (a) Nájera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867–926. (b) Ardeo, A.; Collado, M. I.; Osante, I.; Ruíz, J.; Sotomayor, N.; Lete, E. *Targets Heterocycl. Syst.* **2001**, *5*, 393–418. (c) Afarinkía, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2025–2046. (d) Coldham, I. *J. Chem. Soc, Perkin Trans. 1* **1998**, 1343–1362. (e) Nájera, C.; Yus, M. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 67–96. (f) Coldham, I. *Contemp. Org. Synth.* **1997**, *4*, 136–163. (g) Wills, M. *Contemp. Org. Synth.* **1996**, *3*, 201–228. (h) Nájera, C.; Yus, M. *Trends Org. Chem.* **1991**, *2*, 155–181. (i) Gray, M.; Tinkl, M.; Snieckus, V. *Comprehensive Organometallic Chemistry II*; Able, E. W., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon: Exeter, 1995; Vol. 11, pp 2–92 Chapter 1.
6. (a) Turk, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489–4505. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059–4090.
7. For precedent reviews, see: (a) Bailey, W. F.; Patricia, J. J.

J. Organomet. Chem. **1998**, *352*, 1–46. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300–305.
8. (a) Ref. 5b–h are complementary material of this review. During the preparation of this manuscript a review concerning the synthesis of some carbocyclic and heterocyclic systems by a metal–halogen exchange methodology was published: (b) Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 1–26.
9. Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975–3984.
10. (a) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420–3425. (b) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 1629–1630.
11. (a) Wiberg, K. B.; Skelenak, S.; Bailey, W. F. *J. Org. Chem.* **2000**, *65*, 2014–2021. (b) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 1414–1416. (c) Jedlicka, B.; Crabtree, R. H.; Siegbahn, P. E. M. *Organometallics* **1997**, *16*, 6021–6023.
12. For recent reviews about arene catalysed lithiations, see: (a) Yus, M. *Synlett* **2001**, 1197–1205. (b) Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2000**, 225–237. (c) Yus, M. *Chem. Soc. Rev.* **1996**, *25*, 155–161.
13. (a) Yus, M.; Herrera, R. P.; Guijarro, A. *Chem. Eur. J.* **2002**, *8*, 2574–2584. (b) Yus, M.; Herrera, R. P.; Guijarro, A. *Tetrahedron Lett.* **2001**, *42*, 3455–3458.
14. Kajiyama, K.; Yoshimune, M.; Nakamoto, M.; Matsukawa, S.; Kojima, S.; Akiba, K. *Org. Lett.* **2001**, *3*, 1873–1875.
15. (a) Wang, B.; Li, R.; Sun, J.; Chen, J. *Chem. Commun.* **1998**, 631–632. (b) Xiao, N.; Zhang, S.; Qiu, Z.; Li, R.; Wang, B.; Xu, X.; Sun, J.; Chen, J. *Organometallics* **2002**, *21*, 3709–3715.
16. Berkovich, E. G.; Lenenco, V. S.; Vyshinskaya, L. I.; Vasil'eva, G. A.; Shur, V. B.; Vol'pin, M. E. *J. Organomet. Chem.* **1997**, *535*, 169–173.
17. Astley, D. K.; Astley, S. T. *J. Organomet. Chem.* **1995**, *487*, 253–255.
18. Chen, J.; Yu, Y.; Sun, J. *Organometallics* **1997**, *16*, 3608–3614.
19. Suzuka, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2002**, *67*, 3355–3359.
20. Ma, X.-B.; Regitz, M. *Synthesis* **1995**, 667–670.
21. Yu, Y.; Chen, J.; Wang, X.; Wu, Q.; Liu, Q. *J. Organomet. Chem.* **1996**, *516*, 81–89.
22. Zhu, B.; Wang, R.; Sun, J.; Chen, J. *J. Chem. Soc., Dalton Trans.* **1999**, 4277–4282.
23. Wang, R.; Sun, J.; Chen, J. *J. Organomet. Chem.* **2001**, *617–618*, 292–300.
24. Yu, Y.; Sun, J.; Chen, J. *J. Organomet. Chem.* **1997**, *533*, 13–23.
25. Zhang, S.; Xu, Q.; Sun, J.; Chen, J. *Organometallics* **2001**, *20*, 2387–2399.
26. Fryzuk, M. D.; Jafarpour, L.; Kerton, F. M.; Love, J. B.; Patrick, B. O.; Rettig, S. J. *Organometallics* **2001**, *20*, 1387–1396.
27. Akiba, K.; Fujishima, H.; Ohtani, A.; Kojima, S.; Yamamoto, Y. *Bull. Soc. Chim. Belg.* **1997**, *106*, 577–584.
28. Brandts, J. A. M.; van Leur, M.; Gossage, R. A.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1999**, *18*, 2633–2641.
29. Gleiter, R.; Schimanke, H.; Silverio, S. J.; Büchner, M.; Huttner, G. *Organometallics* **1996**, *15*, 5635–5640.
30. Schmohl, K.; Reinke, H.; Oehme, H. *Eur. J. Org. Chem.* **2001**, 481–489.
31. Schäfer, H.; Saak, W.; Weidenbruch, M. *Organometallics* **1999**, *18*, 3159–3163.
32. Driess, M.; Pritzkow, H.; Winkler, U. *J. Organomet. Chem.* **1997**, *529*, 313–321.
33. Westermann, J.; Imbery, U.; Nguyen, A. T.; Nickisch, K. *Eur. J. Inorg. Chem.* **1998**, 295–298.
34. Fraenkel, G.; Subramanian, S.; Chow, A. *J. Am. Chem. Soc.* **1995**, *117*, 6300–6307.
35. Wehmschulte, R. J.; Power, P. P. *J. Am. Chem. Soc.* **1997**, *119*, 2847–2852.
36. Ishikawa, T.; Ogawa, A.; Hirao, T. *Organometallics* **1998**, *17*, 5713–5716.
37. Watanabe, S.; Yamamoto, K.; Itagaki, Y.; Iwamura, T.; Iwama, T.; Kataoka, T. *Tetrahedron* **2000**, *56*, 855–863.
38. Kitamura, T.; Kotami, M.; Fujiwara, Y. *Tetrahedron Lett.* **1996**, *37*, 3721–3722.
39. Allen, J. M.; Aprahaiman, S. L.; Sans, E. A.; Shechter, H. *J. Org. Chem.* **2002**, *67*, 3561–3574.
40. Marx, L.; Rassat, A. *Tetrahedron Lett.* **2002**, *43*, 2613–2614.
41. Setayesh, S.; Grimsdale, A. C.; Weil, T.; Enkelmann, V.; Müllen, K.; Meghdadi, F.; List, E. J. W.; Leising, G. *J. Am. Chem. Soc.* **2001**, *123*, 946–953.
42. Jeong, I. H.; Park, Y. S.; Chung, M. W.; Kim, B. T. *Synth. Commun.* **2001**, *31*, 2261–2270.
43. Nishida, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569–8573.
44. Hirabayashi, K.; Kondo, T.; Toriyama, F.; Nishihara, Y.; Mosi, A. *Bull. Chem. Soc. Jpn* **2000**, *73*, 749–750.
45. Müller, P.; Nury, P.; Bernardinelli, G.; Eur, *J. Org. Chem.* **2001**, 4137–4147.
46. Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, *4*, 229–232.
47. Smet, M.; Shukla, R.; Fülöp, L.; Dehaen, W. *Eur. J. Org. Chem.* **1998**, 2769–2773.
48. Chen, C. T.; Chao, S.-D. *J. Org. Chem.* **1999**, *64*, 1090–1091.
49. Chen, C. T.; Chao, S.-D.; Yen, K. C.; Chen, C.-H.; Chou, I.-C.; Hon, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 11341–11342.
50. Koike, N.; Hattori, T.; Takeda, A.; Okaishi, Y.; Miyano, S. *Chem. Lett.* **1997**, 641–642.
51. Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Tetrahedron: Asymmetry* **1999**, *10*, 1847–1850.
52. Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1651–1655.
53. Frey, L. F.; Tillyer, R. D.; Caille, A.-S.; Tschaen, D. M.; Dolling, U. H.; Grabowsky, E. J. J.; Reider, P. *J. Org. Chem.* **1998**, *63*, 3120–3124.
54. Meyers, A. I.; Stoianova, D. *J. Org. Chem.* **1997**, *62*, 5219–5221.
55. Chan, Y.; Berthelette, C. *Tetrahedron Lett.* **2002**, *43*, 4537–4540.
56. (a) Isobe, S.; Kubo, K.; Thiemann, T.; Sawada, T.; Yonemitsu, T.; Mataka, S. *Bull. Chem. Soc. Jpn* **2002**, *75*, 773–779. (b) Nudelman, N.; Schulz, H. *J. Chem. Res., (S)* **1999**, 422–423.
57. Wichai, U.; Woski, S. A. *Org. Lett.* **1999**, *1*, 1173–1175.
58. Stéphan, E.; Affergan, T.; Weber, P.; Jaouen, G. *Tetrahedron Lett.* **1998**, *39*, 9427–9430.
59. Lecomte, V.; Foy, N.; Le Bideau, F.; Stéphan, E.; Jaouen, G. *Tetrahedron Lett.* **2001**, *42*, 5409–5411.
60. Chun, J.; He, L.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7634–7640.

61. Costa, A. V.; Barbosa, L. C. A.; Demuner, A. J.; Silva, A. A. *J. Agric. Food Chem.* **1999**, *47*, 4807–4814.
62. Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1996**, *52*, 14341–14348.
63. Guijarro, D.; Yus, M. *Tetrahedron* **2000**, *56*, 1135–1138.
64. Yanihisawa, H.; Miura, K.; Kitamura, M.; Narasaka, K.; Ando, K. *Helv. Chim. Acta* **2002**, *85*, 3130–3135.
65. Bailey, W. F.; Mealy, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6787–6788.
66. Fernández-Gacio, A.; Mouriño, A. *Eur. J. Org. Chem.* **2002**, 2529–2534.
67. Sashida, H. *Heterocycles* **2000**, *53*, 49–53.
68. Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2002**, *4*, 11–14.
69. Schiemenz, B.; Power, P. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2150–2152.
70. Crittendon, R. C.; Beck, B. C.; Su, J.; Li, X.-W.; Robinson, G. H. *Organometallics* **1999**, *18*, 156–160.
71. Shi, X.; Amin, S. R.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 1650–1664.
72. Baker, L.-J.; Clark, G. R.; Rickard, C. E. F.; Roper, W. R.; Woodgate, S. D.; Wright, L. J. *J. Organomet. Chem.* **1998**, *551*, 247–259.
73. Reich, H. J.; Bevan, M.; Gudmundsson, B. O.; Pucket, C. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 3436–3439.
74. Nitschke, J. R.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10183–10190.
75. Yasuike, S.; Iida, T.; Okajima, S.; Yamaguchi, K.; Seki, H.; Kurita, J. *Tetrahedron* **2001**, *57*, 10047–10053.
76. Geng, Y.; Trajkovska, A.; Katsis, D.; Ou, J. J.; Culligan, S. W.; Chen, S. H. *J. Am. Chem. Soc.* **2002**, *124*, 8337–8347.
77. Wong, K.-T.; Wang, C.-F.; Chou, C. H.; Su, Y. O.; Lee, G.-H.; Peng, S.-M. *Org. Lett.* **2002**, *4*, 4439–4442.
78. Blackmore, I. J.; Boa, A. N.; Murray, E. J.; Dennis, M.; Woodward, S. *Tetrahedron Lett.* **1999**, *40*, 6671–6672.
79. Barret, A. G. M.; de Miguel, Y. R. *Tetrahedron* **2002**, *58*, 3785–3792.
80. Smith, K.; Hou, D. *Sulfur Lett.* **2000**, *23*, 193–207.
81. Kondo, Y.; Komine, T.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Comb. Chem.* **1999**, *1*, 123–126.
82. Tillman, E. S.; Nossarev, G. G.; Thieco, E. *J. Pol. Sci., Part A: Pol. Chem.* **2001**, *39*, 3121–3129.
83. Guiver, M. D.; Dai, Y.; Robertson, G. P.; Lee, K. J.; Jho, J. Y.; Kang, Y. S. *Pol. Mat. Sci. Eng.* **2001**, 85–94.
84. Lepoittevin, B.; Hemery, P. *Pol. Adv. Technol.* **2002**, 10–12.
85. Quirk, R. P.; Mathers, R. T.; Cregger, T.; Foster, M. D. *Macromolecules* **2002**, *35*, 9964–9974.
86. Menoret, S.; Fontanille, M.; Deffieux, A.; Desbois, P. *Polymer* **2002**, *43*, 7077–7083.
87. Hirao, A.; Haraguchi, N. *Macromolecules* **2002**, *35*, 7224–7231.
88. Uhrig, D.; Mays, J.-W. *Macromolecules* **2002**, *35*, 7182–7190.
89. Quirk, R. P.; Gomochak, D. L.; Wesdemiotis, C.; Arnould, M. A. *Pol. Mat. Sci. Eng.* **2002**, *87*, 160–161.
90. Verheiden, H.; van Lierde, P.; Szarc, M.; Lituinenco, G.; van Beilen, M. *J. Pol. Sci., Part A:Pol. Chem.* **2002**, *40*, 2148–2157.
91. Tillman, E. S.; Hogen-Esch, T. E. *J. Pol. Sci., Part A:Pol. Chem.* **2002**, *40*, 1081–1091.
92. Hirao, A.; Kawano, H.; Ryn, S. W. *Pol. Adv. Technol.* **2002**, *13*, 275–284.
93. Quirk, R. P.; Mathers, R. T.; Wesdemiotis, C.; Arnould, M. A. *Macromolecules* **2002**, *35*, 2912–2918.
94. Li, J.; Gauthier, M. *Macromolecules* **2001**, *34*, 8918–8924.
95. Loykulnant, S.; Hirao, A. *Macromolecules* **2002**, *34*, 8434–8445.
96. Tillman, E. S.; Nossarev, G. G.; Hogen-Esch, T. E. *J. Pol. Sci., Part A: Pol. Chem.* **2001**, *39*, 3121–3129.
97. Tillman, E. S.; Hogen-Esch, T. E. *Macromolecules* **2001**, *34*, 6616–6622.
98. Knauss, D. M.; Al-Muallem, H. A. *J. Pol. Sci., Part A: Pol. Chem.* **2000**, *38*, 4289–4298.
99. Ryn, S. W.; Hirao, A. *Macromolecules* **2000**, *33*, 4765–4771.
100. Quirk, R. P.; Lee, Y. *J. Pol. Sci., Part A: Pol. Chem.* **2000**, *38*, 145–151.
101. Hirao, A.; Hayashi, M. *Macromolecules* **1999**, *32*, 6450–6460.
102. Liu, S.; Zhang, G.; Jiang, M. *Polymer* **1999**, *40*, 5449–5453.
103. Hayashi, M.; Kojima, K.; Hirao, A. *Macromolecules* **1999**, *32*, 2425–2433.
104. Desbois, P.; Fontanille, M.; Deffieux, A.; Warzelhan, V.; Laetsch, S.; Schade, C. *Macromol. Chem. Phys.* **1999**, *200*, 621–628.
105. Se, K.; Kudoh, S. *J. Appl. Pol. Sci.* **1999**, *71*, 2039–2048.
106. Kim, J.; Kwak, S.; Kim, K. U.; Kim, K. H.; Cho, J. C.; Jo, W. H.; Lim, D.; Kim, D. *Macromol. Chem. Phys.* **1998**, *199*, 2185–2191.
107. Bywater, S. *Macromolecules* **1998**, *31*, 6010–6013.
108. Cho, J. C.; Kim, K. H.; Kim, K. U.; Kwak, S.; Kim, J.; Jo, W. H.; Chun, M. S.; Lee, C. H.; Yeo, J. K.; Quirk, R. P. *J. Pol. Sci., Part A: Pol. Chem.* **1998**, *36*, 1743–1753.
109. Natori, I.; Inoue, S. *Macromolecules* **1998**, *31*, 4687–4694.
110. Summers, G. J.; Quirk, R. P. *J. Pol. Sci., Part A: Pol. Chem.* **1998**, *36*, 1233–1241.
111. Quirk, R. P.; Lizárraga, G. M. *Macromolecules* **1998**, *31*, 3424–3430.
112. Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Tzschucke, C. C. *Org. Lett.* **2001**, *3*, 33–36.
113. Curran, D. P.; Yang, F.; Cheong, J. *J. Am. Chem. Soc.* **2002**, *124*, 14993–15000.
114. Gómez, C.; Huerta, F. F.; Yus, M. *Tetrahedron* **1998**, *54*, 1853–1866.
115. Azzena, U.; Carta, S.; Melloni, G.; Sechi, A. *Tetrahedron* **1997**, *53*, 16205–16212.
116. Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem. Eur. J.* **2002**, *8*, 2034–2046.
117. Sugihura, K.; Ushiroda, K.; Tanaka, T.; Sawada, M.; Sakata, Y. *Chem. Lett.* **1997**, 927–928.
118. Spring, D. R.; Krishnan, S.; Blacwell, H. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354–1363.
119. Przezdziecka, A.; Kurek-Tyrlik, A.; Wicha, J. *Coll. Czech. Chem. Commun.* **2002**, *67*, 1658–1668.
120. Zhdankin, V. V.; Persichini, P. J., III; Zhang, L.; Fix, S.; Kiprof, P. *Tetrahedron Lett.* **1999**, *40*, 6705–6708.
121. Warren, S.; Wyatt, P.; McParthin, M.; Woodroffe, T. *Tetrahedron Lett.* **1996**, *37*, 5609–5612.
122. (a) Toyota, K.; Kawasaki, S.; Yoshifuji, M. *Tetrahedron Lett.* **2002**, *43*, 7953–7959. (b) Powell, M. T.; Porte, A. M.; Reibenspies, J.; Burgess, K. *Tetrahedron* **2001**, *57*, 5027–5038.
123. Hirai, Y.; Nagaoka, H. *Tetrahedron Lett.* **1997**, *38*, 1969–1970.

124. Huang, Y.; Hammond, P. S.; Wu, L.; Mach, R. H. *J. Med. Chem.* **2001**, *44*, 4404–4415.
125. Roussel, F.; Takhi, M.; Schmidt, R. R. *J. Org. Chem.* **2001**, *66*, 8540–8548.
126. Thibault, M. E.; Pacarynuk, L. A.; Closson, T. L. L.; Dibble, P. W. *Tetrahedron Lett.* **2001**, *42*, 789–791.
127. Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13–15.
128. Lampe, J. W.; Giggers, C. K.; Defuw, J. M.; Foglesong, R. J.; Hall, S. E.; Heerding, J. M.; Hollinshead, S. P.; Hu, H.; Hughes, P. F.; Jagdmann, G. E., Jr.; Johnson, M. G.; Lai, Y.-S.; Lowden, C. T.; Lynch, M. P.; Mendoza, J. S.; Murphy, M. M.; Wilson, J. W.; Ballas, L. M.; Carter, K.; Darges, J. W.; Davis, J. E.; Hubbard, F. R.; Stamper, M. L. *J. Med. Chem.* **2002**, *45*, 2624–2643.
129. (a) Huerta, F. F.; Gómez, C.; Yus, M. *Tetrahedron* **1999**, *55*, 4043–4050. (b) Arnauld, T.; Barret, A. G. M.; Hopkins, B. T. *Tetrahedron Lett.* **2002**, *43*, 1081–1083.
130. Sommer, R. D.; Rheingold, A. L.; Goshe, A. J.; Bosnich, B. *J. Am. Chem. Soc.* **2001**, *123*, 3940–3952.
131. Hon, Y.-S.; Lee, C.-F.; Chen, R.-J.; Szu, P.-H. *Tetrahedron* **2001**, *57*, 5991–6001.
132. Nakamura, S.; Oda, M.; Yasuda, H.; Torn, T. *Tetrahedron* **2001**, *57*, 8469–8480.
133. Maier, C. A.; Wünsch, B. *J. Med. Chem.* **2002**, *45*, 438–448.
134. Kumagai, T.; Itsuno, S. K. *Tetrahedron: Asymmetry* **2001**, *12*, 2509–2516.
135. Itsuno, S.; Kumagai, T. *Helv. Chim. Acta* **2002**, *85*, 3185–3196.
136. Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. *J. Am. Chem. Soc.* **2001**, *123*, 1817–1821.
137. Harmata, M.; Wu, Y.; Kahraman, M.; Welch, C. J. *Synth. Commun.* **2001**, *31*, 3345–3359.
138. Sonawane, H. R.; Maji, D. K.; Jana, G. H.; Pandey, G. *Chem. Commun.* **1998**, 1773–1774.
139. Wünsch, B.; Nerdinger, S. *Eur. J. Org. Chem.* **1998**, 711–718.
140. Braslou, R.; Anderson, M. O. *Tetrahedron Lett.* **1998**, *39*, 4227–4230.
141. Furneaux, R. H.; Limberg, G.; Tyler, P. C. *Tetrahedron* **1997**, *53*, 2915–2930.
142. (a) Kato, S.; Nonoyama, N.; Tomimoto, K.; Mase, T. *Tetrahedron Lett.* **2002**, *43*, 7315–7317. (b) Laufer, R. S.; Dmitrenko, G. I. *J. Am. Chem. Soc.* **2002**, *124*, 1854–1855.
143. Plobeck, N.; Delorme, D.; Wei, Z.-Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. H.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. *J. Med. Chem.* **2000**, *43*, 3878–3894.
144. Hoffmann, M.; Kessler, H. *Tetrahedron Lett.* **1997**, *38*, 1903–1906.
145. Deniau, E.; Enders, D. *Tetrahedron Lett.* **2002**, *43*, 8055–8058.
146. Okada, K.; Tanaka, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2704–2711.
147. Comanita, B. M.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1999**, *40*, 5283–5286.
148. Reich, H. J.; Goldenberg, W. S.; Gudmunson, B. O.; Sanders, A. W.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067–8079.
149. Steenwinkel, P.; Kooijman, H.; Smeets, W. J. J.; Spek, A. L.; Grove, D. M.; van Koten, G. *Organometallics* **1998**, *17*, 5411–5426.
150. Janssen, M. D.; Corsten, M. A.; Spek, A. L.; Grove, D. M.; van Koten, G. *Organometallics* **1996**, *15*, 2810–2820.
151. Belzner, J.; Schär, D.; Herbst-Irmer, R.; Kneisel, B. O.; Noltemeyer, M. *Tetrahedron* **1998**, *54*, 8481–8500.
152. Kleij, A. W.; Kleijn, H.; Jastrzebski, J. T. B. H.; Smeets, W. J. J.; Speck, A. L.; van Koten, G. *Organometallics* **1999**, *18*, 268–276.
153. Zhong, Z.; Anslyn, E. V. *J. Am. Chem. Soc.* **2002**, *124*, 9014–9015.
154. Gómez, C.; Huerta, F. F.; Yus, M. *Tetrahedron Lett.* **1997**, *38*, 687–690.
155. Gómez, C.; Ruíz, S.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1397–1400.
156. Gómez, C.; Ruíz, S.; Yus, M. *Tetrahedron* **1999**, *55*, 7017–7026.
157. Minoura, M.; Sagami, T.; Akiba, K.; Modrakowski, C.; Sudau, A.; Seppelt, K.; Wallenhauer, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2660–2662.
158. Steinhuebel, D. P.; Fleming, J. J.; Du Bois, J. *Org. Lett.* **2002**, *4*, 293–295.
159. (a) Molander, G. A.; Köllner, C. *J. Org. Chem.* **2000**, *65*, 8333–8339. (b) Ding, B.; Teng, Z.; Keese, R. *J. Org. Chem.* **2002**, *67*, 8906–8910.
160. Shimada, T.; Kurushima, H.; Cho, Y.-H.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 8854–8858.
161. Brown, J. M.; Pérez-Torrente, J. J. *Organometallics* **1995**, *14*, 1195–1203.
162. (a) Nudelman, N. S.; García, G. V. *J. Org. Chem.* **2001**, *66*, 1387–1394. (b) Nudelman, N. S.; Schulz, H. G.; García, G. V. *J. Phys. Org. Chem.* **1998**, *11*, 1–9.
163. Lysen, M.; Kristensen, J. L.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2002**, *4*, 257–259.
164. Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 9658–9667.
165. Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2001**, *42*, 7501–7502.
166. Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177–179.
167. Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377–3380.
168. Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454–1458.
169. Dankwardt, J. W. *J. Org. Chem.* **1998**, *63*, 3753–3755.
170. Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, *4*, 787–790.
171. Yus, M.; Foubelo, F.; Ferrández, J. V. *Chem. Lett.* **2002**, 726–727.
172. Vicario, J. L.; Badía, D.; Carrillo, L.; Anakabe, E. *Tetrahedron: Asymmetry* **2002**, *13*, 745–751.
173. Reetz, M. T.; Pastó, M. *Tetrahedron Lett.* **2000**, *41*, 3315–3317.
174. Rippert, A. J.; Linden, A.; Hansen, H.-J. *Helv. Chim. Acta* **2000**, *83*, 311–321.
175. Kadyrov, R.; Heinicke, J.; Kindermann, M. K.; Heller, D.; Fischer, C.; Selke, R.; Fischer, A. K.; Jones, P. G. *Chem. Ber./Recueil* **1997**, *130*, 1663–1670.
176. Deskns, J.; Fan, D.; Smith, M. B. *Synth. Commun.* **1998**, *28*, 1649–1655.
177. Lai, C.-H.; Lin, P.-Y.; Peddinti, R. K.; Liao, C.-C. *Synlett* **2002**, 1520–1522.

178. Popova, I. S.; Formanovsky, A. A.; Mikhura, I. V.; Shemyakin, M. M.; Yu, A. *Russ. Chem. Bull.* **2002**, *51*, 540–543.
179. Saednya, A.; Hart, H. *Synthesis* **1996**, 1455–1458.
180. Azzolina, O.; Collina, S.; Brusotti, G.; Rossi, D.; Callegari, A.; Linati, L.; Barbieri, A.; Ghislandi, V. *Tetrahedron: Asymmetry* **2002**, *13*, 1073–1081.
181. Smith, D. W., Jr.; Babb, D. A.; Shah, H. V.; Hoeglund, A.; Traiphol, R.; Perahia, D.; Boone, H. W.; Langhoff, C.; Radler, M. *J. Fluorine Chem.* **2002**, *104*, 109–117.
182. Gómez-Escalonilla, M. J.; Langa, F.; Rueff, J. M.; Oswald, L.; Nierengarten, J.-F. *Tetrahedron Lett.* **2002**, *43*, 7507–7511.
183. Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2000**, *41*, 5211–5214.
184. Plotkin, M.; Chen, S.; Spoors, P. G. *Tetrahedron Lett.* **2000**, *41*, 2269–2273.
185. (a) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Org. Lett.* **2002**, *4*, 2225–2228. (b) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 2791–2793.
186. Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C.; Trabada, M. *Org. Lett.* **2002**, *4*, 1587–1590.
187. Weyermann, P.; Diederich, F. *Helv. Chim. Acta* **2002**, *85*, 599–617.
188. Morgan, A. B.; Jurs, J. L.; Tour, J. M. *J. Appl. Pol. Sci.* **2000**, *76*, 1257–1268.
189. Tan, Y.-L.; White, A. J. P.; Widdowson, D. A.; Wilhelm, R.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3269–3280.
190. Sugimura, T.; Kurita, S.-Y.; Inoue, S.; Fujita, M.; Okuyama, T.; Tai, A. *Enantiomer* **2001**, *6*, 35–42.
191. Yamashita, M.; Yamamoto, Y.; Akiba, K.; Nagase, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4055–4058.
192. Park, J. W.; Ediger, M. D.; Green, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 49–56.
193. Manickam, G.; Schlüter, A. D. *Eur. J. Org. Chem.* **2000**, 3475–3481.
194. Jew, S.-S.; Kim, H.-A.; Kim, J.-H.; Park, H.-G. *Heterocycles* **1997**, *46*, 65–70.
195. Chordia, M. D.; Yuan, H.; Jagtap, P. G.; Kadow, J. F.; Long, B. H.; Fairchild, C. R.; Johnston, K. A.; Kingston, D. G. I. *Bioorg. Med. Chem.* **2001**, *9*, 171–178.
196. Kaiser, F.; Schwiink, L.; Velder, J.; Schmalz, H. G. *J. Org. Chem.* **2002**, *67*, 9248–9256.
197. Aketami, S.; Tanaka, K.; Yamamoto, K.; Ishiyama, A.; Cao, H.; Tengeiji, A.; Hiraoka, S.; Shiro, M.; Shionoya, M. *J. Med. Chem.* **2002**, *45*, 5594–5603.
198. Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899–5904.
199. Rigolet, S.; McCort, I.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 8129–8132.
200. Simas, A. B. C.; Coelho, A. L.; Costa, P. R. R. *Synthesis* **1999**, 1017–1021.
201. Léo, P.-M.; Morin, C.; Philouze, C. *Org. Lett.* **2002**, *4*, 2711–2714.
202. Tsoungas, P. G.; Searcey, M. *Tetrahedron Lett.* **2001**, *42*, 6589–6592.
203. Harrowven, D. C.; Hannam, J. C. *Tetrahedron Lett.* **1998**, *39*, 9573–9574.
204. Morihiraa, K.; Nishimoria, T.; Kusamaa, H.; Horiguchia, Y.; Kuwahimaa, I.; Tsuruob, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2973–2976.
205. Nicolaou, K. C.; Koide, K.; Bunnage, M. E. *Chem. Eur. J.* **1995**, *1*, 454–466.
206. Quideau, S.; Lebon, M.; Lamidey, A.-M. *Org. Lett.* **2002**, *4*, 3957–3978.
207. Ramacciotti, A.; Fiaschi, R.; Napolitano, E. *Tetrahedron: Asymmetry* **1996**, *7*, 1101–1104.
208. Mehta, G.; Islam, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2396–2398.
209. Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607–3617.
210. Hudlicky, T.; Rinner, U.; González, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726–8743.
211. Kato, Y.; Niiyama, K.; Jona, H.; Okada, S.; Akao, A.; Hiraga, S.; Tsuchiya, Y.; Tomimoto, K.; Mase, T. *Chem. Pharm. Bull.* **2002**, *50*, 1066–1072.
212. Song, Z. J.; Zhao, M.; Frey, L.; Li, J.; Tan, L.; Chen, C. Y.; Tschaen, D. M.; Tillyer, R.; Grabowski, E. J. J.; Volante, R.; Reider, P. J.; Kato, Y.; Okada, S.; Nemoto, T.; Sato, H.; Akao, A.; Mase, T. *Org. Lett.* **2001**, *3*, 3357–3360.
213. Evans, D.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411–12413.
214. Knölker, H.-J.; Fröhner, W.; Wagner, A. *Tetrahedron Lett.* **1998**, *39*, 2947–2950.
215. Knölker, H.-J.; Fröhner, W. *Synlett* **1997**, 1108–1109.
216. Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624–6628.
217. Kao, C.-L.; Chern, J.-W. *Tetrahedron Lett.* **2001**, *42*, 1111–1113.
218. Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772–6787.
219. Wünsch, B.; Nerdinger, S.; Höfner, G. *Liebigs Ann.* **1995**, 1303–1312.
220. Orito, K.; Miyazawa, M.; Suginome, H. *Tetrahedron* **1995**, *51*, 2489–2496.
221. Barrero, A. F.; Álvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tetrahedron Lett.* **1998**, *39*, 2425–2428.
222. Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290–1296.
223. Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229–3246.
224. Katoh, T.; Ohmori, O.; Iwasaki, K.; Inoue, M. *Tetrahedron* **2002**, *58*, 1289–1299.
225. Kozikowski, A. P.; Tückmantel, W.; Hu, Y. *J. Org. Chem.* **2001**, *66*, 1287–1296.
226. Bungard, C. J.; Morris, J. C. *Org. Lett.* **2002**, *4*, 631–633.
227. Schlosser, M.; Geneste, H. *Tetrahedron* **1998**, *54*, 10119–10124.
228. Shi, H.; Liu, H.; Bloch, R.; Mandville, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1423–1428.
229. Fukatsu, K.; Fujii, N.; Ohkawa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1521–1526.
230. Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143–10144.
231. Takao, K.; Sasaki, T.; Kozaki, T.; Yanagisawa, T.; Yanagisawa, Y.; Tadano, K.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291–4294.
232. Katoh, T.; Ohmori, O. *Tetrahedron Lett.* **2000**, *41*, 465–469.
233. Tatsuta, K.; Nakano, S.; Narazaki, F.; Nakamura, Y. *Tetrahedron Lett.* **2001**, *42*, 7625–7628.
234. Roush, W. R.; Madar, D. J.; Coffey, D. S. *Can. J. Chem.* **2001**, *79*, 1711–1726.

235. Roush, W. R.; Coffey, D. S. *J. Org. Chem.* **1995**, *60*, 4412–4418.
236. Brimble, M. A.; Elliot, R. J. R. *Tetrahedron* **2002**, *58*, 183–189.
237. Cox, C.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2899–2902.
238. Uno, H.; Sakamoto, K.; Honda, E.; Fukuhara, K.; Ono, N.; Tanaka, J.; Sakanaka, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 229–238.
239. Vedejs, E.; Zajac, M. A. *Org. Lett.* **2001**, *3*, 2451–2454.
240. Vedejs, E.; Wang, J. *Org. Lett.* **2000**, *2*, 1031–1032.
241. Vedejs, E.; Barda, D. A. *Org. Lett.* **2000**, *2*, 1033–1035.
242. Irwin, J. L.; Sherburn, M. S. *Org. Lett.* **2001**, *3*, 225–227.
243. Barret, E. S.; Irwin, J. L.; Turner, P.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 8227–8229.
244. Larsen, M.; Jørgensen, M. *J. Org. Chem.* **1996**, *61*, 6651–6655.
245. Larsen, M.; Krebs, F. C.; Jørgensen, M.; Harrit, N. *J. Org. Chem.* **1998**, *63*, 4420–4424.
246. Shearer, J. M.; Rokita, S. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 501–504.
247. Jolivet, C.; Rivalle, C.; Bisagni, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 511–515.
248. Kelly, T. R.; Cavero, M. *Org. Lett.* **2002**, *4*, 2653–2656.
249. Stanetty, P.; Krumpak, B.; Rodler, I. K. *J. Chem. Res. (S)* **1995**, *9*, 342–343.
250. Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synlett* **1999**, 945–947.
251. Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594–2595.
252. Bailey, W. F.; Jiang, X.-L. *J. Org. Chem.* **1996**, *61*, 2596–2597.
253. Bailey, W. F.; Carson, M. W. *Tetrahedron Lett* **1997**, *38*, 1329–1332.
254. Jensen, J.; Tejler, J.; Wärnmark, K. *J. Org. Chem.* **2002**, *67*, 6008–6014.
255. Yamashita, M.; Kamura, K.; Yamamoto, Y.; Akiba, K. *Chem. Eur. J.* **2002**, *8*, 2976–2979.
256. Kozlecki, T.; Syper, L.; Wilk, K. A. *Synthesis* **1997**, 681–684.
257. Kano, N.; Komatsu, F.; Kawashima, T. *Chem. Lett.* **2001**, 338–339.
258. Foy, N.; Stéphan, E.; Jaouen, G. *Tetrahedron Lett.* **2000**, *41*, 8089–8092.
259. (a) Maspoch, D.; Catalá, L.; Gerbier, P.; Ruíz-Molina, D.; Vidal-Gancedo, J.; Wurst, K.; Rovira, C.; Veciana, J. *Chem. Eur. J.* **2002**, *8*, 3635–3645. (b) Shultz, D. A.; Gwaltney, K. P.; Lee, H. *J. Org. Chem.* **1998**, *63*, 769–774.
260. Becker, D. P.; Li, H.; Flynn, D. L. *Synth. Commun.* **1996**, *26*, 3127–3135.
261. Reetz, M. T.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083–4085.
262. Liu, Y.; Stringfellow, T. C.; Ballweg, D.; Guzei, I. A.; West, R. *J. Am. Chem. Soc.* **2002**, *124*, 49–57.
263. Matsuura, A.; Nishinaga, T.; Komatsu, K. *Tetrahedron Lett.* **1997**, *38*, 4125–4128.
264. Nishinaga, T.; Inoue, R.; Matsuura, A.; Komatsu, K. *Org. Lett.* **2002**, *4*, 1435–1438.
265. Leroux, F.; Schlosser, M. *Angew. Chem., Int. Ed.* **2002**, 4272–4274.
266. Radl, S.; Hezky, P.; Taimr, J.; Krejci, I. *J. Heterocycl. Chem.* **1999**, *36*, 1017–1022.
267. Yoon, K.; Son, D. Y. *Macromolecules* **1999**, *32*, 5210–5216.
268. Schmittel, M.; Ganz, A.; Fenske, D. *Org. Lett.* **2002**, *4*, 2289–2292.
269. Kendall, J. K.; Engler, T. A.; Shechter, H. *J. Org. Chem.* **1999**, *64*, 4255–4266.
270. Zhao, D.; Xu, F.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron* **1999**, *55*, 6001–6018.
271. Tamborski, C.; Chen, L. S. *J. Fluorine Chem.* **1995**, *75*, 117–120.
272. Bo, Z.; Schlüter, A. D. *J. Org. Chem.* **2002**, *67*, 5327–5332.
273. Mongin, F.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2771–2777.
274. Lee, Y.; Silverman, R. B. *Tetrahedron* **2001**, *57*, 5339–5352.
275. Kottsieper, K. W.; Kühner, U.; Stelzer, O. *Tetrahedron: Asymmetry* **2001**, *12*, 1159–1169.
276. Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Demontis, S.; Fattuoni, C.; Melis, S. *Tetrahedron* **2002**, *58*, 4529–4533.
277. Yus, M.; Foubelo, F.; Ferrández, J. V. *Tetrahedron Lett.* **2002**, *43*, 7205–7207.
278. Zhao, D.; Xu, F.; Chen, C.; Tillier, R. D.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron* **1999**, *55*, 6001–6018.
279. Tan, L.; Chen, C.; Chen, W.; Frey, L.; King, A. O.; Tillyer, R. D.; Xu, F.; Zhao, D.; Grabowski, E. J. J.; Reider, P. J.; O'Shea, P.; Dagneau, P.; Wang, X. *Tetrahedron* **2002**, *58*, 7403–7410.
280. Lamrani, M.; Hamasaki, R.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 2499–2501.
281. Guillaneaux, D.; Kagan, H. B. *J. Org. Chem.* **1995**, *60*, 2502–2505.
282. Chieffi, A.; Comasseto, J. V.; Snieckus, V. *Synlett* **2000**, 269–271.
283. Hua, D. H.; Lagneau, N. M.; Chen, Y.; Robben, P. M.; Clapham, G.; Robinson, P. D. *J. Org. Chem.* **1996**, *61*, 4508–4509.
284. Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893–2899.
285. Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511–3514.
286. Koide, H.; Uemura, M. *Chem. Commun.* **1998**, 2483–2484.
287. Clark, A. M.; Rickard, C. E. F.; Roper, W. R.; Wright, L. J. *Organometallics* **1998**, *17*, 4535–4537.
288. Berthiaume, S. L.; Bray, B. L.; Hess, P.; Liu, Y.; Maddox, M. L.; Muchowski, J. M.; Scheller, M. E. *Can. J. Chem.* **1995**, *73*, 675–684.
289. Koike, T.; Shinohara, Y.; Nishimura, T.; Hagiwara, M.; Tobinaga, S.; Takeuchi, N. *Heterocycles* **2000**, *53*, 1351–1359.
290. Groenendaal, L.; Pieterse, K.; Vekemans, J.; A, J. M.; Meijer, E. W. *Synth. Commun.* **1997**, *27*, 257–266.
291. Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574–9579.
292. Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207–208.
293. Katritzky, A. R.; Xie, L. *J. Org. Chem.* **1995**, *60*, 3707–3710.
294. Herbert, J. M.; Maggiani, M. *Synth. Commun.* **2001**, *31*, 947–951.
295. Merlic, C. A.; McInnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 7661–7664.
296. Merlic, C. A.; McInnes, D. M.; You, Y. *Tetrahedron Lett.* **1997**, *38*, 6787–6790.
297. Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277–7280.
298. Della Sala, G.; Capozzo, D.; Izzo, I.; Giorgano, A.;

Iommazzo, A.; Spinella, A. *Tetrahedron Lett.* **2002**, *43*, 8839–8841.
299. Pirrung, M. C.; Li, Z.; Park, K.; Zhu, J. *J. Org. Chem.* **2002**, *67*, 7919–7926.
300. Hoerrner, R. S.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 3455–3458.
301. Amat, M.; Hadida, S.; Sathyanarayana, S.; Bosch, J. *Org. Synth.* **1997**, *74*, 248–256.
302. Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2002**, *67*, 5850–5853.
303. Amat, M.; Seffar, F.; Llor, N.; Bosch, J. *Synthesis* **2001**, 267–275.
304. Kawasaki, I.; Katsuma, H.; Nakayama, Y.; Yamashita, M.; Ohta, S. *Heterocycles* **1998**, *48*, 1887–1901.
305. Claridge, T. D. W.; Long, J. M.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron* **1997**, *53*, 4035–4050.
306. Liu, Y.; Gribble, G. W. *Tetrahedron Lett.* **2002**, *43*, 7135–7137.
307. Carbonelle, A.-C.; González-Zamora, E.; Beaugelmans, R.; Roussi, G. *Tetrahedron Lett.* **1998**, *39*, 4467–4470.
308. Graña, P.; Paleo, M. R.; Sardina, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 12511–12514.
309. Chen, X.-T.; Gutteridge, C. E.; Bhattcharya, S. K.; Zhou, B.; Pettus, T. R. R.; Hascall, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 185–187.
310. Okamura, H.; Yamauchi, K.; Miyawaki, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1997**, *38*, 263–266.
311. Watanabe, H.; Onoda, T.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 2545–2548.
312. Müller, M.; Schröder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **1998**, *39*, 4655–4656.
313. Furuichi, N.; Hata, T.; Soetjipto, H.; Kato, M.; Katsumura, S. *Tetrahedron* **2001**, *57*, 8425–8442.
314. Hui, C. W.; Lee, H. K.; Wong, N. C. *Tetrahedron Lett.* **2002**, *43*, 123–126.
315. Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477–12487.
316. Kaelin, D. E.; López, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937–6938.
317. Arroyo, Y.; Rodríguez, J. F.; Sanz-Tejedor, A.; Santos, M. *Tetrahedron Lett.* **2002**, *43*, 9129–9132.
318. Harada, K.; Tonoi, Y.; Kato, H.; Fukuyama, Y. *Tetrahedron Lett.* **2002**, *43*, 3829–3832.
319. Kanoh, N.; Ishihara, J.; Yamamoto, Y.; Murai, A. *Synthesis* **2000**, 1878–1893.
320. Álvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. *Tetrahedron* **1996**, *52*, 4065–4078.
321. Piettre, S. R.; André, C.; Chanal, M.-C.; Ducep, J.-B.; Lesur, B.; Piriou, F.; Raboisson, P.; Rondeau, J. M.; Schelcher, C.; Zimmermann, P.; Ganzhorn, A. J. *J. Med. Chem.* **1997**, *40*, 4208–4221.
322. Soós, T.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **1999**, *40*, 8607–8609.
323. Coppola, G. M.; Damon, R. E.; Yu, H. *J. Heterocycl. Chem.* **1996**, *33*, 687–696.
324. Albers, W. M.; Canters, G. W.; Reedijk, J. *Tetrahedron* **1995**, *51*, 3895–3904.
325. van Hal, P. A.; Beckers, E. H. A.; Meskers, S. C. J.; Janssen, R. A. J.; Jousselme, B.; Blanchard, P.; Roncali, J. *Chem. Eur. J.* **2002**, *8*, 5415–5429.
326. Zhang, Y.; Hoernfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 435–444.
327. Chong, I. C.; Lew, W.; Lee, D.; Pham, P.; Burdett, M. T.; Lam, J. W.; Wiesmann, C.; Luong, T. N.; Fahr, B.; Delano, W. L.; McDowell, R. S.; Allen, D. A.; Erlanson, D. A.; Gordon, E. M.; O'Brien, T. *J. Med. Chem.* **2002**, *45*, 5005–5022.
328. Michaelides, M. R.; Hong, Y.; DiDomenico, S., Jr.; Bayburt, E. K.; Asin, K. E.; Britton, D. R.; Lin, C. W.; Shiosaki, K. *J. Med. Chem.* **1997**, *40*, 1585–1599.
329. Vidal, P.-L.; Divisia-Brohorn, B.; Bidan, G.; Hazemann, J.-L.; Kern, J. M.; Sauvage, J.-P. *Chem. Eur. J.* **2000**, *6*, 1663–1673.
330. Uchida, K.; Takata, A.; Nakamura, S.; Irie, M. *Chem. Lett.* **2002**, 476–477.
331. Spagnolo, P.; Zaniato, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 963–964.
332. Balle, T.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1999**, *64*, 5366–5370.
333. Swaleh, S.; Liebscher, J. *J. Org. Chem.* **2002**, *67*, 3184–3193.
334. Bach, T.; Heuser, S. *J. Org. Chem.* **2002**, *67*, 5789–5795.
335. Takami, S.; Kawai, T.; Irie, M. *Eur. J. Org. Chem.* **2002**, 3796–3800.
336. Gómez, I.; Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **2000**, *56*, 4043–4052.
337. Lützen, A.; Hapke, M. *Eur. J. Org. Chem.* **2002**, 2292–2297.
338. Wakabayashi, S.; Sugihara, Y.; Takakura, K.; Murata, S.; Tomioka, H.; Ohnishi, S.; Tatsumi, K. *J. Org. Chem.* **1999**, *64*, 6999–7008.
339. Bhasin, K. K.; Venugolapan, P.; Singh, J. Phosphorous. *Sulfur, Silicon Relat Elem* **2002**, *177*, 2579–2587.
340. Lepêtre, A.; Turk, A.; Plé, N.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 3709–3715.
341. Yokohama, M.; Toyoshima, H.; Shimizu, M.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 29–33.
342. Mongin, F.; Trécourt, F.; Mongin, O.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 309–314.
343. Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1781–1782.
344. Wang, X.; Rabbat, P.; O'Shea, P.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 4335–4338.
345. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885–2890.
346. Yao, Y.; Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 2805–2810.
347. Bull, S. D.; Davies, S. G.; Fox, D. J.; Gianotti, M.; Kelly, P.-P.; Pierres, C.; Savory, E. D.; Smith, A. D. *J. Chem. Soc., Prekin Trans. 1* **2002**, 1858–1868.
348. Cai, D.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537–2540.
349. Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 4285–4287.
350. Stang, P.; Olenyuk, B. *Synthesis* **1995**, 937–938.
351. Romanelli, M. N.; Manetti, D.; Scapecchi, S.; Borea, P. A.; Dei, S.; Bartolini, A.; Ghelardini, C.; Gualtieri, F.; Guandalini, L.; Varani, K. *J. Med. Chem.* **2001**, *44*, 3946–3955.
352. Simkovsky, N. M.; Ermann, M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1847–1849.
353. Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394–5397.
354. Zhai, H.; Liu, P.; Luo, S.; Fang, F.; Zhao, M. *Org. Lett.* **2002**, *4*, 4385–4386.
355. Dix, I.; Doll, C.; Hopf, H.; Jones, P. G. *Eur. J. Org. Chem.* **2002**, 2547–2556.

356. Harrowven, D. C.; Nunn, M. I. T.; Blumire, N. J.; Fenwick, D. R. *Tetrahedron* **2001**, *57*, 4447–4454.
357. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 3323–3328.
358. Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3689–3697.
359. Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760–768.
360. Sollogoub, M.; Fox, K. R.; Powers, V. E. C.; Brown, T. *Tetrahedron Lett.* **2002**, *43*, 3121–3223.
361. Baldwin, J. E.; Adlington, R. M.; Conte, A.; Irlapati, N. R.; Márquez, R.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 2125–2127.
362. Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 4369–4373.
363. Coudret, C. *Synth. Commun.* **1996**, *26*, 3543–3547.
364. Lamothe, M.; Panwels, P. J.; Belliard, K.; Schambel, P.; Halazy, S. *J. Med. Chem.* **1997**, *40*, 3542–3550.
365. Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255–4257.
366. Comins, D. L.; Saha, J. K. *J. Org. Chem.* **1996**, *61*, 9623–9624.
367. Mongin, F.; Fourquez, J. M.; Rault, S.; Levacher, V.; Godard, A.; Trécourt, F.; Quéguiner, G. *Tetrahedron Lett.* **1995**, *36*, 8415–8418.
368. Sugimoto, O.; Sudo, M.; Tanji, K. *Tetrahedron* **2001**, *57*, 2133–2138.
369. Yokoyama, M.; Ikeue, T.; Ochiai, Y.; Momokate, A.; Yamaguchi, K.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2185–2188.
370. Wellmar, U.; Hoernfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1995**, *32*, 1159–1163.
371. Wellmar, U.; Hoernfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1996**, *33*, 409–414.
372. Vitse, O.; Bompart, J.; Subra, G.; Viols, H.; Escale, R.; Chapat, J. P.; Bonnet, P. A. *Tetrahedron* **1998**, *54*, 6485–6496.
373. Parra, S.; Vitse, O.; Benezech, V.; Deleuze-Masquefa, C.; Subra, G.; Bompart, J.; Escale, R.; Chapat, J. P.; Bonnet, P. A. *J. Heterocycl. Chem.* **2001**, *38*, 41–44.

Biographical sketch

Carmen Nájera was born in Nájera (La Rioja) in 1951 and was graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), at the Dyson Perrins Laboratory (Oxford), at Harvard University and at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante, where she is currently the head of the Organic Chemistry Department. She is co-author of more than 150 papers, her current research interest being focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis, palladium-catalysed reactions and peptide coupling reagents.

José Miguel Sansano was born in Rojales (Alicante), Spain in 1965. He studied chemistry at the University of Alicante where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. After spending a two years postdoctoral stay at the University of Leeds (UK) he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. His current research interests include asymmetric synthesis, sulfones, amino acids and organometallic chemistry.

Miguel Yus was born in Zaragoza in 1947. He received the B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoct at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to the University of Oviedo where he became Associate Professor in 1977, being promoted to full Professor in 1987 at the same university. In 1988 he moved to a chair in organic chemistry at the University of Alicante. Professor Yus has been visiting professor at different institutions such as ETH-Zürich and the universities at Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris VI and Strasbourg. He is member or fellow of the chemical societies of Argentina, England, Germany, Japan, Spain, Switzerland, and United States. He is co-author of more than 300 papers mainly in the field of the development of new methodologies involving organometallic intermediates in synthetic organic chemistry. Among others, he has recently received the Spanish-French Prize (1999), the Japan Society for the Promotion of Science Prize (2000) and the Stiefvater Memorial Lectureship Award (2001).