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Directed aromatic functionalization

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Editorial

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Guest Editor: V. Snieckus

The title of this Thematic Series brings to the minds of most organic chemists the beautifully logical aromatic electrophilic substitution (S_EAr) [1-5] and, to a lesser extent, nucleophilic aromatic substitution (S_NAr) [2,6,7] reactions as taught to many generations of students in their first organic chemistry courses [8] (Figure 1). Being less steeped in history, radical nucleophilic substitution ($S_{RN}1$) [9] and vicarious nucleophilic substitution (VNS) [10-12], in spite of their considerable synthetic utility, are given sparse mention. By the time students reach the upper years of study, aromatic chemistry receives the label “classical” and is disregarded or relegated to brief coverage. Apart from in English schools [13], heteroaromatic chemistry suffers the same fate. As a consequence, a fresh graduate entering the pharmaceutical industry, who invariably faces a complex aromatic or heteroaromatic as his or her first target molecule, is either lost or must grope around with insufficient background knowledge.

Since the late 1970s, over thirty years since the independent discoveries by Gilman and Wittig, the directed *ortho* metalation (DoM) reaction has trickled into the armamentarium of the synthetic chemist (but not significantly into textbooks [8,14]), as a general and rational strategy for the construction of polysubstituted aromatics and heteroaromatics [15-17]. While comparison with S_EAr and S_NAr should never be denied, the DoM approach offers incontestable *ortho* regioselectivity, mild conditions, and perhaps most significantly, broad post-DoM synthetic potential. As a result, it has been called upon, with increasing favor and frequency, by academic and medicinal chemists for small-scale synthesis and by process chemists for multi-kilogram scale routes for clinical candidates and commercial pharmaceuticals and agrochemicals [18-24].

Once an aryl metal species was available by DoM and metal–halogen exchange or metal insertion, the gates of the syn-

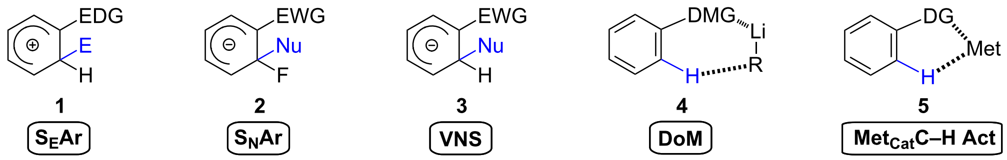

Figure 1: Directed aromatic functionalization methods.

thetic arena were spectacularly opened to the 2010 Nobel Prize chemistry and the general theme of transition metal-catalyzed reactions. Thus, the named reactions of Kumada–Corriu, Negishi, Suzuki–Miyaura, Stille and, most recently, Hiyama have all given new insights into how sp, sp^2, and sp^3, and –O, –N, and –S bonds are made to the aromatic ring carbon [25]. These strategies rapidly furnish biaryls/heterobiaryls, and condensed complex aromatics/heteroaromatics whose construction by previous generation methods (e.g., diazonium and radical coupling) has been clearly superseded by these venerable reactions [26,27] especially to the benefit of the medicinal and process chemist [28].

The currently lively area of metal-catalyzed C–H activation reactions (which has an early history but which commanded our attention by the publication of the Murai monograph [29,30]) is also causing a revolution in how we think about the preparation of aromatic/heteroaromatic molecules. Here, conceptually similar to the complex-induced proximity effect (CIPE) [31], which is operational in DoM reactivity, chelation of heteroatom groups to transition metals may be invoked, with an important exception [32-34], to rationalize *ortho* selectivity. The aromatic ring annulative chemistry, which can be achieved by C–H-activation mediated processes, perhaps best exemplified by gold-catalyzed reactions [35,36], is astonishing and defies retrosynthetic analysis. While as yet mostly empirically derived, mechanistically inadequately defined, and practically untested, the C–H activation methodologies will compete with, supersede, and replace our existing practices in synthetic aromatic chemistry in the next decade.

Perhaps of interest to the in-depth reader of this Thematic Series are a number of other methods for the synthesis of polysubstituted aromatics which are scattered, poorly systematized, and therefore underappreciated and primed for future reviews [37-46].

What else is on the aromatic chemistry horizon? Within the area of DoM (and related metal–halogen exchange) chemistry, alternative and competitive combinational metal amide bases are rapidly appearing [47,48]. The first successful glimpses of the much sought after complementary, cleaner, regiodefined, and milder procedures to *ortho, para* versus *meta* S_EAr reactions are being seen in Cu-catalyzed *meta*-selective reactions [49,50]. The fleeting benzyne species, representing aromatic 1,2-dipole reactivity, is experiencing a renaissance due to milder and dependable methodologies for its generation [51,52]. Somewhat akin to $S_{RN}1$ and, to a lesser extent VNS, the Minisci radical aromatic substitution chemistry [53] requires supplementary contemporary synthetic work in order to vigorously test its viability. The prospect of metal-catalyzed dehydrogenative conversion of cycloalkanes to aromatics as new source of aromatic feedstocks is also on the immediate horizon [54].

In this Thematic Series, you will find a fine assortment of forefront contributions in the field of manipulation and modification of aromatic compounds. Since it is a “moving” Series, my introductory comments required synchronization in order to adequately reflect the breadth of the contributions.

A cornucopia of reports, representative of the subject areas described above, demonstrates the current activity in aromatic chemistry. For example, the DoM reaction as applied to the construction of molecules of value for asymmetric synthesis is nicely presented by Rob Britton; lithiation chemistry in service of heterocyclic synthesis and modification is clearly demonstrated by the work of Jonathan Clayden, Jacques Mortier and Keith Smith; the major influence of DoM tactics are comprehensively demonstrated by the review of Marco Ciufolini; the new wave of very useful magnesiation and zincation is developed by Paul Knochel and Roberto Sanz; a hint of the potential of *meta* metalation by mixed metal/amide bases is posited by Robert Mulvey; and the application of such base combinations for the ready construction of planar chiral metacyclophanes is delightfully revealed by Donal O’Shea; striking evidence of the power of aryl metal species, derived from metal–halogen exchange, for transition metal-catalyzed cross-coupling reactions towards biaryl synthesis is furnished by Frederic Leroux; the next generation of heteroaromatic functionalization through C–H activation may be gleaned from the review of the Rouen group presented by Christophe Hoarau. From the breadth of topic coverage, you will see that the “moving” Thematic Series covers a modern “moving” field.

I hope that the taste of topics covered vis-à-vis the above generalizations will stimulate the palate for the preparation of future Thematic Series highlighting progress in synthetic aromatic chemistry. My wish is that you will find the chemistry in this Thematic Series to your interest and utility, and hence read past the graphical abstract. I thank authors and all coauthors for their meticulously prepared contributions for which it has been my privilege to serve as editor.

Kingston, August 2011

Victor Snieckus

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A simple and convenient one-pot synthesis of substituted isoindolin-1-ones via lithiation, substitution and cyclization of *N′*-benzyl-*N,N*-dimethylureas

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Full Research Paper

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Abstract

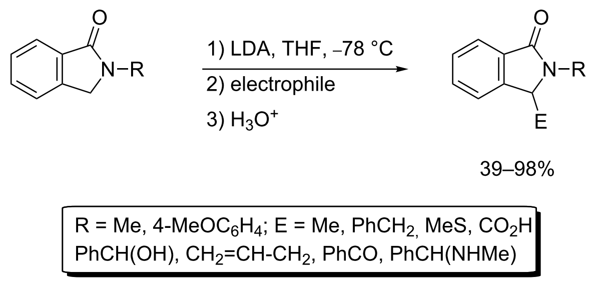
Lithiation of *N′*-benzyl-*N,N*-dimethylurea and its substituted derivatives with *t*-BuLi (3.3 equiv) in anhydrous THF at 0 °C followed by reaction with various electrophiles afforded a range of 3-substituted isoindolin-1-ones in high yields.

Introduction

In recent years there has been a great deal of interest in compounds possessing an isoindolinone ring system since it represents the core unit of numerous naturally occurring substances [1-8]. Also, some members that possess this moiety have shown interesting biological properties [9-15].

Several traditional methods are available for the synthesis of isoindolinones [16-25], based on the use of Grignard reagents [26], Diels–Alder reactions [27], Wittig reagents [28], reduction processes [29,30], rearrangement processes [31] and photochemical reactions [32,33]. However, such methods generally require multiple reaction steps and are unsatisfactory both in yield and generality. In recent years several new approaches have been developed for the synthesis of substituted isoindolines, of which the most generally useful involve palladium-catalysed reactions [34-42] or lithiation procedures [43-54].

In particular, among the various lithiation methods two useful approaches to the synthesis of isoindolin-1-ones have been reported (Scheme 1 and Scheme 2) [43,45]. One method simply involves lithiation of a preformed isoindolin-1-one ring system at the 3-position followed by treatment with an electrophile (Scheme 1) [43]. While this approach is straightforward, clearly, its general utility depends on the availability of appropriately substituted analogues of the isoindolin-1-one ring system.

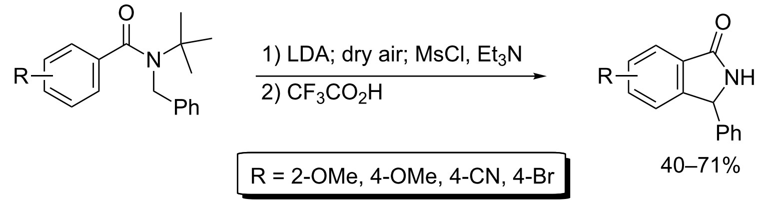


Scheme 1: Lithiation and substitution of isoindolin-1-ones [43].

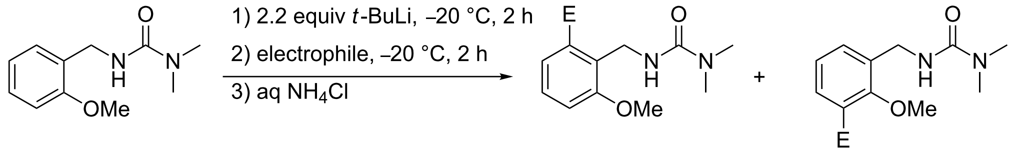
The other, potentially more useful approach involves generation of the heterocyclic ring system during the lithiation step. For example, lithiation of *N*-*tert*-butyl-*N*-benzylbenzamides gives intermediates that cyclise to form de-aromatised species. Oxidation to re-aromatise the benzenoid system, followed by treatment with trifluoroacetic acid to remove the *tert*-butyl group, gives the corresponding isoindolin-1-ones (Scheme 2) [45]. However, this approach gives more modest yields, requires an additional step to remove the *tert*-butyl group, and also involves incorporating the eventual C-3 substituent into the starting material, which limits the generality. Moreover, the reaction works well only with 3-aryl substituents.

Clayden has improved the yield of isoindolin-1-ones by using 2-methoxybenzamides as the starting materials; in this case the methoxy group acts as a leaving group, which avoids the need for an oxidation step [45]. However, this approach still requires an additional step to remove the *tert*-butyl group and incorporation of the 3-substituent into the starting material.

As a result of our own interest in the use of lithium reagents in organic synthesis [55-67], we have had occasion to investigate lithiation of various aromatic compounds containing substituted amino groups. Factors that influence the site(s) of lithiation of such compounds can be quite subtle. For example, lithiation of *N*,*N*-dimethyl-*N′*-(substituted phenyl)ureas can occur predominantly on the *N*,*N*-dimethyl group (e.g., for the unsubstituted, 4-methyl or 4-methoxy-compounds with *t*-BuLi at −20 °C) or on the ring next to the urea group (e.g., for the 4-chloro-, 4-fluoro- or 4-trifluoromethyl compounds with either *n*-BuLi or *t*-BuLi at 0 °C) [59]. However, a recent report indicates that replacement of the dimethylamino group by a more hindered dialkylamino group in the unsubstituted phenyl derivative results in lithiation on the ring [68]. We have also developed procedures for the lithiation of various substituted benzylamines [69-71]. Similar subtleties over the site(s) of lithiation are also observed for these compounds. The site(s) of lithiation depend on the substituents at nitrogen, the nature and positions of substituents on the aryl ring and/or on the nature of the lithium reagent. For example, lithiation of *N*-benzylpivalamide with *t*-BuLi gives a mixture of ring (2-position) and side-chain lithiated species, whereas for *N′*-benzyl-*N,N*-dimethylurea side-chain lithiation does not occur [69]. Of particular relevance for the present study was the observation that lithiation of *N′*-(2-methoxybenzyl)-*N,N*-dimethylurea (**1**) with two equivalents of *t*-BuLi in THF at −20 °C for 2 h followed by reactions with a range of electrophiles gave mixtures of products (Scheme 3) involving ring substitution both next to the urea-containing group (*o*-substitution; 47–51% yields) and next to the methoxy group (*o*'-substitution; 38–40% yields) [69]. Formation of **2** and **3** presumably involved lithium intermediates **4** and **5**, respectively (Figure 1).



Scheme 2: Lithiation and cyclization of *N*-*tert*-butyl-*N*-benzylbenzamides [45].



1

2 (47–51%)

3 (38–40%)

Scheme 3: Lithiation and substitution of **1** at −20 °C [69].

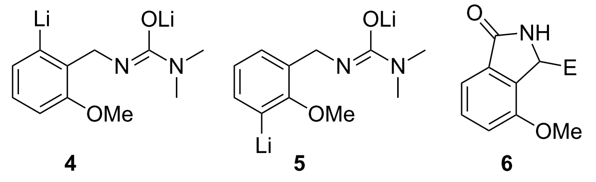


Figure 1: Structures of **4–6**.

We found that when the lithiation reaction was carried out at 0 °C rather than at −20 °C, followed by reaction with an electrophile, it produced lower yields of the corresponding substituted products **2** and **3**, along with some residual **1** and a small amount of a new product of structure **6** (Figure 1). By increasing the amount of lithiating agent and extending the period of the lithiation reaction, we were able to increase the yield of **6**, and in a preliminary communication we reported that directed lithiation of various *N′*-benzyl-*N,N*-dimethylureas with *t*-BuLi (3.3 equiv) in anhydrous THF at 0 °C followed by reaction with various electrophiles afforded the corresponding 3-substituted isoindolin-1-ones in high yields [72]. We now report full details of that work, extend the scope of the reaction and examine the diastereoselectivity of the reaction with prochiral electrophiles.

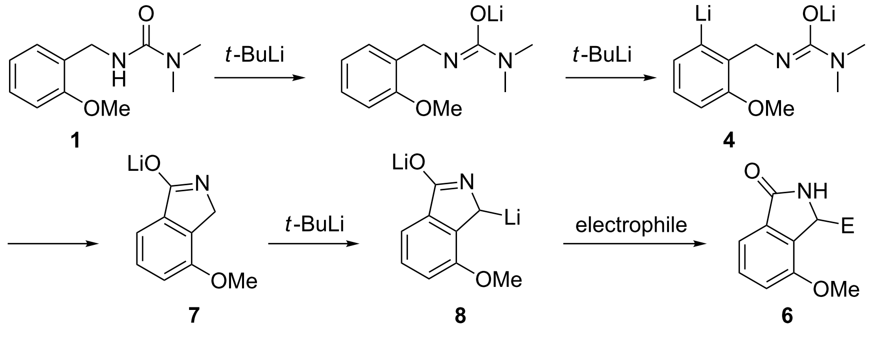
Results and Discussion

As noted above, when lithiation of **1** was carried out at 0 °C rather than at −20 °C prior to reaction with an electrophile, lower yields of **2** and **3** along with some residual **1** and a small amount of **6** were obtained. A possible mechanism for the formation of **6** is shown in Scheme 4. According to this scheme, compounds of the general structure **6** would arise by cyclization of **4** to give **7**, followed by further lithiation to give **8**, which on reaction with an electrophile would give **6**. It appeared likely that the yield of **6** could be increased by use of a larger quantity of *t*-BuLi and an extended reaction time; therefore, we investigated this possibility.

Indeed, lithiation of **1** with *t*-BuLi (3.3 equiv) in anhydrous THF at 0 °C for 6 h, followed by treatment with iodomethane, gave **9** (i.e., **6**, where E = Me) in 79% yield (Table 1). While an increased yield of **6** (E = Me, i.e., **9**, produced from **7**) and the disappearance of **2** (produced from **4**) were expected, the disappearance of **3** (produced from **5**) was a surprise. It would appear that at 0 °C, not only did **4** cyclize to give **7**, but **5** was also in equilibrium with **4**, allowing its eventual conversion into **7** and then **8**.

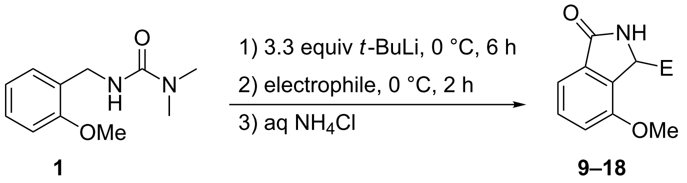
This fortuitous finding appeared to offer potential as a general synthetic method and the same lithiation procedure was therefore used with a range of other electrophiles including other haloalkanes, water, symmetrical and unsymmetrical ketones, and aldehydes. After work-up of the reaction mixtures, the crude products were triturated and/or washed with diethyl ether to give products **10–18** in high yields (Table 1).

From the results recorded in Table 1, it appeared that the reaction was a general process for production of 3-substituted 4-methoxyisoindolin-1-ones **9–18** in high yields from reactions with a variety of electrophiles. The identity of the ring system was confirmed by the crystallization of **12** and subjecting it to X-ray crystallography (Figure 2). All the products were analysed by standard spectroscopic methods and showed, for example, the expected molecular ions in their mass spectra. Compounds **10–14** were readily identified by their NMR spectra, which showed all the expected signals. In the ^{1}H NMR spectra of compounds **10** and **11**, the expected diastereotopicity of the two hydrogens of the CH_2 groups closest to the ring was evident. For compound **13** the two phenyl groups appeared as separated signals in the ^{13}C NMR spectrum, verifying that they were also diastereotopic, and similarly, the two sides of the cyclohexane ring in compound **14** also appeared as separated signals. The NMR spectra of products **15–18** were relatively complex. Therefore, in order to get further information about these products, they were each crystallized from ethyl acetate. The ^{1}H NMR spectra of the



Scheme 4: A possible mechanism for the formation of **6**.

Table 1: Synthesis of 3-substituted 4-methoxyisoindolin-1-ones **9–18**.

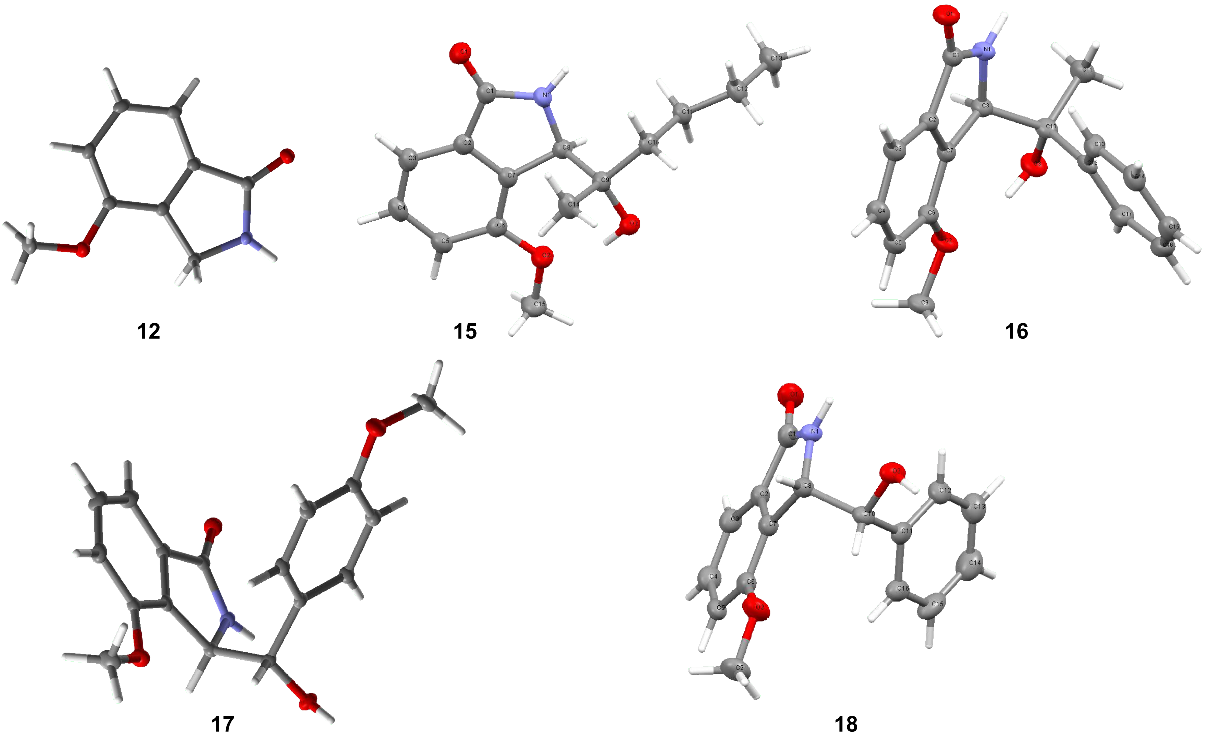


Product	Electrophile	E	Yield (%)[a]
9	MeI	Me	79
10	EtI	Et	84
11	BuBr	Bu	72
12	H_2O	H	82
13	Ph_2CO	$Ph_2C(OH)$	81
14	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	78
15	BuCOMe	BuC(OH)Me	78
16	PhCOMe	PhC(OH)Me	80
17	$4\text{-}MeOC_6H_4CHO$	$4\text{-}MeOC_6H_4CH(OH)$	81
18	PhCHO	PhCH(OH)	80

[a]Yield of material isolated by washing or triturating the crude product with diethyl ether.

crystallized materials showed what appeared to be a single component in each case. The crystalline products were therefore subjected to X-ray crystallography. The structures found are illustrated in Figure 2.

The X-ray crystal structures of the isolated crystals of products **15**, **17** and **18** showed that they were α-(*R**)-3-(*S**)-diastereoisomers, while that of **16** showed that it was the α-(*R**)-3-(*R**)-diastereoisomer (Figure 2). With this information in hand, the


12 15 16

17 18

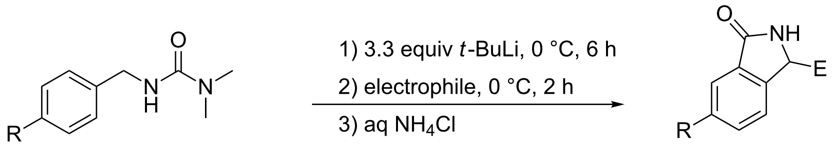
Figure 2: X-Ray crystal structures of crystallized compounds **12** and **15–18**.

NMR spectra of the initial products obtained by trituration or washing of the original crude products were re-examined. These spectra showed the presence of the crystallized product and a second component, the identifiable resonances of which were consistent with the other diastereoisomer. The two diastereoisomers were present in nearly equal proportions (between 47:53 and 42:58), with the α-(*R**)-3-(*R**)-diastereoisomer being the somewhat predominant diastereoisomer in all cases.

We have shown previously that lithiation of *N′*-benzyl-*N,N*-dimethylurea and *N′*-(4-substituted benzyl)-*N,N*-dimethylureas with *t*-BuLi (two equiv) in THF at −78 °C for 4 h followed by reactions with a variety of electrophiles gave high yields of products involving substitution at the 2-position [69]. Therefore, it was of interest to investigate further the scope of the process represented in Table 1 with other ring-substituted *N′*-benzyl-*N,N*-dimethylureas **19** (R = H, 4-OMe, 4-Me; Table 2). Each substrate was lithiated according to the standard procedure with *t*-BuLi (3.3 equiv) in anhydrous THF at 0 °C for 6 h, and then treated with various electrophiles. After work-up, as described above, the substituted isoindolin-1-ones **20–40** were obtained in high yields (Table 2).

The ^{1}H NMR spectra of compounds **22–24**, **29–31** and **35–38** showed diastereotopicity features similar to those for compounds reported in Table 1. The NMR spectra of **25**, **26**, **32**, and **38–40** showed the presence of two racemic diastereoisomers in unequal proportions (up to ca. 38:62). However, the NMR spectra of the products after crystallization from ethyl acetate all exhibited one set of signals, indicating that the isolated crystalline product in each case was a single racemic diastereoisomer. X-ray crystallography of the isolated crystals of compounds **38** and **39** showed them to be the α-(*R**)-3-(*R**)-diastereoisomers (Figure 4). The ^{1}H NMR spectra of the isolated

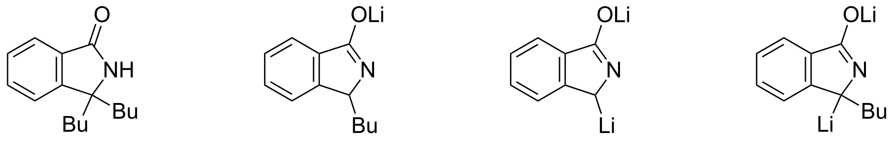
Table 2: Synthesis of various substituted isoindolin-1-ones **20–40**.



19 **20–40**

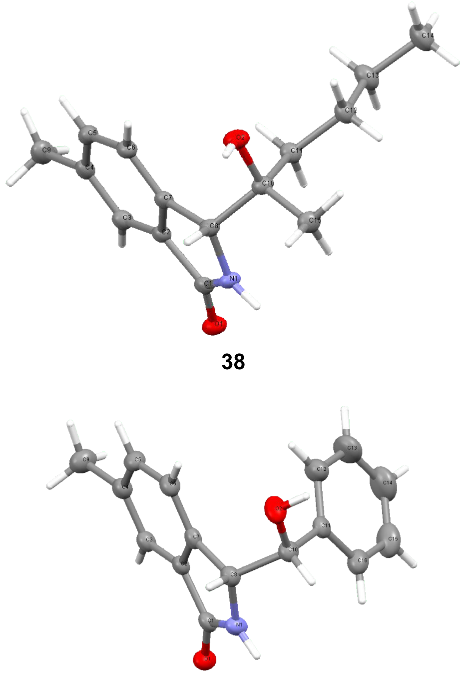
Product	R	Electrophile	E	Yield (%)^a
20	H	H_2O	H	71
21	H	MeI	Me	75
22	H	EtI	Et	77
23	H	BuBr	Bu	76^b
24	H	Ph_2CO	$Ph_2C(OH)$	74
25^c	H	PhCHO	PhCH(OH)	73
26^d	H	4-MeOC_6H_4CHO	$4\text{-MeOC}_6H_4CH(OH)$	78
27	OMe	H_2O	H	70
28	OMe	MeI	Me	76
29	OMe	EtI	Et	78
30	OMe	BuBr	Bu	77
31	OMe	Ph_2CO	$Ph_2C(OH)$	72
32^c	OMe	4-MeOC_6H_4CHO	$4\text{-MeOC}_6H_4CH(OH)$	75
33	Me	H_2O	H	75
34	Me	MeI	Me	78
35	Me	EtI	Et	75
36	Me	$(CH_2)_5C{=}O$	$(CH_2)_5C(OH)$	72
37	Me	Ph_2CO	$Ph_2C(OH)$	85
38^e	Me	MeCOBu	MeC(OH)Bu	77
39^e	Me	PhCHO	PhCH(OH)	79
40^d	Me	4-MeOC_6H_4CHO	$4\text{-MeOC}_6H_4CH(OH)$	83

[a] Yield of product isolated by trituration or washing of the initial reaction mixture with diethyl ether. [b] Compound **41** (Figure 3) was obtained in 5% yield. [c] The ^{1}H NMR spectrum of the solid after crystallization showed the structure to be the α-(*R**)-3-(*R**)-isomer. [d] The ^{1}H NMR spectrum of the solid after crystallization showed the structure to be the α-(*R**)-3-(*S**)-isomer. [e] X-Ray crystallography showed the product isolated by crystallization to be the α-(*R**)-3-(*R**)-isomer (Figure 4).



41 **42** **43** **44**

Figure 3: Structures of compounds **41**–**44**.



38

39

Figure 4: X-ray crystal structures of compounds **38** and **39**.

crystalline products **26**, **32** and **40** indicated that the crystals were α-(*R**)-3-(*S**)-diastereoisomers, while the ^{1}H NMR spectrum of the crystallized product **25** showed it to be α-(*R**)-3-(*R**)-isomer. With the help of the NMR spectra of the crystallized diastereoisomers, re-examination of the spectra of the materials obtained by simple trituration or washing of the original crude product allowed calculation of the proportions of the two diastereoisomers and in all cases the major diastereoisomer was again the α-(*R**)-3-(*R**)-isomer, as was the case when 2-methoxybenzyl-*N,N*-dimethylurea was the starting material.

Compound **41** (Figure 3) was obtained as a side product in 5% yield when 1-bromobutane was used as the electrophile. Compound **41** arose due to further lithiation at position 3 of **42**, produced in situ from **43**, to generate the lithium intermediate **44** (Figure 3). Reaction of the latter with a further equivalent of 1-bromobutane affords **41**.

Conclusion

We have developed a novel, simple, efficient, general and high yielding procedure for synthesis of isoindolin-1-ones in a one-step reaction. It allows easy addition of a range of substituents to the initial benzene ring and incorporation of a range of substituents derived from the electrophiles used. Isolation of the pure products is also extremely easy, involving simple trituration and/or washing of the crude product after work up, except in the cases where two diastereoisomers are produced. In such cases the α-(*R**)-3-(*R**)-isomer is somewhat predominant (ratios of ca. 47:53 to 38:62); crystallization of these mixtures produces one pure diastereoisomer in all cases. The method promises to be a very useful new approach for synthesis of substituted isoindolin-1-ones.

Experimental

General information

Melting point determinations were performed by the open capillary method with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 or AV500 spectrometer at 400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C measurements. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. ^{13}C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra (see Supporting Information File 1) were recorded on a Quattro II spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) at 50 eV by the use of NH_3 as ionization gas. Atmospheric pressure chemical ionization (APCI) mass spectra were measured on a Waters LCT Premier XE instrument. Electrospray (ES) analyses were performed on a ZQ4000 spectrometer in positive and negative ionisation modes. Accurate mass data were obtained on a MAT900 instrument. IR spectra (see Supporting Information File 1) were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer or a Perkin Elmer 1600 series FT-IR spectrometer. Microanalyses for representative compounds were performed by Warwick analytical service at the University of Warwick. The

X-ray single-crystal diffraction data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K_α, ($\lambda = 0.71073$ Å) radiation. Crystal and structure refinement data are shown in the Supporting Information File 1. The structures were solved by direct methods using SHELXS-96 [73] and refined with all data on F^2 full-matrix least squares using SHELXL-97 [74]. Non-hydrogen atoms were generally refined anisotropically. Hydrogen atom positions were located from difference Fourier maps and a riding model with atomic displacement parameters 1.2 times (1.5 times for methyl groups) those of the atom to which they are bonded were used for subsequent refinements. Full crystallographic data have been deposited with the CCDC, reference numbers 737411 (compound **12**), 762624 (compound **15**), 766180 (compound **16**), 737415 (compound **17**), 762623 (compound **18**), 766182 (compound **38**) and 766181 (compound **39**), and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif. Alkyl lithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham [75]. Other reagents and starting materials were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl.

General procedure for the synthesis of 3-substituted isoindolin-1-ones 9–18 and 20–40. A solution of *t*-BuLi in heptane (3.9 mL, 1.7 M, 6.6 mmol) was added to a cold (0 °C), stirred solution of *N'*-(substituted benzyl)-*N,N*-dimethylurea (**1** or **19**; 2.0 mmol) in anhydrous THF (20 mL) under a N_2 atmosphere. Formation of the monolithium reagent was observed as a yellow solution and the dilithium reagent was observed as a reddish orange solution, after which the colour changed to deep red. The mixture was stirred at 0 °C for 6 h after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at 0 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was triturated with diethyl ether (20 mL) to give a white solid which was filtered and washed with diethyl ether (20 mL) to give the pure product. The solid obtained was recrystallized from ethyl acetate. Some of the products were previously reported and in these cases the melting point and the spectral data were in agreement with reported values. Of those compounds that had not been reported previously, representative examples were subjected to microanalysis, and in all cases gave analyses consistent with the assigned structures. For other compounds, therefore, proof of purity was established by a combination of tlc (single spot), sharp melting point and clean NMR spectra. Elemental composition of a molecular ion or pseudo molecular ion confirmed the formula.

Supporting Information

Supporting Information File 1

Characterization data of all compounds given in the article and NMR spectra and X-ray information for representative compounds. CCDC 737411, 737415, 762623, 762624, 766180, 766181 and 766182.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-142-S1.pdf]

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Selectivity in *C*-alkylation of dianions of protected 6-methyluridine

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Full Research Paper

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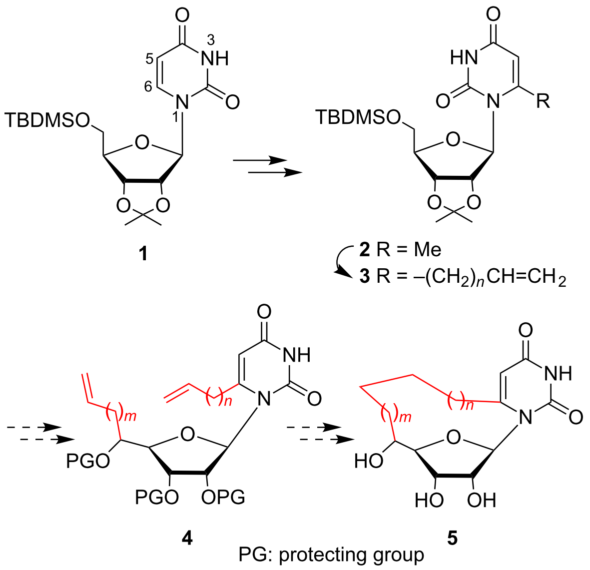
Abstract

A regioselective synthesis of 6-ω-alkenyluridines **3**, precursors of potent antiviral and antitumor cyclonucleosides **5**, is described. While ω-alkenyl halides do not alkylate 6-lithiouridine, compounds **3** were prepared in a regioselective manner by sequential treatment of 6-methyluridine **2** with LTMP or LDA (4 equiv) in THF at −30 °C followed by alkylation with ω-alkenyl bromides.

Introduction

Conformationally restricted C–C bridged cyclonucleosides bearing a linkage between the sugar moiety and the nucleobase, exhibit a broad spectrum of antiviral and antitumor activities [1-4]. Cyclonucleosides are excellent tools for studying the role of the conformational parameters that are critical for the design of new nucleoside drug candidates [4-8]. These cyclic compounds are expected to have a beneficial biological impact especially toward enzymatic repair processes [9].

As part of an ongoing program directed by one of us (C. L.) toward the synthesis and development of new cyclonucleosides **5** [5,6], we envisioned that the general transformation outlined in Scheme 1 might afford a facile entry to **5** from dialkenyl precursors **4** by ring-closing metathesis [10-12]. The strategy relies on the preparation of unknown 6-ω-alkenyluridine key intermediates **3**. We report herein that sequential ring lithiation/methylation of the simple protected uridine **1** leading to **2** fol-



Scheme 1: Synthesis of potent antiviral and antitumor cyclonucleosides **5**.

lowed by lateral lithiation/alkylation with ω-alkenyl bromides provides a useful regioselective chain-extension procedure and an efficient route to **3**.

Results and Discussion

Most methods for the construction of *C*-substituted nucleosides are based on ring lithiation of nucleoside derivatives followed by their reaction with appropriate electrophiles. Thus, sequential lithiation of 2',3'-*O*-isopropylideneuridine (**6**) with LDA in THF (Figure 1) and electrophilic quenching with *n*-bromobutane was reported to give 6-*n*-butyl-2',3'-*O*-isopropylideneuridine (**8**) in a regiospecific manner (60%) [13]. It seems likely that the reaction proceeds via trianion **7** where the 5'-OLi group can easily participate in the stabilization of the 6-lithio intermediate. ω-Alkenyl bromides are known to be poor electrophiles toward organolithiums [14], and indeed, **7** failed to react, in our experiments, with 4-bromo-but-1-ene to give **9**.

We then turned our attention to the metalation of the 5'-*O*-TBDMS protected nucleoside **10** (Figure 2). Treatment with LDA (5 equiv) in THF at −70 °C followed by addition of D_2O provided **12** in 82% yield (evaluated by NMR) with exclusive deuterium incorporation at the C6 position. However, almost complete recovery of the starting material was observed when dianion **11** was allowed to react with 4-bromobut-1-ene [15]. Lithium–copper transmetallation was also attempted. Unfortunately, addition of 0.25 equiv of Li_2CuCl_4 [16-18] to **11** followed by quenching with 4-bromobut-1-ene failed to produce **3a**.

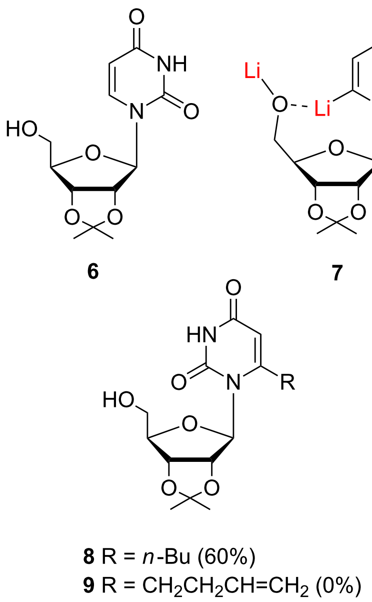


Figure 1: Lithiation of 2',3'-*O*-isopropylideneuridine (**6**).

Consequently, lateral lithiations were examined. Lateral lithiation of benzenoid aromatics requires a stabilizing group capable of either delocalizing negative charge or stabilizing an organolithium by coordination [19,20]. Primary, allylic, and benzylic halides usually give good yields of laterally alkylated products. Secondary and acetylenic halides have been used in several instances. Successful reaction with these substrates is noteworthy since many aryllithiums arising from *ortho*-lithiation reactions do not alkylate, or give poor yields, with any halides

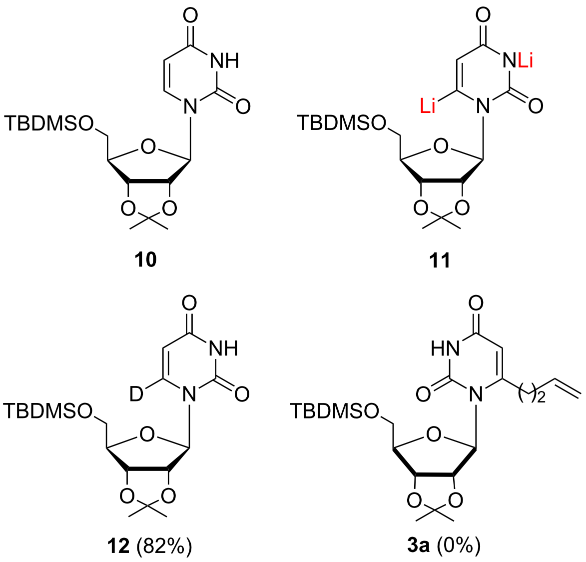
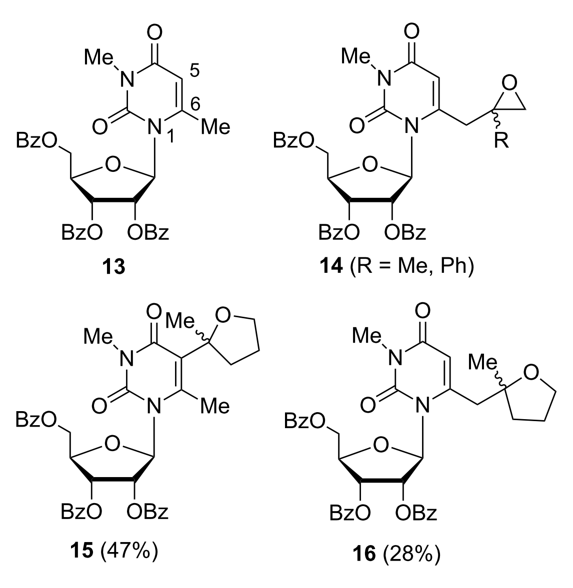


Figure 2: Metalation of 5'-*O*-TMDMS protected nucleoside **10**.

other than iodomethane [21-24]. Competing base-induced elimination reactions are presumably observed with iodoethane and higher homologues [19,20,25,26]. It has also been proposed that poor reactivity of lithiated carbanions toward alkyl halides may result from steric hindrance [24,27]. Recently, the lateral lithiation of 4-hydroxy-6,7-dimethoxy-8-methyl-2-naphthoic acid was applied to the regioselective efficient construction of a series of 5,5'-didesisopropyl-5,5'-dialkylapogossypol derivatives that are potent pan-active inhibitors of anti-apoptotic Bcl-2 family proteins [28].

Literature furnishes little information regarding lateral lithiations in the nucleoside field and the data, scarce as they are, even appear to be inconsistent at first sight. Treatment of 2',3',5'-tri-*O*-benzoyl-3,6-dimethyluridine (**13**) with chloroacetone or 2-chloroacetophenone in the presence of LDA (1.2 equiv, THF, −78 °C) afforded 6-(oxiranylmethyl)uridine derivatives **14** exclusively (Figure 3) [29]. With 5-chloro-2-pentanone, the reaction led to a mixture of 5- and 6-substituted uridine regioisomers **15** and **16** in 47% and 28% yield, respectively. It was suggested that the *N*-1 sugar moiety in the *syn* orientation of the nucleoside might affect the access of a very sterically demanding electrophile, such as 5-chloro-2-pentanone, to the 6-position. This hypothesis was confirmed by a probe experiment where an even more sterically hindered racemic 3-bromocamphor was used as an electrophile. The corresponding C5-alkylated uridine derivative was obtained as the only recovered product, in low yield (23%), besides the unreacted substrate.



13

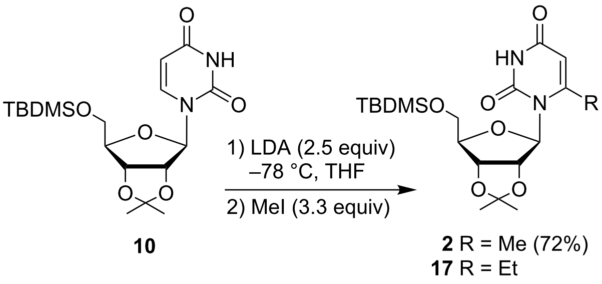
14 (R = Me, Ph)

15 (47%)

16 (28%)

Figure 3: Lithiation/alkylation of 2',3',5'-tri-*O*-benzoyl-3,6-dimethyluridine (**13**) using LDA.

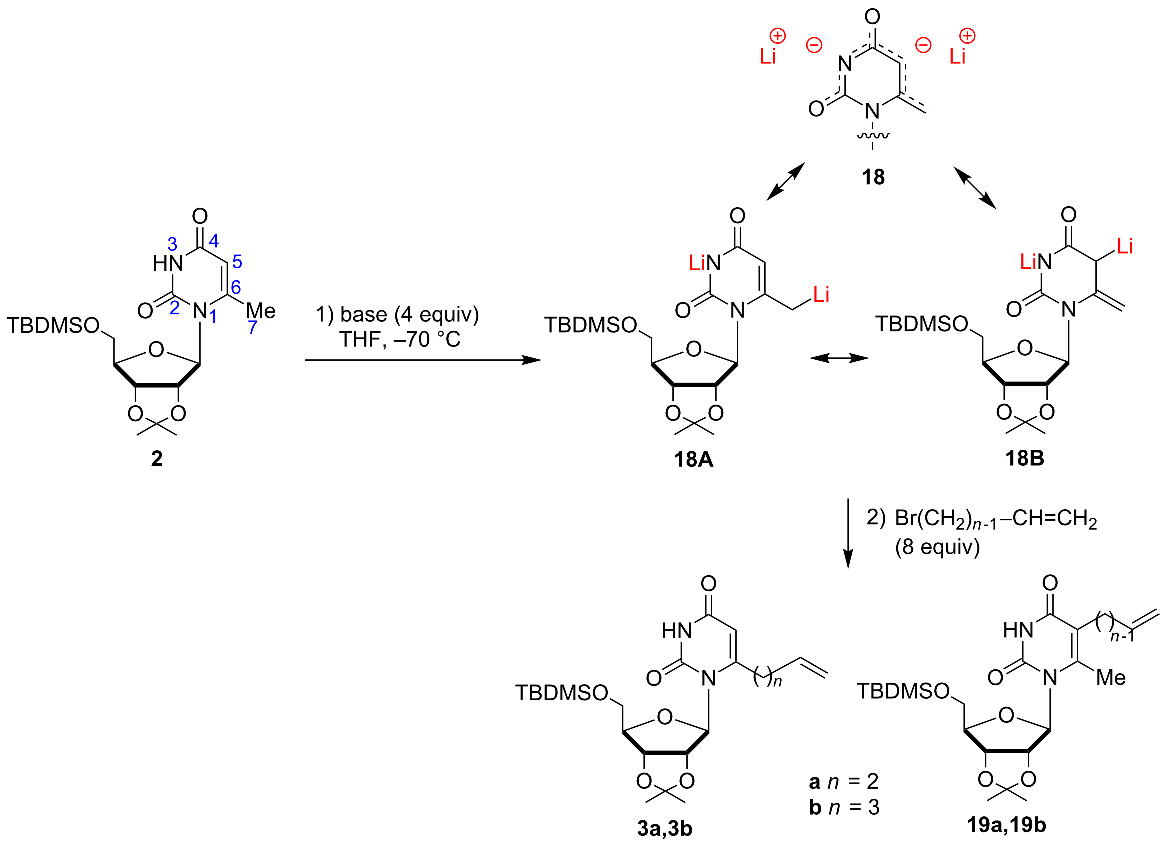
Having these precedents in mind, we decided to investigate the preparation of 6-ω-alkenyluridines **3** by lithiation of 6-methyluridine derivative **2**. Miyasaka et al. observed concomitant formation of 6-ethyl derivative alongside the expected 6-methyl derivative when 2',3'-*O*-isopropylideneuridine (**6**) was allowed to react with LDA and treated with MeI [13]. We found similarly that **10** in the presence of LDA (2.5 equiv) followed by addition of MeI (3.3 equiv) at −78 °C gave a mixture of 6-methyluridine **2** (44%) and 6-ethyluridine **17** (17%) (Scheme 2). By slow addition of the preformed dianion **11** to a THF solution of MeI (reverse-addition mode) [30,31], **2** was produced in satisfactory yield (72%) while formation of 6-ethyluridine **17** was reduced to <5%. Apparently LDA does not coordinate with the substrate in this transformation [32]. 6-Methyluridine can also be synthesized from 5'-*O*-(*tert*-butyldimethylsilyl)-6-iodo-2',3'-*O*-isopropylideneuridine via palladium-catalyzed cross-coupling with Me_4Sn [33].



Scheme 2: Preparation of 2',3'-*O*-isopropylidene-5'-*O*-(*tert*-butyldimethylsilyl)-6-methyluridine (**2**).

We have then embarked on a detailed investigation of the lithiation/alkylation of 6-methyluridine **2**, varying the base, metalation temperature, and exposure times (Scheme 3). We were concerned with the question of relative acidity of the methyl (C7) and the C5 centers that can compete through **18A** or **18B** [34-36]. In fact the two negative charges at N3 and C5/C7 are delocalized through the O2-C2-N3-C4-O4-C5-C6-C7 bond system rather than being localized dianions: All these forms are resonance structures of the same extended dianionic enolate **18** [37].

In the past, the regioselectivity of reactions of allyl anions have sometimes been explained using the HSAB theory [34]. In the present case, soft electrophiles (ω-alkenyl bromides) are used in the alkylation reaction. However, it is not straightforward to predict the softest center of **18**. In the literature, the regioselectivity of lithiation of allyl anions substituted by one nitrogen at the central carbon (C=C(N)–C) has scarcely been studied [38-40]. Deprotonation of simple enamines or allylamines employing *n*-BuLi and *t*-BuLi/*t*-BuOK produced nitrogen-



Scheme 3: Lateral lithiation/alkylation of 6-methyluridine **2**.

substituted allylic anions which undergo protonation, alkylation, trimethylsilylation and reaction with carbonyl compounds and epoxides either exclusively or predominantly at the γ-position [41-43]. Previous work also showed that cyclic enaminoketones, esters and nitriles were converted into their enolate with *n*-BuLi and alkylated with a variety of alkylating agents, affording the product of an exclusive γ-alkylation [42-45].

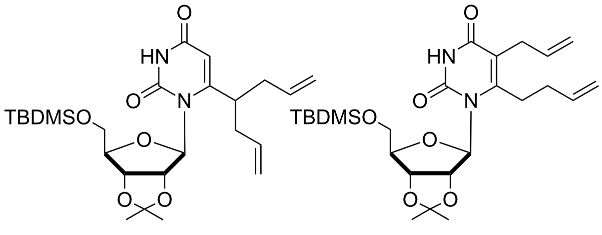
The results are summarized in Table 1. An excess of LDA (4 equiv) at −70 °C produced a dilithium reagent, which was presumed to be **18**, as a yellow solution. The colour faded when allyl bromide (8 equiv/ −70 °C → rt/12 h) was introduced, providing a mixture of regioisomers **3a** and **19a** which were separated by chromatography (entry 1, 58% and 10% yield, respectively). With LTMP, the delivery of a less acidic conjugated amine (TMP) in the reaction medium could be expected to prevent protonation of lithiated intermediates and thus to allow more efficient trapping by an electrophile [46,47]. Indeed, LTMP gave a better yield, but a slight decrease in the regioselectivity was observed (**3a**/**19a** 65:20). The ^{1}H NMR spectrum

Table 1: Lateral lithiation/alkylation of 6-methyluridine **2**.

entry	base	*n*	**3a**,**b** (%)	**19a**,**b** (%)	others (%)
1	LDA	2	58	10	—
2	LTMP	2	65	20	—
3	LDA	3	44	0	—
4	LTMP	3	56	0	—
5	LiHMDS	2	0	0	**20** (40), **21** (18)
6	*s*-BuLi/TMEDA	3	38	0	—

of **19a** displayed a singlet at 2.31 ppm, attributed to the C7-methyl group, and the disappearance of the H5 signal at 5.57 ppm. 4-Bromobut-1-ene underwent exclusive C7-carbanion alkylation to **3b** in good yield, with no indication of products resulting from C5-alkylation (entries 3 and 4).

Allyl bromide is a good electrophile that can react with both mesomeric forms **18A** and **18B** to give **3a** and **19a**. Apparently dianion **18B** is not nucleophilic enough to react with 4-bromobut-1-ene to give **19b**, and **3b** is formed exclusively. The lateral alkylation of uridine enolate **18** was best accomplished through use of LDA or LTMP as the carbanion generating species, rather than LiHMDS or *s*-BuLi/TMEDA. The bis-allylated products **20** and **21** (Figure 4) were obtained in 40% and 18% yield, respectively with LiHMDS at −70 °C and quenched with allyl bromide (entry 5). This result suggests the remetalation of **3a** is faster than the destruction of LiHMDS by the excess of allyl bromide. Structure of **20** was confirmed by ^{1}H NMR and a two-dimensional COSY experiment, which allowed the assignment of the proton–proton correlations of H7 and the allylic methylene groups. Metalation with *s*-BuLi/TMEDA complex was less efficient although the reaction did not lead to degradation products (entry 6). Ring/internal lithiations of uridine derivatives with *s*-BuLi/TMEDA are usually performed with fully TBDMS-protected ribofuranose nucleosides to allow better regiochemical control and to prevent nucleophilic attack of the base on the sugar moiety [48].



20

21

Figure 4: Bis-allylated products **20** and **21**.

Conclusion

In summary, a straightforward approach to 6-ω-alkenyluridines **3** from readily available protected uridine **1** is proposed. Whereas direct ring alkylation of 6-lithiated uridine **11** with ω-alkenyl bromides failed, our approach relies on lateral lithiation/alkylation of 6-methyluridine **2**. The total synthesis and biological properties of cyclonucleosides **5** will be reported separately.

Supporting Information

Supporting Information File 1

Experimental section (preparation and spectral data of compounds).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-143-S1.pdf]

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Meta-metallation of *N*,*N*-dimethylaniline: Contrasting direct sodium-mediated zincation with indirect sodiation-dialkylzinc co-complexation

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Robert E. Mulvey*, Charles T. O'Hara and Stuart D. Robertson

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Abstract

Previously we reported that direct zincation of *N*,*N*-dimethylaniline by the mixed-metal zincate reagent **1** ((TMEDA)Na(TMP)(*t*-Bu)Zn(*t*-Bu)) surprisingly led to *meta*-metallation (zincation) of the aniline, as manifested in the crystalline complex **2** ((TMEDA)Na(TMP)(*m*-C_6H_4-NMe_2)Zn(*t*-Bu)), and that iodination of these isolated crystals produced the *meta*-isomer *N*,*N*-dimethyl-3-iodoaniline quantitatively. Completing the study here we find that treating the reaction solution with iodine produces a 72% conversion and results in a mixture of regioisomers of *N*,*N*-dimethyliodoaniline, with the *meta*-isomer still the major product (*ortho*:*meta*:*para* ratio, 6:73:21), as determined by NMR. In contrast to this bimetallic method, sodiation of *N*,*N*-dimethylaniline with *n*-BuNa produced the dimeric, *ortho*-sodiated complex **3** (((TMEDA)Na(*o*-C_6H_4-NMe_2))$_2$), as characterised by X-ray crystallography and NMR. No regioisomers were observed in the reaction solution. Introducing *t*-Bu_2Zn to this reaction solution afforded a cocrystalline product in the solid-state, composed of the bis-anilide **4** ((TMEDA)Na(*o*-C_6H_4-NMe_2)$_2$Zn(*t*-Bu)) and the Me_2N–C cleavage product **5** ($\{(TMEDA)_2Na\}^+\{(t\text{-}Bu_2Zn)_2(\mu\text{-}NMe_2)\}^-$), which was characterised by X-ray crystallography. NMR studies of the reaction mixture that produces **4** and **5** revealed one additional species, but the mixture as a whole contained only *ortho*-species and a trace amount of *para*-species as established by iodine quenching. In an indirect variation of the bimetallic reaction, TMP(H) was added at room temperature to the reaction mixture that afforded **4** and **5**. This gave the crystalline product **6** ((TMEDA)Na(TMP)(*o*-C_6H_4-NMe_2)Zn(*t*-Bu)), the *ortho*-isomer of the *meta*-complex **2**, as determined from X-ray crystallographic and NMR data. Monitoring the regioselectivity of the reaction by iodination revealed a 16.6:1.6:1.0 *ortho*:*meta*:*para* ratio. Interestingly, when the TMP(H) containing solution was heated under reflux for 18 hours more *meta*-isomer was produced (corresponding ratio 3.7:4.2:1.0). It is likely that this change has its origin in a retro reaction that produces the original base **1** as an intermediate. Theoretical calculations at the DFT level using the B3LYP method and the 6-311G** basis set were used to probe the energetics of both monometallic and bimetallic systems. In accord with the experimental results, it was found that *ortho*-metallation was favoured by sodiation; whereas *meta*- (closely followed by *para*-) metallation was favoured by direct sodium-mediated zincation.

Introduction

While the metallation reaction remains an essential tool for constructing substituted aromatic compounds [1,2], the quest for new improved reagents capable of selectively abstracting hydrogen from organic substrates continues. Routinely, organolithium reagents have been employed for this purpose with the high electropositivity of lithium affording polar, reactive $C^{\delta-}$–$Li^{\delta+}$ bonds proficient in metallating C–H bonds in organic, especially aromatic and heteroaromatic, compounds [3-5]. Although, alkyllithium or lithium amide reagents are regarded as the preferred metallating agents for many transformations, there are major limitations associated with their use, with prominent drawbacks including poor functional group tolerance and low stability of the developing lithio-intermediates necessitating the use of sub-ambient temperatures to effect the desired reactions and avoid decomposition or side reactions. In recent years, as improvements on the existing metallating agents have been sought, research groups around the world have investigated innovative bimetallic alternatives to the customary homometallic reagents.

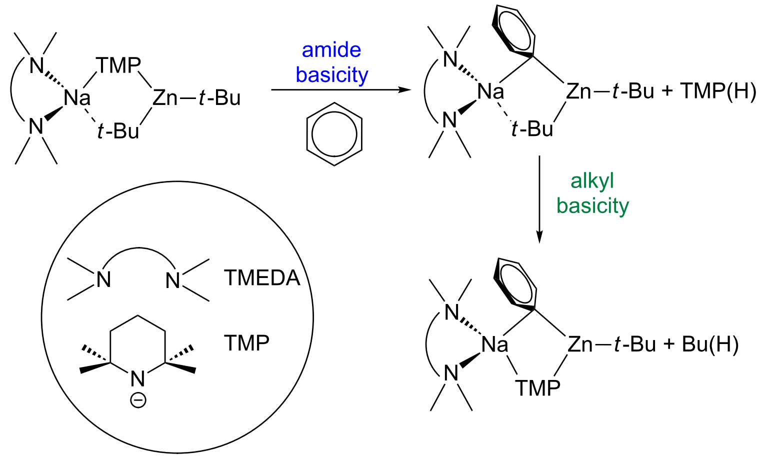
As part of these innovations the zinc–hydrogen exchange reaction has undergone a significant revolution in recent times propelling it into the spotlight. Despite finding utility in various types of organic reaction [6], simple zinc reagents (alkyls, amides) are kinetically sluggish bases and consequently ineffectual for deprotonative metallation [7]. Nonetheless, when part of an intricate multi-component composition, a striking enhancement in reactivity can be bestowed upon the zinc reagent as a result of cooperative effects between the different components. The work of Knochel uncovered a special reactivity and selectivity that can be realised with a mixed lithium halide–magnesium amide complex sometimes labelled a “turbo-Grignard” reagent [8]. It has been proposed that LiCl breaks up the magnesium amide aggregates allowing more soluble mixed-metal, mixed-anion reagents such as (TMPMgCl·LiCl) to perform regioselective functionalisation of aromatic and heteroaromatic compounds (TMP: 2,2,6,6-tetramethylpiperidide). Modified from their magnesiating “turbo-Grignard” reagents, Knochel’s three component system ($(TMP)_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$) allows direct zincation of functionalised arenes and heteroarenes [9,10]. However, common limitations have been noted for the use of this reagent with some electron poor and heterocyclic compounds which suffer from the drawback of limited regioselectivity, whilst several activated aromatic compounds bearing sensitive functional groups necessitate the use of sub-ambient temperatures. These problems can be circumvented by the use of the commercially available, more selective zinc base TMPZnCl·LiCl that executes chemo- and regioselective zincation of aryl and heteroaryl substrates containing sensitive groups typically at ambient temperature [11] and on the multigram scale with metallation rates comparable to those obtained for small scale processes [12]. Alkali metal zincates have also been given consideration, principally two-component dialkylamido zincates $MZn(NR_2)R'_2$. The reagent “(LiZn(TMP)(*t*-Bu)$_2$)”, introduced by Kondo and Uchiyama, is capable of directly zincating a range of similar substrates [13,14]. The sodium zincate **1** ((TMEDA)Na(TMP)(*t*-Bu)Zn(*t*-Bu); TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), reported by our group, is a potent and versatile zincating agent for a wide range of aromatic molecules usually inert towards orthodox organozinc reagents including benzene [15] and naphthalene [16]. These studies – that have been structurally supported by X-ray crystallography in tandem with NMR spectroscopy – have uncovered the chemical synergy that these mixed-metal alternatives can exhibit, which enabled such reagents to perform special metallation reactions that cannot be reproduced by either of the single-metal components that constitute the mixed-metal reagent. While the alkali metal component is essential for the synergic metallation to follow its course, it is the less electropositive zinc that replaces the departing hydrogen atom, prompting metallations of this type to be best regarded as “Alkali-Metal-Mediated Zincations (AMM*Zn*)” [17].

Directed *ortho*-metallation (D*o*M) is a special sub-category of deprotonative metallation. Defined as a metallation (nearly always lithiation) of an aromatic ring directed towards a position adjacent (*ortho*) to an activating heteroatom-containing functional group, it is widely regarded as the number one methodology for constructing regiospecifically substituted aromatic rings [18,19]. However, by channelling the special synergic chemistry of sodium TMP-zincates, it is possible to overcome D*o*M effects and direct metallation to more remote positions. Of particular interest to this work, we previously reported that *N*,*N*-dimethylaniline can be monozincated by the base **1** at the normally inaccessible *meta*-position [20] (while complexation of *N*,*N*-dimethylaniline with $Cr(CO)_3$ leads to a mixture of *ortho*-, *meta*- and *para*-deprotonation upon lithiation [21], other situations of *meta*-deprotonation require a special combination of substituents on the aromatic ring. Such situations, which because of the multiple substitution limit the number of sites available for deprotonation, are usually dictated by steric constraints and therefore should be clearly distinguished from monosubstituted aromatic rings in which *meta*-deprotonation is far more difficult to attain [22]). Another example of a synergic metallation can be found with the alkyl arene toluene. With conventional metallating reagents such as the alkyllithium BuLi·TMEDA, toluene is normally deprotonated at the methyl (lateral) site to generate the resonance stabilised benzyl "carbanion" ($PhCH_2^-$) [23,24]. In contrast, toluene has been directly zincated by reaction with the heteroleptic sodium zincate **1** to afford a statistical mixture of the *meta*- and *para*-regioisomers of (TMEDA)Na(TMP)(C_6H_4-Me)Zn(*t*-Bu) with the methyl substituent remaining intact [25].

The structural insight offered by these findings has been augmented by a complementary theoretical study. Filling in the gaps between the crystallographically characterised starting materials and the thermodynamic final products, Uchiyama and Nobuto have studied and evaluated the possible reaction pathways of the deprotonative metallation of benzene with sodium TMP-zincate **1** computationally [26]. Their DFT studies propose that these distinctive deprotonations proceed via a stepwise mechanism, whereby zincate **1** serves kinetically as an amide base (due to the greater kinetic lability of the Zn–N bonds) with concomitant release of TMP(H) with the formation of a bisalkyl(aryl) zincate intermediate (Scheme 1). In the second step, it follows that the co-existent, strongly acidic N–H bond of TMP(H) is deprotonated by this intermediate to afford the final thermodynamic product of the reaction identified by the aforementioned X-ray crystallographic studies, and isobutane.

Recently, we have sought to identify the structures of the reaction intermediates suggested by the theoretical studies. In addition to a closely related study for the AMM*Zn* of anisole by the analogous lithium TMP-zincate ((THF)Li(TMP)(*t*-Bu)Zn(*t*-Bu)) [27], these mechanistic and structural studies were then extended to the metallation of trifluoromethylbenzene by the bimetallic base **1** [28]. Providing a greater understanding of the mechanisms involved, the reaction was structurally traced by isolation of the kinetic solvent-separated *ortho*-deprotonated product ($\{(TMEDA)_2Na\}^+\{Zn(o\text{-}C_6H_4\text{-}CF_3)(t\text{-}Bu)_2\}^-$) before exploring its reactivity towards TMP(H) mirroring the second, multipart step of the AMM*Zn* process. Intriguingly, this second step was found to affect strongly the conclusion, swaying not only the product yield but also the final regioselectivity of the metallation with a complex mixture of *ortho*-, *meta*- and *para*-regioisomeric products observed in solution. These findings provided the first experimental evidence for a two-step mechanism in deprotonative metallations with TMP-zincates but additionally pose the question; "is the unique *meta*-metallation of *N*,*N*-dimethylaniline a consequence of TMP induced isomerisation?" This study attempts to answer this important question.

Herein we investigate in detail the reaction of **1** with *N*,*N*-dimethylaniline, exploring the proposed two-step mechanism and shedding light on the special synergic facet of the AMM*Zn* reaction. We report the synthesis and structural elucidation of *ortho*-metallated *N*,*N*-dimethylaniline complexes **3** ($((TMEDA)Na(o\text{-}C_6H_4\text{-}NMe_2))_2$) and **4** ($(TMEDA)Na(o\text{-}C_6H_4\text{-}NMe_2)_2Zn(t\text{-}Bu)$) prepared by direct metallation with *n*-BuNa followed by (in the case of **4**) co-complexation with $t\text{-}Bu_2Zn$, before surveying the latter's reactivity towards TMP(H) replicating the second step of the stepwise procedure. Offering increased understanding of the possible mechanisms involved in



Scheme 1: Proposed stepwise mechanism for the zincation of benzene.

the reactions of TMP-zincates, the solid-state structural features of an isolated decomposition product **5** ($\{(TMEDA)_2Na\}^+\{(t\text{-}Bu_2Zn)_2(\mu\text{-}NMe_2)\}^-$) are also discussed, thus overall providing an illustrative example of the subtle, yet prodigious reactivity of the bimetallic base **1**.

Results and Discussion

The original direct *meta*-zincation reaction. In comparison to tertiary amides and *O*-carbamates, anilines are relatively modest metallation directing groups [19,29]. Activation of *N*,*N*-dimethylaniline transpires primarily from the acidifying effect of the N atom; the coordination effect of the N atom is believed to be less important as a result of the conjugation of its lone pair with the π-system of the ring, even so *N*,*N*-dimethylaniline undergoes D*o*M with phenyllithium in poor yield [30] or *n*-butyllithium in good yield under forcing conditions [31]. Varying the metallation agent from these mainstream homometallic species to heterometallic **1** remarkably switched the orientation of the deprotonation to the *meta*-site, with the metallated heterotrianionic product of the reaction **2** ($(TMEDA)Na(TMP)(m\text{-}C_6H_4\text{-}NMe_2)Zn(t\text{-}Bu)$) isolated at ambient temperature in a stable crystalline form which allowed its molecular structure to be ascertained by X-ray crystallography (Figure 1).

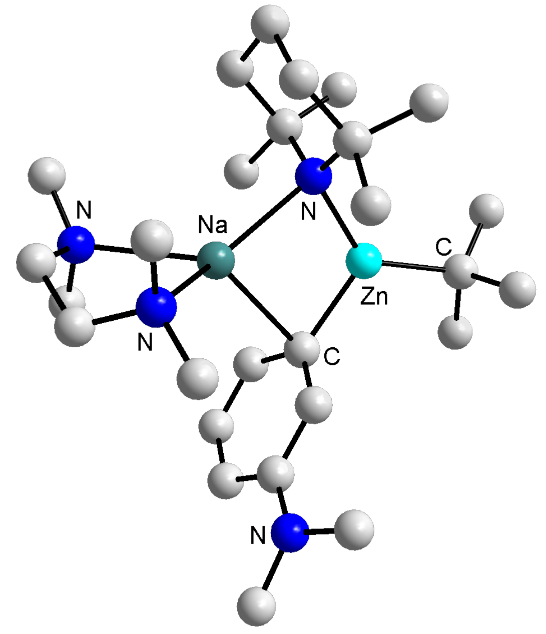
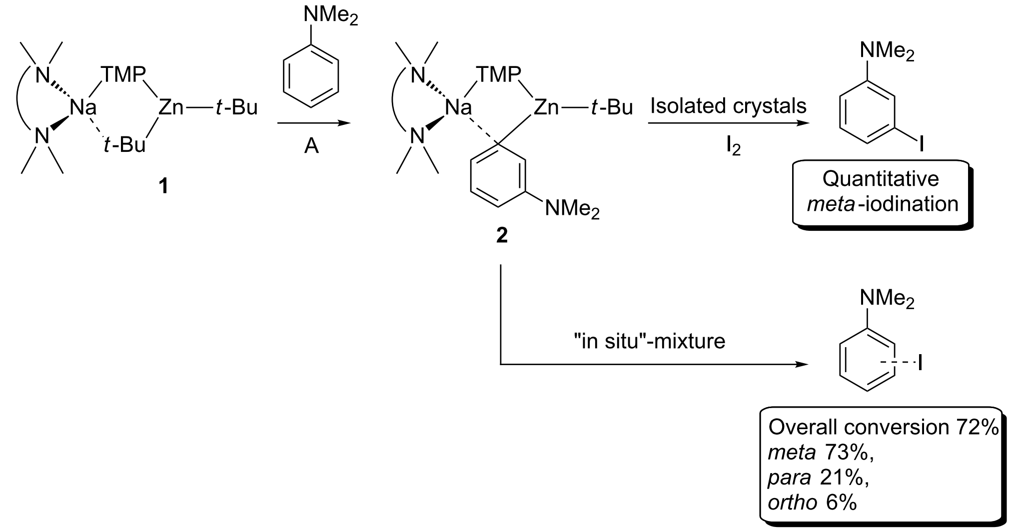


Figure 1: Molecular structure of **2** with selective atom labelling. Hydrogen atoms and minor disorder components are omitted for clarity [20].

As reported, a preliminary reaction of isolated crystals of **2** in THF with I_2 was carried out to establish whether these *meta*-zincated dimethylaniline complexes could be intercepted by electrophiles. ^{1}H NMR spectroscopic experiments revealed quantitative iodination and the formation of *N*,*N*-dimethyl-3-iodoaniline. Now we are looking to paint the complete picture of this surprising synergic *meta*-deprotonation of *N*,*N*-dimethylaniline.

The direct *meta*-zincation reaction: a closer look. Revisiting the reaction, sodium TMP-zincate **1** was prepared in situ in hexane solution and reacted with one molar equivalent of *N*,*N*-dimethylaniline at room temperature to afford a yellow solution which was subsequently treated with iodine (Scheme 2). NMR



Scheme 2: Synergic metallation of *N*,*N*-dimethylaniline (**A**) with sodium TMP-zincate **1 to** produce **2**, which was subsequently quenched with I_2 to produce iodo-anilines.

spectroscopic analysis (^{1}H and ^{1}H–^{1}H COSY NMR spectra in deuterated benzene) of the crude reaction solution revealed a complex mixture of iodinated products that contained all three possible ring regioisomers for the monometallation of *N*,*N*-dimethylaniline. In agreement with the X-ray crystallographic analysis, the *meta*-isomer was the principal product, but additionally in the aromatic region two doublets at 7.42 and 6.13 ppm were observed for the next most abundant component, i.e., the *para*-product and finally four multiplets at 7.75, 6.99, 6.73, and 6.46 ppm for the minor *ortho*-product in an overall 11.6:3:1 ratio.

The indirect sequential sodiation-dialkylzinc co-complexation approach. Closely imitating the constituents of sodium zincate **1**, *N*,*N*-dimethylaniline was *ortho*-sodiated by reaction with *n*-BuNa in hexane at 0 °C to give the product as a light orange precipitate in 64% yield. We employed *n*-BuNa because in our hands NaTMP, with or without the addition of TMEDA, was not sufficiently basic to abstract the *ortho*-hydrogen of *N*,*N*-dimethylaniline. In an attempt to produce crystals of the resulting sodium anilide, the red filtrate (after isolation of the precipitate) was concentrated in vacuo to yield yellow/orange crystals following storage in a refrigerator. X-ray crystallography identified the product as the dimeric, *ortho*-sodiated **3** (((TMEDA)Na(*o*-C_6H_4-NMe_2))$_2$) (Figure 2).

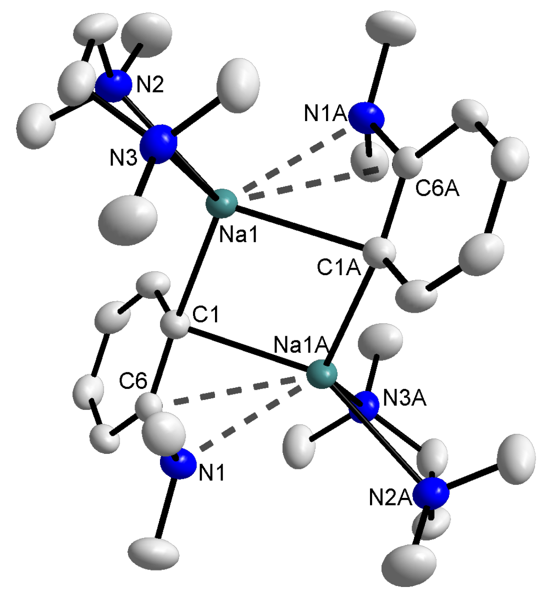


Figure 2: Molecular structure of **3** with selective atom labelling and thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity. The long Na···C_{ipso} and Na···N contacts are highlighted by dashed lines. Symmetry operation to generate equivalent atoms denoted A: 1−x, −y, 1−z. Selected bond distances (Å) and angles (°): Na(1)–N(2) 2.5363(14), Na(1)–N(3) 2.5350(14), Na(1)–C(1) 2.5442(15), Na(1)–C(1A) 2.5903(16), Na(1)···C(6A) 2.9231(15), Na(1)···N(1A) 2.6749(14), N(3)–Na(1)–N(2) 73.37(5), N(3)–Na(1)–C(1) 129.64(5), N(2)–Na(1)–C1) 104.31(5), N(3)–Na(1)–C(1A) 97.45(5), N(2)–Na(1)–C(1A) 150.27(5), C(1)–Na(1)–C(1A) 103.12(4), N(3)–Na(1)–N(1A) 106.68(4), N(2)–Na(1)–N(1A) 99.59(5), C(1)–Na(1)–N(1A) 122.86(5).

Sodiated aniline **3** adopts a simple dimeric centrosymmetric molecular structure based on a four membered (Na_2(μ-C)$_2$) ring, which is strictly planar. Occupying a tetrahedral geometry (mean angle around Na: 109.76°) the sodium atom in **3** is bound to a chelating TMEDA ligand and two deprotonated aniline units, the latter primarily through a close contact with the two *ortho*-deprotonated carbon atoms of the aromatic ring (Na(1)−C(1) 2.5442(15); Na(1)–C(1A) 2.5903(16) Å). In addition to these primary contacts, sodium also engages in longer, weaker secondary contacts with both the *ipso*-carbon and nitrogen atom of the anilide unit (Na(1)···C(6A) 2.9231(15) and Na(1)···N(1A) 2.6749(14) Å). The Na(1)–C(1A) distance is comparable to similar distances in the solvent-free sodium aryl derivative (NaC_6H_3–2,6-Mes_2)$_2$ prepared by Power (mean Na–C bond distance of 2.609 Å) [32], whilst they are naturally longer than those in the lithium dimer ({1-(dimethylamino)-8-naphthyl}-lithium·THF)$_2$ (2.207(4), 2.223(4) Å) [33]. In this latter compound the lithium atoms are located ca. 0.37 Å above and 1.05 Å below the naphthyl planes. By way of comparison, the sodium atoms in **3** are positioned 0.6565(5) Å above and 1.8248(5) Å below the aryl ring as a result of the increased size of sodium; a trend also reflected in the distance between the averaged main planes of the aromatic rings (1.176(1) Å in **3** and a surprisingly small 0.68 Å between the naphthyl rings of the lithium compound).

For the purposes of NMR spectroscopic analysis, the optimum solubility of **3** was achieved in deuterated cyclohexane solution. The salient observation from the NMR spectra of the solid material and indeed the mother liquor left following its isolation is that there is no sign of any other metallated products/isomers. Therefore the *ortho*-sodiated *N*,*N*-dimethylaniline was the sole metallated product detected during the course of the reaction. ^{1}H NMR spectroscopic analysis of a d_{12}-cyclohexane solution of **3** revealed three multiplets at 7.78, 6.79 and 6.58 ppm representing the *ortho*-deprotonated aromatic ring (overlap at 6.58 ppm between the *ortho'*- and *para*-protons) with the NMe_2 singlet resonance of the aniline appearing at 2.83 ppm, a shift of 0.12 ppm downfield from that in *N*,*N*-dimethylaniline. Completing the assignment, signals for the TMEDA ligand are found at 2.22 and 2.04 ppm. Emphasising the synthetically limiting reactivity of **3**, it appears to react with THF, while undesired deprotonation of toluene furnished crystals of the known compound TMEDA solvated benzylsodium as confirmed by NMR analysis [34]. Indeed, Slocum et al. have recently developed a selective *ortho*-metallation protocol which permits the retention of the bromine substituent in *para*-bromoanisole by the use of *ortho*-lithiodimethylaniline, which presumably must exhibit a reduced reactivity compared to its sodium analogue **3**, when employed as the metallating agent [35]. Indeed upon storage in a dry box, the shelf life of sodium anilide **3** is no more than a couple of days.

Continuing with the experimental studies, to introduce the second metal component one molar equivalent of *t*-Bu_2Zn (dissolved in hexane solution) was added to a suspension of **3** in hexane, which was prepared in situ, and the mixture was stirred at 0 °C for 1 hour and then for a further 2 hours at room temperature (Scheme 3). Following gentle heating of the mixture, colourless crystals were deposited upon slow cooling of the Schlenk tube in a Dewar flask of hot water overnight. X-ray crystallography indicated that this was a 2:1 co-crystalline mixture of two products, **4** ((TMEDA)Na(*o*-C_6H_4-NMe_2)$_2$Zn(*t*-Bu)) and **5** ({(TMEDA)$_2$Na}$^+${(*t*-Bu_2Zn)$_2$(μ-NMe_2)}$^-$).

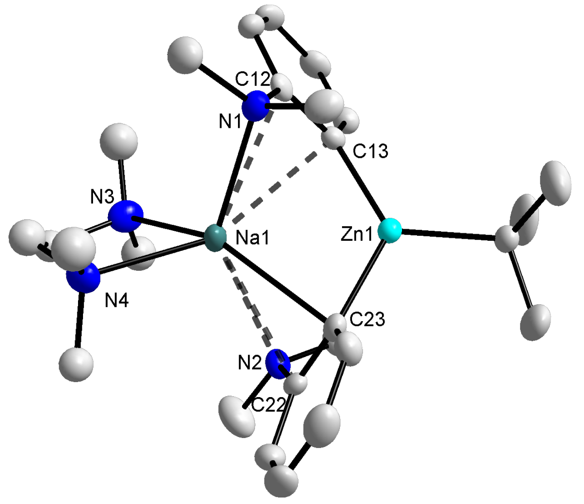
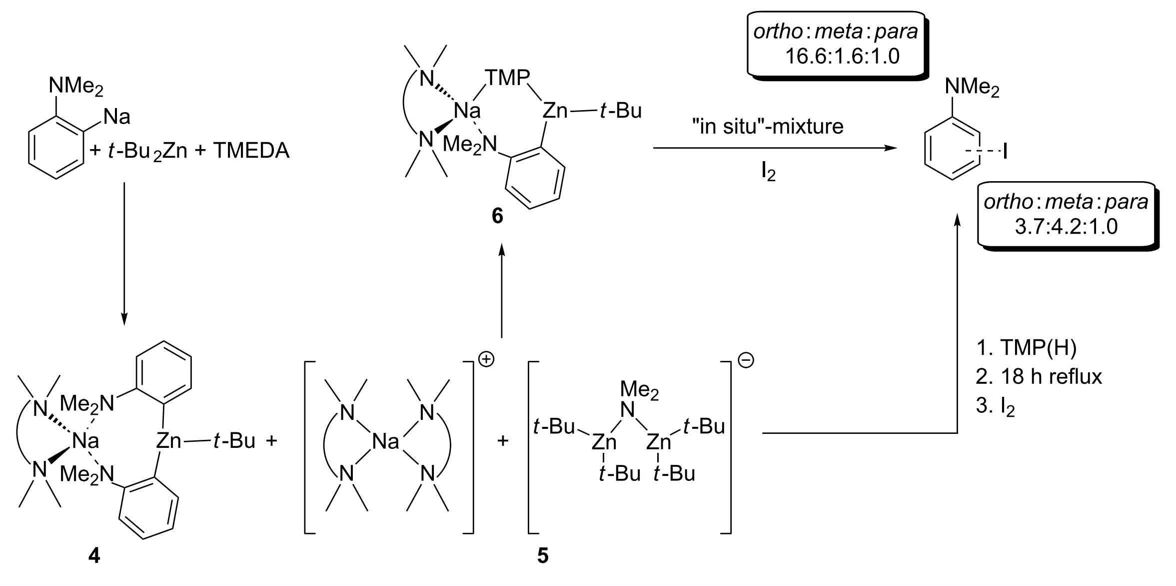


Figure 3: Molecular structure of **4** with selective atom labelling and thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and disordered component of TMEDA are omitted for clarity. Secondary contacts between sodium and the anilide rings are denoted by dashed lines. Only one of the crystallographically independent molecules is displayed, the parameters for the other are the same within experimental error. Selected bond distances (Å) and angles (°): Zn(1)–C(13) 2.025(3), Zn(1)–C(23) 2.042(3), Na(1)–N(1) 2.663(3), Na(1)···C(12) 2.848(3), Na(1)···C(13) 2.799(3), Na(1)···N(2) 2.851(2), Na(1)···C(22) 2.884(3), Na(1)–C(23) 2.663(3), Na(1)–N(3) 2.473(2), Na(1)–N(4) 2.473(3), C(13)–Zn(1)–C(23) 123.30(11), N(3)–Na(1)–N(4) 74.20(9), N(4)–Na(1)–C(23) 112.74(10), N(3)–Na(1)–C(23) 147.52(9), N(4)–Na(1)–N(1) 102.85(8), N(3)–Na(1)–N(1) 114.85(9), C(23)–Na(1)–N(1) 95.05(9).

Bisaryl **4** (Figure 3) can be considered a mixed-metal product of the co-complexation reaction between **3** and *t*-Bu_2Zn, despite the incorporation of a second deprotonated organic substrate. Although, a *tert*-butyl group has been formally lost, the formation of **4** may not necessarily be a result of a second deprotonation, with a disproportionation pathway potentially at play. The molecular structure of **4** can be described as a contacted ion-pair with the anionic moiety containing a trigonal planar zinc centre bonded to three carbon atoms, two from the *ortho*-metallated aniline fragments and one from the *tert*-butyl group. In addition to the nitrogen atoms of the chelating TMEDA, the sodium atoms primary coordination sphere is completed by bonding to the nitrogen of one of the anilide units (Na(1)–N(1) 2.663(3) Å) and the *ortho*-deprotonated carbon of the second aromatic ring (Na(1)–C(23) 2.663(3) Å), resulting in sodium adopting a distorted tetrahedral geometry (mean angle around Na: 107.87°). Furthermore, the multihapto-sodium centre engages in weaker, secondary contacts to the *ipso*-carbons of both anilides (Na(1)···C(12) 2.848(3) and Na(1)···C(22) 2.884(3) Å) and addi-



Scheme 3: Indirect zincation of *N*,*N*-dimethylaniline producing **4**, **5** and **6**, which was then quenched with I_2 to produce iodo-anilines.

tionally, interacts with not only the second deprotonated carbon (Na(1)···C(13) 2.799(3) Å) but also the second aniline N atom (a long Na(1)···N(2) length of 2.851(2) Å compared to the $Na–N_{TMEDA}$ bond lengths of Na(1)–N(3) 2.473(2) and Na(1)–N(4) 2.473(3) Å). Notably, the carbanion which was initially bound to sodium is now directly attached to the more carbophilic zinc as illustrated by the short, strong zinc–carbon σ-bonds (Zn(1)–C(13) 2.025(3), Zn(1)–C(23) 2.042(3)). A search of the Cambridge Structural Database [36] found that the bisaryl model has precedent in alkali-metal zincate chemistry, for example, the previously prepared biscarboxamide ((TMEDA)Li{2-(1-C(O)N(*i*-Pr)$_2$)C_6H_4}$_2$Zn(*t*-Bu)) [37], however the donor ability of the different directing groups limits comparison with **4**. A salient feature of this structure is the bond between lithium and the Lewis basic carbonyl oxygen atoms which close a ten-membered ring, resulting in a contracted Ph–Zn–Ph bond angle of 111.76(10)°. In contrast, as a result of the dimethylamino groups modest directing ability, with coordination less important, the sodium atom in **4** engages the π-system of the arene ring, in turn increasing the C(13)–Zn(1)–C(23) bond angle to 123.30(11)°.

The solvent-separated ion-pair co-product **5** ({(TMEDA)$_2$Na}$^+${(*t*-Bu$_2$Zn)$_2$(μ-NMe$_2$)}$^-$) (Figure 4) adopts a markedly different structural motif from that of **4**. The cation comprises a nearly square planar sodium centre coordinated by two TMEDA molecules (near square planar alkali-metals are rare) [38], whereas the anion consists of two di-*tert*-butylzinc units bridged by a dimethylamino group. The unexpected manifestation of this bridging amide is almost certainly a consequence of utilising the robust homometallic reagent *n*-BuNa at fairly ambient temperatures, with decomposition of either *N*,*N*-dimethylaniline or with precedent in the literature, TMEDA potentially leading to the presence of this cleaved amide fragment [39]. The zinc-nitrogen bond distances in **5** (Zn(3)–N(13) 2.059(2) and Zn(4)–N(13) 2.062(2) Å) are the same within experimental error to each other and in good agreement with related distances in the zinc bisamide ({(PhCH$_2$)$_2$N}Zn)$_2$·C_6H_6 (2.0083(13) and 2.0620(12) Å) [40] and in dimeric methyl(diphenylamido)zinc (average value of 2.072(8) Å for the four distinct Zn–N bond lengths) [41]. The best comparison for **5** is possibly provided by the dinuclear zinc guanidinate complex ({Zn(OAr)}$_2$(μ-{Me$_2$NC(N*i*-Pr)$_2$})(μ-NMe$_2$)) prepared by Coles [42]. In both complexes, the zinc atoms adopt a distorted trigonal planar geometry (sum of bond angles at Zn(3) and Zn(4) in **5** equal to 358.31° and 358.28°, respectively) but with each zinc atom bound to a bulky aryloxide and guanidinate ligand, the Zn–(μ-amidoN)–Zn bond angle is compressed to 97.34°, in contrast to 103.67(9)° in the more open structure of **5**. A possible consequence of this increased steric hindrance in the guanidinate complex is the shorter zinc–nitrogen bond distances (1.990(3) and 1.982(3) Å) in comparison to those in **5**.

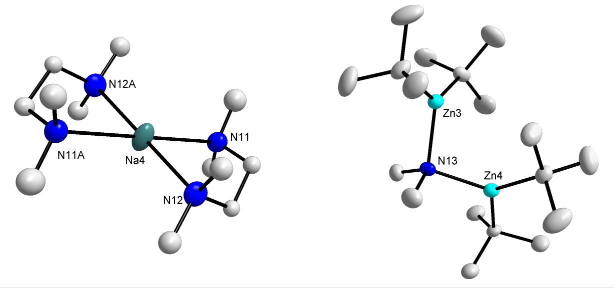


Figure 4: Solvent-separated ion-pair structure of **5** with selective atom labelling and thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and disordered component of TMEDA are omitted for clarity. Only one of the crystallographically independent cations is displayed, the parameters for the other are the same within experimental error. Symmetry operations to generate equivalent atoms denoted A: 1−x, 1−y, −z. Selected bond distances (Å) and angles (°): Zn(3)–N(13) 2.059(2), Zn(4)–N(13) 2.062(2), Zn(3)–N(13)–Zn(4) 103.67(9), Na(4)–N(11) 2.516(2), Na(4)–N(12) 2.494(3), N(11)–Na(4)–N(12) 75.21(8), N(11)–Na(4)–N(11A) 180.0, N(11)–Na(3)–N(12A) 104.79(8), N(12)–Na(3)–N(12A) 180.0.

The ^{1}H NMR spectrum in deuterated benzene solution of the reaction of **3** and *t*-Bu$_2$Zn, which produced crystals of **4** and **5**, revealed the presence of a third distinct species. Four multiplets at 8.03, 7.17, 7.06, and 6.72 ppm are observed for the major *ortho*-metallated product but additionally, shadowing these signals, another different *ortho*-metallated product is evident from four multiplets at 7.87, 7.01, 6.86, and 6.60 ppm. Potentially, this additional unidentified product could be the related dialkyl(aryl) sodium zincate ((TMEDA)Na(*o*-C_6H_4-NMe$_2$)*t*-BuZn*t*-Bu), reminiscent of the lithium congeners ((THF)$_3$Li(*o*-C_6H_4-OMe)*t*-BuZn*t*-Bu) and ((PMDETA)Li(*o*-C_6H_4-OMe)*t*-BuZn*t*-Bu) prepared by co-complexation reactions of lithiated anisole with *t*-Bu$_2$Zn and the relevant Lewis base [27]. The metallation regioselectivity exhibited in the crystalline material is confirmed by treatment of the in situ reaction mixture with iodine. Electrophilic quenching of the two different *ortho*-deprotonated organometallic compounds is depicted in the ^{1}H NMR of the crude residue, with a 20.2:1.0 mixture of the *ortho*- and *para*-isomers of iodo-*N*,*N*-dimethylaniline obtained and significantly, a negligible quantity of the *meta*-iodinated product present.

According to theoretical studies, compound **4** and its related bisalkyl(aryl) derivative could be putative intermediates in the first step of the metallation of *N*,*N*-dimethylaniline by TMP-zincates. Thus, the reactivity of this in situ mixture towards the amine TMP(H) was studied, purposely for the formation of (TMEDA)Na(TMP)(C_6H_4-NMe$_2$)Zn(*t*-Bu) products. First the reactivity towards 1 molar equivalent of TMP(H) at room temperature was investigated and within 30 minutes a white solid precipitated which could be recrystallised from hexane to afford a small amount of translucent crystals.

An X-ray crystallographic study showed the molecular structure of these crystals to be **6** ((TMEDA)Na(TMP)(o-C_6H_4-NMe_2)Zn(t-Bu)) (Figure 5). Revealing a contact ion-pair structure, **6** comprises of the Na–TMP–Zn structural backbone of bimetallic base **1** where TMEDA chelates the sodium atom and zinc is bound to a terminal *tert*-butyl group. In keeping with previous illustrations of the AMM*Zn* reaction, zinc has filled the position vacated by the departing hydrogen atom and significantly in **6**, zinc resides in the *ortho*-position of the aromatic ring. Comparing the regioisomers **2** and **6**, a strong Zn–C σ-bond is formed between the metal and deprotonated carbon atom in both compounds (2.035(4) and 2.079(2) Å in **2** and **6**, respectively), as a result the main difference between the structures arises from the manner in which the metallated arene interacts with the alkali metal. In **2**, with the NMe_2 unit detached from sodium, the alkali metal interacts more with the π-system of the aromatic ring, principally with the deprotonated *meta*-carbon (2.691(4) Å) generating a four-membered (NaNZnC) ring. In contrast, for **6** the close proximity of the NMe_2 group enables it to bind with the sodium centre giving a slightly longer than average Na(1)–N(3) bond distance of 2.6991(19) Å (compared to a Na(1)–N(1) bond distance of 2.663(3) Å in **4** and Na–N bond distances in the range 2.448(4)–2.621(3) Å for a series of mononuclear zinc compounds) [36], which closes a larger six-membered highly puckered (NaNZnCCN) central ring. Nevertheless, sodium still π-engages with the aromatic ring (transannular distances of 2.917(2) and 2.768(2) Å) in the characteristic fashion of several AMM*Zn* products.

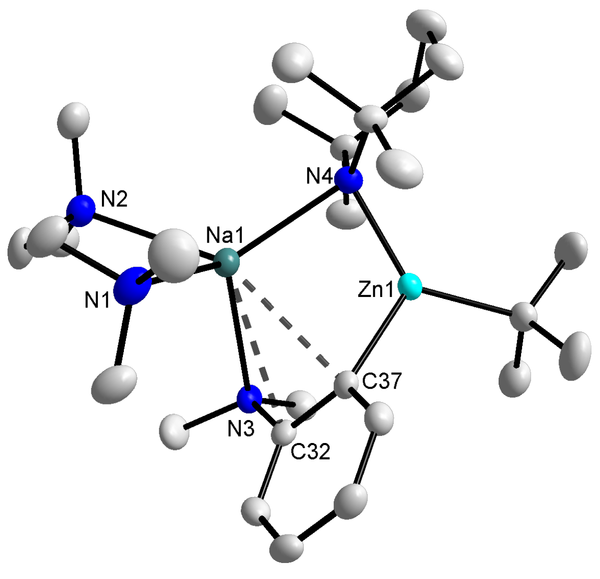


Figure 5: Molecular structure of **6** with selective atom labelling and thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms are omitted for clarity. Secondary contacts between sodium and the anilide rings are denoted by dashed lines. Selected bond distances (Å) and angles (°): Na(1)–N(1) 2.586(2), Na(1)–N(2) 2.568(2), Na(1)–N(3) 2.6991(19), Na(1)–N(4) 2.469(2), Na(1)···C(32) 2.917(2), Na(1)···C(37) 2.768(2), Zn(1)–C(37) 2.079(2), Zn(1)–N(4) 2.0279(17), N(1)–Na(1)–N(4) 131.05(7), N(2)–Na(1)–N(4) 122.82(7), N(1)–Na(1)–N(2) 72.56(6), N(3)–Na(1)–N(4) 105.70(6), N(2)–Na(1)–N(3) 109.31(6), N(1)–Na(1)–N(3) 111.60(7), N(4)-Zn(1)–C37) 114.27(8).

The relatively simple ^1H NMR spectrum of the white precipitate in deuterated THF solution revealed the solid to be exclusively product **6**, whereby *N*,*N*-dimethylaniline has been *ortho*-metallated with only four resonances, two doublets (7.48 and 6.81 ppm) and two triplets (6.92 and 6.75 ppm) observed in the aromatic region. Furthermore, the analysis of the aliphatic region of both the ^1H and $^{13}C\{^1H\}$ NMR spectra showed resonances for both *tert*-butyl and TMEDA but notably, resonances which can be attributed to coordinated TMP at 1.74, 1.37 and 1.20 ppm were observed (note that ^1H NMR resonances of TMP(H) in d_8-THF appear at 1.63, 1.29 and 1.06 ppm).

Regenerating the TMP bridge between sodium and zinc can be considered a copy of the second step of Uchiyama and Nobuto's theoretically proposed stepwise mechanism. However, should the AMM*Zn* reaction proceed by the two-step procedure, then the *meta*-isomer might emerge as the predominant product despite the isolation of **6**. To establish the complete constitution of an in situ reaction mixture, it was treated with iodine, the crude ^1H NMR spectrum (Figure 6) revealing that while much of the *ortho*- and *para*-substitution pattern is retained, a small portion of these zincated aryl molecules have isomerised to the *meta*-position (overall *ortho*:*meta*:*para* ratio of 16.6:1.6:1.0 from an *ortho*:*meta*:*para* ratio of 20.2:0:1.0 before TMP(H) addition). For the addition of TMP(H) to the isolated, *ortho*-metallated kinetic intermediate ($\{(TMEDA)_2Na\}^+\{Zn(o\text{-}C_6H_4\text{–}CF_3)(t\text{-Bu})_2\}^-$), we previously reported that the secondary amine facilitates rearrangement of some *ortho*-zincated aryl molecules to *meta*- and *para*-isomers (in a 4.3:2.6:1 ratio, resulting from the amination reaction of TMP(H) with one *t*-Bu group) [28]. The smaller degree of isomerisation in the *N*,*N*-dimethylaniline system can be rationalised at least in part by considering the electronic nature of the different directing groups. With respect to NMe_2, CF_3 exerts an increased inductive effect thus weakening the Zn–C_{ortho} bond to a greater extent, potentially leading to an easier cleavage and thus isomerisation. However, stimulated by this result, the TMP induced isomerisation was pursued with the aim of transforming more *ortho*-material to *meta*. In order to meet this aspiration, the reaction mixture was refluxed overnight, aiding the solubility of **6** and thus presenting greater opportunity for regioisomerisation.

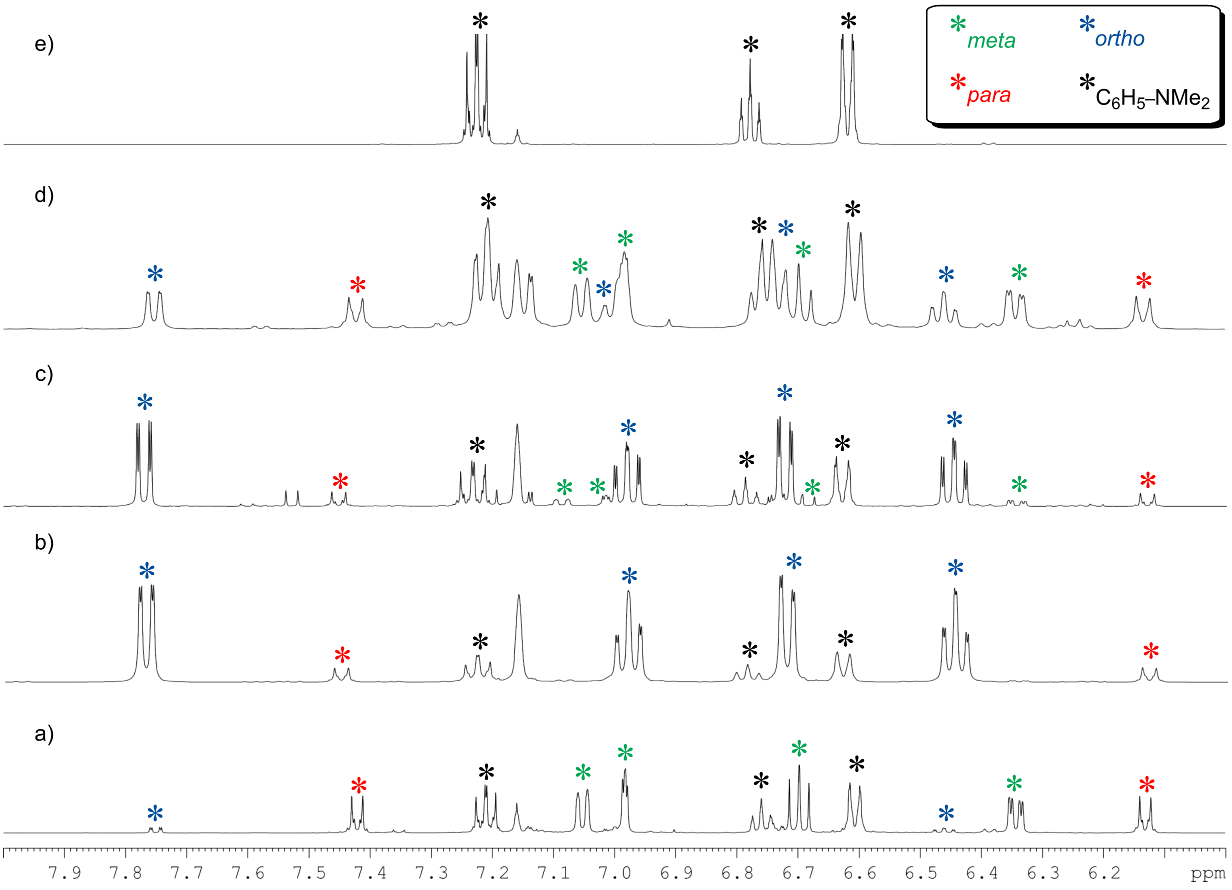


Figure 6: Aromatic region of ^{1}H NMR spectra for deuterated benzene solutions of (a) the crude mixture obtained from the reaction of **1** ((TMEDA)Na(TMP)(*t*-Bu)Zn(*t*-Bu)) with 1 equivalent of *N*,*N*-dimethylaniline at room temperature following iodine quenching; (b) the crude mixture obtained from the reaction of BuNa·TMEDA, *N*,*N*-dimethylaniline and *t*-Bu_2Zn at room temperature following iodine quenching; (c) the crude mixture obtained from the reaction of BuNa·TMEDA, *N*,*N*-dimethylaniline, *t*-Bu_2Zn and TMP(H) at room temperature following iodine quenching; (d) the crude mixture obtained from the reaction of BuNa·TMEDA, *N*,*N*-dimethylaniline, *t*-Bu_2Zn and TMP(H) following an overnight reflux and iodine quenching; (e) a standard of *N*,*N*-dimethylaniline.

Following the addition of TMP(H) and an 18 hour reflux, the yellow solution was treated with iodine. ^{1}H NMR spectroscopic analysis revealed that the make-up of the solution had dramatically changed, with each of the three regioisomers for the mono-iodination of *N*,*N*-dimethylaniline present. Notably, the predominant isomer of iodo-*N*,*N*-dimethylaniline is now the *meta*-substituted product denoted by three multiplets at 7.05, 6.70, and 6.34 and a singlet at 6.98 ppm (Figure 6). The *ortho*-product is still well represented denoted by four multiplets at 7.75, 7.02, 6.74, and 6.46 ppm, while two doublets at 7.42 and 6.13 ppm denote the minor *para*-product with the three regioisomers present in an overall *ortho*:*meta*:*para* 3.7:4.2:1.0 ratio. However, the spectrum also revealed a substantial amount of free *N*,*N*-dimethylaniline (multiplets at 7.22, 6.77, and 6.60 ppm and a singlet at 2.55 ppm for the NMe_2 group). Simulating the multipart-step of the AMM*Zn* reaction in the aforementioned trifluoromethyl benzene study [28] – by reacting isolated crystals of ($\{(TMEDA)_2Na\}^+\{Zn(C_6H_4\text{-}CF_3)(t\text{-}Bu)_2\}^-$) with TMP(H) and monitoring by ^{1}H NMR spectroscopy – highlighted the significance of this second step in determining not only the final regioselectivity of the metallation but also the reaction yield with the amine found to partially target the metallated aryl anion regenerating sodium TMP-zincate **1** and trifluoromethylbenzene. The existence of such a parallel competitive reaction path could promote the re-formation of *N*,*N*-dimethylaniline and when in the presence of concomitant zincate **1**, be responsible for the increase observed in the *meta*-deprotonated substrate. Further evidence for the regeneration of bimetallic base **1** comes in the identity of two unknown products in the crude mixture, although evidently *N*,*N*-dimethylaniline derivatives, positive identification from NMR analysis was made difficult by the complexity of the aromatic region (two distinct singlets visible in NMe_2 region at 2.35 and 2.29 ppm). GC-MS (CI mode) analysis verified the presence of the three regioisomers of iodo-*N*,*N*-dimethylaniline but also shed light on the identity of the two unknown species with the MH^+ peaks at *m*/*z*

373.8 consistent with regioisomers of diiodo-*N*,*N*-dimethylaniline. Thus following the addition of TMP(H), the presence of sodium TMP-zincate **1** in conjunction with the harsher reflux conditions is likely to be the cause for a degree of di-deprotonation of the aromatic molecule.

DFT calculations

In an attempt to rationalise the different metallation regioselectivities afforded by the homo and heterobimetallic bases, theoretical calculations at the DFT level using the B3LYP method and the 6-311G** basis set were employed to compute the relative stabilities of the four possible regioisomers for the monometallation of *N*,*N*-dimethylaniline.

The relative stabilities of the four model regioisomers (*ortho*-, *meta*-, *para*- and methyl-positions), in which the aniline ring is sodium substituted were calculated and in support of the experimental studies, the *ortho*-isomer is the energetically preferred product (relative energy: 0.00 kcal mol^{-1}) with the presence of a Na–N interaction helping its stability. Closely following is the methyl isomer (at 1.61 kcal mol^{-1}) but destabilised are the *meta*- and *para*-isomers (by 8.60 and 8.71 kcal mol^{-1}, respectively).

On modelling the introduction of TMEDA, the *ortho*-isomer remains the energy minimum structure at 0.00 kcal mol^{-1}, however, the energy gap to the other three regioisomers decreases slightly (methyl at 1.35 kcal mol^{-1}; *meta* at 6.93 kcal mol^{-1}; and *para* at 7.15 kcal mol^{-1}). Inspecting the dimensions of the *ortho*-product, TMEDA chelation of the Na atom results in a longer and thus weaker Na–NMe$_2$ secondary interaction (increase from 2.289 to 2.501 Å), while the *meta*- and *para*-isomers benefit from TMEDA's participation with the energies of TMEDA coordination equal to −20.86 and −20.74 kcal mol^{-1}, respectively. Tellingly, although the overall energy of reaction for these isomers is exothermic by −5.81 and −5.59 kcal mol^{-1}, by way of comparison the product of *ortho*-deprotonation is significantly more exothermic by −12.74 kcal mol^{-1}.

With respect to dimerisation the most disfavoured is the methyl isomer (relative energy of 8.60 kcal mol^{-1}) but in contrast the *meta* (at 4.65 kcal mol^{-1}) and *para* (at 5.48 kcal mol^{-1}) regioisomers benefit in relation to the *ortho*-product (Figure 7). The −22.08 kcal mol^{-1} energy of dimerisation gained by the *ortho*-isomer is relatively low (compared to −31.29 kcal mol^{-1} for the *meta*-isomer) due to a combination of increased steric repulsions and loss of stabilising interactions. On dimerisation, the

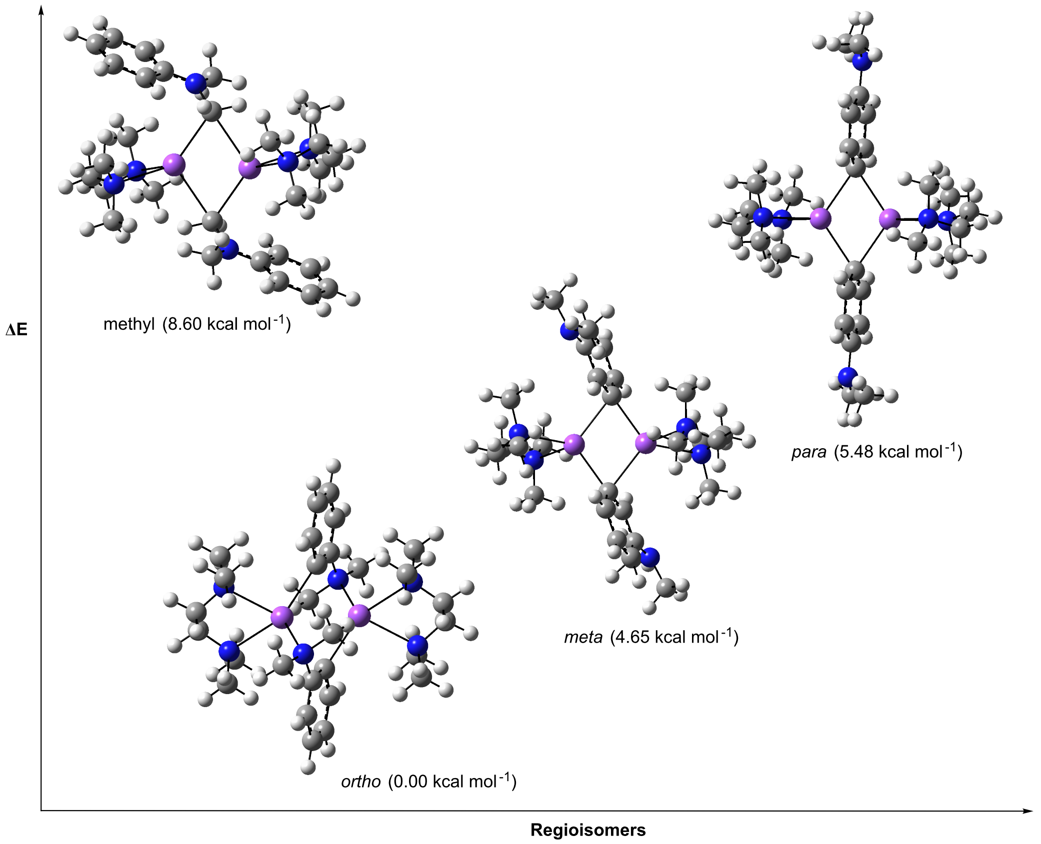


Figure 7: Relative energy sequence of the four theoretical regioisomers of the experimentally observed product **3**.

Na–N interaction in the *ortho*-product increases in length from 2.501 to 2.662 Å with the Na atom now involved in bonding with two *ortho*-deprotonated C atoms, while there is also a noticeable increase in the Na–N(TMEDA) bond lengths from 2.521 and 2.533Å to 2.604 to 2.674 Å. Through these modelling studies, *ortho*-deprotonation and dimerisation is found to be the energetically preferred metallation pathway by the homometallic reagent, the overall reaction found to be exothermic by −47.55 kcal mol^{-1}. Incidentally, on addition of *t*-Bu_2Zn to each of the three monomeric sodiated regioisomers there is very little difference in the energies of the three products (*ortho* at 0.00 kcal mol^{-1}; *meta* at 0.32 kcal mol^{-1}; and *para* at 0.41 kcal mol^{-1}).

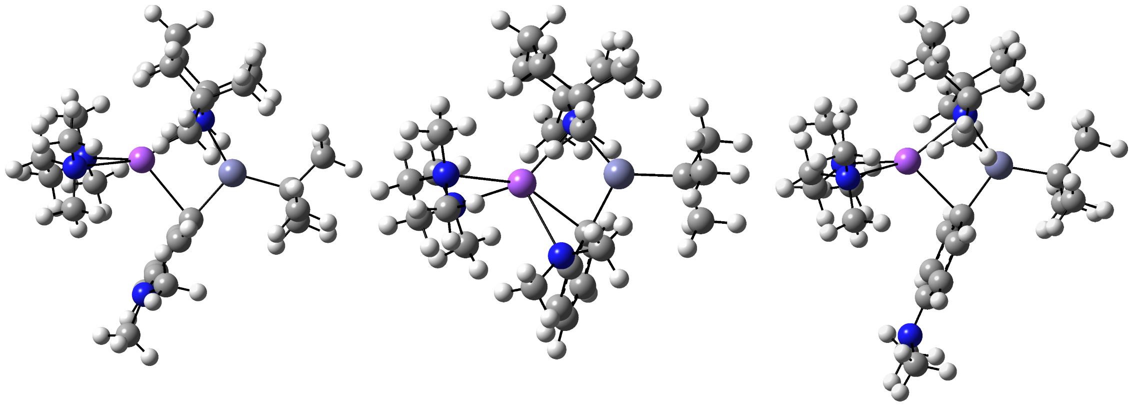
Moving to calculations on the sodium TMP-zincate **1**, concurring with the experimental findings and in sharp contrast to the product obtained via monometallic *n*-BuNa/TMEDA, the *meta*-isomer **2A** is found to be the minimum energy structure (relative energy: 0.00 kcal mol^{-1}) but is closely followed by the *para*-isomer **7** (at 0.66 kcal mol^{-1}). Notably, the *ortho*-isomer **6A** is destabilised further (at 4.32 kcal mol^{-1}); and the least stable of all is metallation at the methyl group (at 9.01 kcal mol^{-1}). Hence in the synergic twofold metal system, the *meta*- and *para*-regioisomers are the thermodynamic products. Modelling studies reveal all four deprotonations to be exothermic, with the *meta*-isomer most exothermic by −21.46 kcal mol^{-1}.

The modest difference in the relative energies for **2A** and **7** could explain the formation of the sizeable proportion of *para*-product observed experimentally. A comparison of the dimensions in these regioisomers, reveal that the Na contacts to the aryl C atoms are systematically shorter in the energetically preferred *meta*-isomer **2A** (bond distances: 2.594, 3.070, 3.212, 3.959, 4.097, 4.403 Å) than in the analogous *para*-product **7** (bond distances: 2.596, 3.178, 3.239, 4.135, 4.185, 4.596 Å), whereas the Zn–C(aryl) bonds are within 0.001 Å of each other (2.084 and 2.083 Å, respectively) (Table 1). In the *ortho*-isomer **6A**, the product found previously to be expected from conventional (non-synergic, single metal) metallation, the Na–C(*ortho*) bond is decidedly longer (2.747 Å) and thus, weaker than the Na–C(*meta*) bond in the favoured *meta*-isomer **2A** as a result of increased steric constraints. Additionally, with the sodium atom bonding to the NMe_2 group in **6A**, lone pair–lone pair repulsion between the lone pair of the nitrogen and the nearby *ortho*-carbanion may be a factor in the relative instability of **6A**. Consequently, the principal distinction lies in maximising the strength of the Na···Cπ contacts, and although they may be weak individually, collectively they must contribute appreciably to the overall stability of the unexpected *meta*-deprotonated product.

Conclusion

Closing remarks on direct AMM*Zn* versus indirect sodiation-zinc co-complexation approaches. The results of this study highlight the inherent complexity of these metallation reactions even at the metal stage, with a diverse array of organometallic complexes isolated, prior to the recognised intricacies of subsequent electrophilic interception.

Table 1: Selected bond distances calculated for the three regioisomers **2A**, **6A** and **7**.



2A (0.00 kcal mol^{-1}) **6A** (4.32 kcal mol^{-1}) **7** (0.66 kcal mol^{-1})

Bond distance (Å)	2A	6A	7
Zn–$C_{metallated}$	2.084	2.107	2.083
Na–$C_{metallated}$	2.594	2.747	2.596
Na···C_{aryl}	3.070, 3.212	2.937	3.178, 3.239

Collectively, these results emphasise the synthetic utility of the AMM*Zn* reaction with the employment of a synergic bimetallic base providing entry to previously inaccessible metallation regioselectivities. The AMM*Zn* of *N*,*N*-dimethylaniline by sodium zincate **1** ((TMEDA)Na(TMP)(*t*-Bu)Zn(*t*-Bu)) has been shown to afford a mixture of *ortho*-, *meta*- and *para*-regioisomers in solution, however, the predominant *meta*-substituted derivative **2** ((TMEDA)Na(TMP)(*m*-C_6H_4-NMe_2)Zn(*t*-Bu)) – a regioselectivity normally closed to synthetic aromatic chemistry – can be isolated in reasonable yields in a clean, pure crystalline form.

In an attempt to try and advance our knowledge of the synergic facet of the AMM*Zn*, some control reactions with *N*,*N*-dimethylaniline were performed. With the toothless base *t*-Bu_2Zn, incapable of directly zincating aromatics, *N*,*N*-dimethylaniline was treated with *n*-BuNa·TMEDA to afford dimeric **3** (((TMEDA)Na(*o*-C_6H_4-NMe_2))$_2$) , which in keeping with conventional metallation chemistry exhibits *ortho*-deprotonated anilines. The instability of **3** at ambient temperatures is reflected in its deprotonation of toluene under mild conditions and following co-complexation with the dialkyl zinc, a mixture of two products were isolated from the reaction, namely **4** ((TMEDA)Na(TMP)(*o*-C_6H_4-NMe_2)$_2$Zn(*t*-Bu)) and **5** ({$(TMEDA)_2Na$}$^+${(*t*-Bu_2Zn)$_2$(μ-NMe_2)}$^-$). The ion-pair product **5** contains a cleaved NMe_2 group, exemplifying nicely how the reactivity of an alkali-metal can be attenuated when incorporated in a mixed-metal system but to a point where it is still able to play its part in conducting synthetically useful smooth metallations.

The final component of bimetallic base **1**, TMP(H) was introduced at this stage, in what could be considered a copy of the second, multipart-step of the AMM*Zn* process and led to the isolation of **6** ((TMEDA)Na(TMP)(*o*-C_6H_4-NMe_2)Zn(*t*-Bu)), a regioisomer of **2** where the aromatic ring remains *ortho*-zincated. In search of the elusive *meta*-deprotonated derivative **2**, the reaction mixture was refluxed overnight and as a result of the harsher conditions and potentially, regeneration of sodium zincate **1**, the mono-deprotonated *meta*-derivative emerged as the predominant product.

Significantly, these results underline the importance of the acid/base character of TMP(H)/TMP$^-$ and the synergic bridge it provides between the two metals, for only when it is present, does the unique *meta*-regioselectivity materialise. Although this product has been engineered from the homometallic components, there are pitfalls in this indirect approach. The low kinetic stability of the *ortho*-sodiated intermediate leads to undesired side reactions such as deprotonation of solvent and decomposition of co-present reactants at temperatures tolerated by the synergic base, and the harsh reflux conditions required to bring about the presence of the *meta*-zincated derivative offers less control, ultimately leading to competing di-metallation of the aromatic substrate.

In addition DFT studies probing the different metallation regioselectivities obtained from homometallic and heterobimetallic bases highlight the importance of the interactions between the alkali metal and the aromatic substrate. With the conventional monometallic reagent *n*-BuNa/TMEDA, metallation is directed to the *ortho*-position by the secondary interaction between Na and the N atom of the NMe_2 group. In contrast, in the reaction of **1** with *N*,*N*-dimethylaniline, the *meta*-isomer is energetically the most preferred and analysis of the dimensions of the model structures suggest that the strength of the combined Na···Cπ contacts contribute at least in part to its stability. This favourable enthalpic effect, along with the communication between the metals provided by the TMP bridge play a defining role in offering the unique regioselectivity observed in the AMM*Zn* of *N*,*N*-dimethylaniline.

Finally, looking at the bigger picture, this study drives home the fact that bimetallic reagents can offer chemistry distinct to that when two monometallic reagents are added sequentially to the same substrate. The secret to unlocking special synergic reactivity may be found in coupling both metals within the same bimetallic reagent. We plan to capitalise on this advantage in ongoing studies, investigating the generality of the concept.

Experimental

General

All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. Hexane, THF and toluene purchased from Sigma-Aldrich, were dried by heating to reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. *n*-BuNa [43], *t*-Bu_2Zn [15] and subsequently **1** ((TMEDA)Na(TMP)(*t*-Bu)Zn(*t*-Bu)) [15] were prepared according to literature procedures. The ^1H NMR spectroscopic experiments were performed on a Bruker DPX400 spectrometer at an operating frequency of 400.13 MHz. The ^{13}C NMR spectra were obtained on the same instrument at an operating frequency of 100.62 MHz. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyser. Due to the extreme air and moisture sensitivity of **3**, **4/5** and **6**, ideal analyses could not be obtained. GC–MS analysis was performed on an Agilent 7890A apparatus, GC with 5975C triple axes detector, run under CI mode (methane).

X-ray crystallography

All data were collected at 123(2) K on an Oxford Diffraction Gemini S Diffractometer with Mo Kα radiation (λ = 0.71073

Å). Structures were solved using SHELXS-97 [44] while refinements were carried out on F^2 against all independent reflections by the full-matrix least-squares method using the SHELXL-97 program [44]. With the exception of the carbon atoms of the disordered components of TMEDA present in **4** and **5** all non-hydrogen atoms were refined using anisotropic thermal parameters. CCDC 813771 (**3**), 813772 (**4**/**5**) and 813773 (**6**) contain the full supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for **3**: $C_{28}H_{52}N_6Na_2$, M = 518.74, monoclinic, $P2_1/c$, a = 8.8060(9), b = 17.5089(12), c = 11.1635(11) Å, β = 111.693(12)°, V = 1599.3(3) $Å^3$, Z = 2. 8277 reflections collected, 3797 were unique, R_{int} = 0.0454, R = 0.0471, R_w = 0.1133, GOF = 0.905, 169 refined parameters, max and min residual electron density = 0.233 and −0.161 $e \cdot Å^{-3}$.

Crystal data for **4**/**5**: $C_{82}H_{164}N_{13}Na_3Zn_4$, M = 1662.71, triclinic, $P{-}1$, a = 9.3229(2), b = 20.0052(4), c = 26.2813(6) Å, α = 86.732(2)°, β = 82.721(2)°, γ = 87.247(2)°, V = 4850.10(18) $Å^3$, Z = 2. 57508 reflections collected, 19054 were unique, R_{int} = 0.0630, R = 0.0413, R_w = 0.0680, GOF = 0.839, 956 refined parameters, max and min residual electron density = 0.969 and −0.682 $e \cdot Å^{-3}$. Disorder in the TMEDA groups was treated as being over two sites, appropriate restraints on atom-atom distances and temperature factors in these groups were applied.

Crystal data for **6**: $C_{27}H_{53}N_4NaZn$, M = 522.09, orthorhombic, $Pbca$, a = 16.1371(5), b = 17.2078(5), c = 21.6306(5) Å, V = 6006.5(3) $Å^3$, Z = 8. 32010 reflections collected, 7240 were unique, R_{int} = 0.0540, R = 0.0371, R_w = 0.0853, GOF = 0.881, 311 refined parameters, max and min residual electron density = 0.804 and −0.289 $e \cdot Å^{-3}$.

Synthesis of 3 ((($(TMEDA)Na(C_6H_4\text{-}NMe_2))_2$) : *n*-BuNa (2 mmol, 0.16 g) was suspended in hexane (10 mL) and sonicated for 10 min to form a fine dispersion. The Schlenk tube was then cooled to 0 °C in an ice bath before the dropwise introduction of TMEDA (2 mmol, 0.3 mL). *N*,*N*-dimethylaniline (2 mmol, 0.25 mL) was then added dropwise to the clear yellow solution to give an orange solution which was stirred at 0 °C for 2 hours and the resulting light orange precipitate was removed by filtration (0.33 g, 64% – based on monomeric unit). The deep red filtrate solution was concentrated in vacuo and stored in a refrigerator (5 °C) to yield a small amount of X-ray quality, orange crystalline material. ^{1}H NMR (400.13 MHz, d_{12}-cyclohexane, 300 K) δ 7.78 (d, 1H, H_{meta}), 6.79 (t, 1H, $H_{meta'}$), 6.58 (m, 2H, H_{para} and $H_{ortho'}$), 2.83 (s, 6H, $N(CH_3)_2$), 2.22 (s, 4H, CH_2 (TMEDA)), 2.04 (s, 12H, CH_3 (TMEDA)); ^{13}C NMR (100.62 MHz, d_{12}-cyclohexane, 300 K) δ 182.3 (Na–C_{ortho}), 164.1 (C_{ipso}), 142.7 (C_{meta}), 124.6 ($C_{meta'}$), 120.2 (C_{para}), 111.5 ($C_{ortho'}$), 58.6 (CH_2 (TMEDA)), 46.0 (CH_3 (TMEDA)), 45.0 ($N(CH_3)_2$).

Synthesis of 4 ($(TMEDA)Na(TMP)(C_6H_4\text{-}NMe_2)_2Zn(t\text{-}Bu)$) and 5 ($\{(TMEDA)_2Na\}^+\{(t\text{-}Bu_2Zn)_2(\mu\text{-}NMe_2)\}^-$): A hexane solution of *t*-Bu_2Zn (2 mmol, 0.36 g) was added via cannula to a suspension of **3**, prepared as described above. The mixture was allowed to stir for 1 hour at 0 °C, and then slowly warmed to room temperature and stirred for a further two hours at this temperature. The suspension was gently heated for a couple of minutes to obtain (as close as possible) a yellow homogeneous solution: The latter was left in a Dewar flask filled with hot water overnight to afford 0.6 g of colourless crystals. ^{1}H NMR (400.13 MHz, d_6-benzene, 300 K) δ 8.03 (d, 1H, H_{meta}), 7.87 (d, 0.27H, H_{meta}), 7.17 (overlap with solvent, 2.5H, $H_{meta'}$), 7.06 (t, 1H, H_{para}), 7.01 (t, 0.29H, H_{para}), 6.86 (t, 0.29H, $H_{meta'}$), 6.72 (d, 1H, $H_{ortho'}$), 6.60 (d, 0.28H, $H_{ortho'}$); ^{13}C NMR (100.62 MHz, d_6-benzene, 300 K) δ 159.4 (Na–C_{ortho} (major)), 157.0 (C_{ipso} (major)), 140.2 (C_{meta} (major)), 139.5 (C_{meta} (minor)), 126.0 ($C_{meta'}$ (major)), 125.4 (C_{para} (minor)), 120.9 (C_{para} (major)), 119.5 ($C_{meta'}$ (minor)), 113.8 ($C_{ortho'}$ (major)), 112.2 ($C_{ortho'}$ (minor)). The relevant resonances for the remaining quaternary carbons in the minor *ortho*-deprotonated product, C_{ipso} and Na–C_{aryl} could not be detected. Due to the presence of three species and resulting complexity, no correlation could be drawn between these signals and those in the aliphatic region.

Synthesis of 6 ($(TMEDA)Na(TMP)(C_6H_4\text{-}NMe_2)Zn(t\text{-}Bu)$): The above-mentioned procedure was repeated and TMP(H) (2 mmol, 0.34 mL) was introduced to the mixture. The resulting yellow suspension was allowed to stir overnight, after which time the resulting white precipitate was collected by filtration (0.32 g, 31%). The precipitate was re-dissolved in warm hexane and allowed to cool to ambient temperature to afford a small amount of colourless crystals (recrystallised yield: 0.07 g, 7% – not optimised). ^{1}H NMR (400.13 MHz, d_8-THF, 300 K) δ 7.48 (d, 1H, H_{meta}), 6.92 (t, 1H, $H_{meta'}$), 6.81 (d, 1H, $H_{ortho'}$), 6.75 (t, 1H, H_{para}), 2.70 (s, 6H, $N(CH_3)_2$), 2.31 (s, 4H, CH_2 (TMEDA)), 2.15 (s, 12H, CH_3 (TMEDA)), 1.74 (m, 2H, γ-TMP), 1.37 (br, 4H, β-TMP), 1.20 (s, 12H, CH_3 (TMP)), 0.98 (s, 9H, CH_3 (*t*-Bu)); ^{13}C NMR (100.62 MHz, d_8-THF, 300 K) δ 165.0 (Zn–C_{ortho}), 160.1 (C_{ipso}), 141.2 (C_{meta}), 125.5 ($C_{meta'}$), 122.2 (C_{para}), 114.9 ($C_{ortho'}$), 58.9 (CH_2 (TMEDA)), 53.1 (α-TMP), 46.8 ($N(CH_3)_2$), 46.2 (CH_3 (TMEDA)), 40.7 (β-TMP), 36.1 (CH_3 (TMP)), 35.7 (CH_3 (*t*-Bu)), 20.6 (γ-TMP), 19.8 (C_q (*t*-Bu)).

Electrophilic quenching reactions: The solutions prepared as described above, were treated with a freshly prepared solution of 1 M iodine in THF (7 mmol, 7 mL) and allowed to stir overnight. A solution of NH_4Cl (5 mL) was added along with a saturated $Na_2S_2O_3$ solution until bleaching occurred (5 mL). The organic layer was separated from the aqueous layer and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give a yellow oil. The NMR spectrum of the crude material was recorded to determine the yield of the iodo-product relative to *N*,*N*-dimethylaniline.

2-Iodo-*N*,*N*-dimethylaniline: ^{1}H NMR (400.13 MHz, d_6-benzene, 300 K) δ 7.76 (d, 1H, H_{meta}), 6.98 (t, 1H, $H_{meta'}$), 6.72 (d, 1H, $H_{ortho'}$), 6.46 (t, 1H, H_{para}), 2.45 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100.62 MHz, d_6-benzene, 300 K) δ 155.4 (C_{ipso}), 140.5 (C_{meta}), 129.1 ($C_{meta'}$), 125.2 (C_{para}), 120.9 ($C_{ortho'}$), 97.9 (I–C_{ortho}), 44.7 ($N(CH_3)_2$).

3-Iodo-*N*,*N*-dimethylaniline: ^{1}H NMR (400.13 MHz, d_6-benzene, 300 K) δ 7.05 (d, 1H, H_{para}), 6.98 (s, 1H, H_{ortho}), 6.70 (t, 1H, $H_{meta'}$), 6.34 (d, 1H, $H_{ortho'}$), 2.32 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100.62 MHz, d_6-benzene, 300 K) δ 151.8 (C_{ipso}), 130.6 ($C_{meta'}$), 125.5 (C_{para}), 121.4 (C_{ortho}), 111.7 ($C_{ortho'}$), 96.0 (I–C_{meta}), 39.7 ($N(CH_3)_2$).

4-Iodo-*N*,*N*-dimethylaniline: ^{1}H NMR (400.13 MHz, d_6-benzene, 300 K) δ 7.42 (d, 2H, H_{meta}), 6.13 (d, 2H, H_{ortho}), 2.36 (s, 6H, $N(CH_3)_2$); ^{13}C NMR (100.62 MHz, d_6-benzene, 300 K) δ 150.9 (C_{ipso}), 137.8 (C_{meta}), 115.0 (C_{ortho}), 77.7 (I–C_{para}), 39.8 ($N(CH_3)_2$).

GC–MS (CI) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{10}IN$, 246.9; found, 247.9.

For unidentified species, GC–MS (CI) *m*/*z*: $[M + H]^+$ calcd for $C_8H_9I_2N$, 372.8; found, 373.8.

Supporting Information

Supporting Information File 1

Computational details and NMR spectra for compounds **3**, **4**, **5** and **6**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-144-S1.pdf]

Supporting Information File 2

CIF files giving crystallographic data for compounds **3**, **4**, **5** and **6**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-144-S2.txt]

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Use of mixed Li/K metal TMP amide (LiNK chemistry) for the synthesis of [2.2]metacyclophanes

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Full Research Paper

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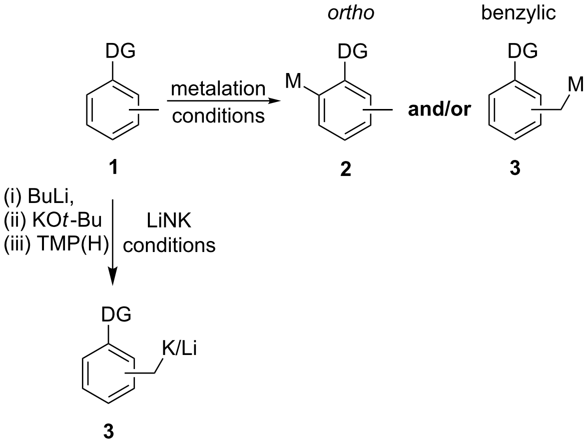
Abstract

A new two-step general approach to [2.2]metacyclophane synthesis from substituted *m*-xylenes is described. The strategy employs a selective benzylic metalation and oxidative C–C bond formation for both synthetic operations. Regioselective benzylic metalation is achieved using the BuLi, KO*t*-Bu, TMP(H) (2,2,6,6-tetramethylpiperidine) combination (LiNK metalation conditions) and oxidative coupling with 1,2-dibromoethane. The synthetic ease of this approach compares favourably with previously reported methods and allows for ready access to potentially useful planar chiral derivatives.

Introduction

While direct metalation reactions are an essential contribution to the repertoire of modern synthetic methods, an underlying and often underestimated challenge remains in the achievement of predictable selective metalations of substrates that offer several potential sites of reaction. Examples of such challenges include the selective aryl metalation of arenes containing more than one directing group (DG), arene metalation in positions not *ortho* to the directing group, or the identification of reaction conditions to achieve selective benzylic metalation of substituted toluenes **1** to provide **3** (Scheme 1) [1-5]. We recently reported that mixed Li/K metal TMP amide (LiNK metalation conditions) is uniquely suited for the selective achievement of challenging metalations. Specifically, the use of the reagent triad BuLi/KO*t*-Bu/TMP(H) to generate a mixed Li/K metal TMP amide in situ has proven to be an efficient and general method to achieve vinyl and benzylic metalations with excellent selectivity [6,7]. We now exploit this selective benzylic metalation protocol for the specific synthesis of [2.2]metacyclophanes.

Chemists have a long-standing fascination for the [2.2]cyclophane structures and have extensively studied their unusual



Scheme 1: Selective benzylic metalation with LiNK conditions. DG = directing group.

physical and chemical properties induced by the close spatial proximity of their aryl rings [8]. Undoubtedly the most studied of the series (*ortho*, *meta* and *para*) are the [2.2]paracyclophanes, which have seen a recent resurgence of interest notably as planar chiral scaffolds for asymmetric catalysis [9-13]. Surprisingly, the [2.2]metacyclophanes, which also have the potential to be exploited as planar chiral templates, have received scant attention since the seminal reports of Schlögl in the early 1970s [14-16]. One possible explanation for this is the cumbersome methods required for their synthesis. Typical approaches have utilised Wurtz coupling, the oxidation and thermal (500–600 °C) extrusion of SO_2 from dithia[3.3]cyclophanes or the photochemical ring contraction of diselena[3.3]cyclophanes [17-21].

We envisaged that our LiNK metalation conditions with in situ oxidative coupling could offer a facile general approach to [2.2]metacyclophanes, which would be of general synthetic interest (Scheme 2). Oxidative homo-coupling of benzyl anions has previously been noted, but it has remained relatively unexplored as a synthetic procedure [22-24]. We speculated that if oxidative coupling of the benzyl metalated xylenes **5** could be achieved to form the open dimer **6**, then a second metalation and oxidative ring closure would yield the [2.2]metacyclophanes **8**. A stepwise approach, as shown in Scheme 2, could allow for the introduction of different groups on each of the aryl rings. In addition, it could facilitate the synthesis of planar chiral derivatives without the complication of mixtures with achiral isomers being generated, which occurs if, for example, a 1-substituted-2,4-bis(halomethyl)benzene is used as the starting compound [15].

Results and Discussion

In order to examine the scope and potential of this approach, five differently substituted xylenes were investigated, namely *m*-xylene (**4a**), mesitylene (**4b**), 1-methoxy-3,5-dimethylbenzene (**4c**), (3,5-dimethylphenyl)dimethylamine (**4d**) and 2,4-dimethylbenzoic acid (**4e**) (Figure 1). These xylenes present interesting challenges for metalation selectivity in that for derivatives **4a**–**d** both methyl groups are equivalent and so the

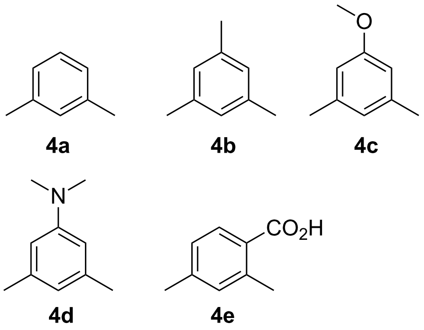
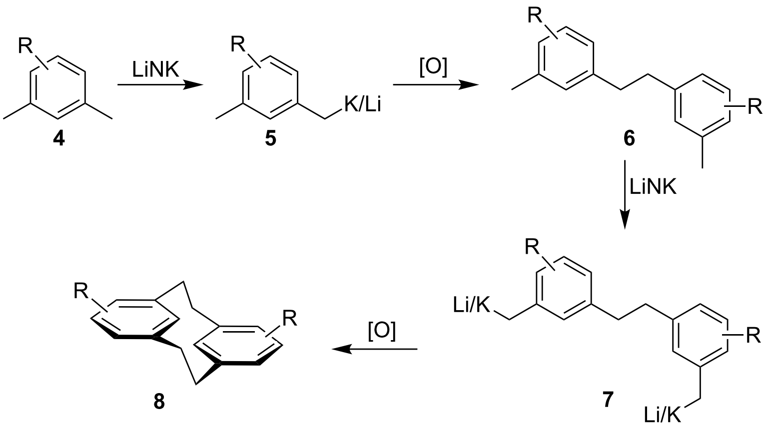


Figure 1: Xylene substrates.



Scheme 2: Iterative LiNK/oxidative coupling synthesis of [2.2]metacyclophanes.

alternative metalation sites are in the aryl ring, whereas the challenge is elevated for **4e** as it contains two differing benzylic sites and an *ortho*-aryl position primed for metalation by a strong directing group.

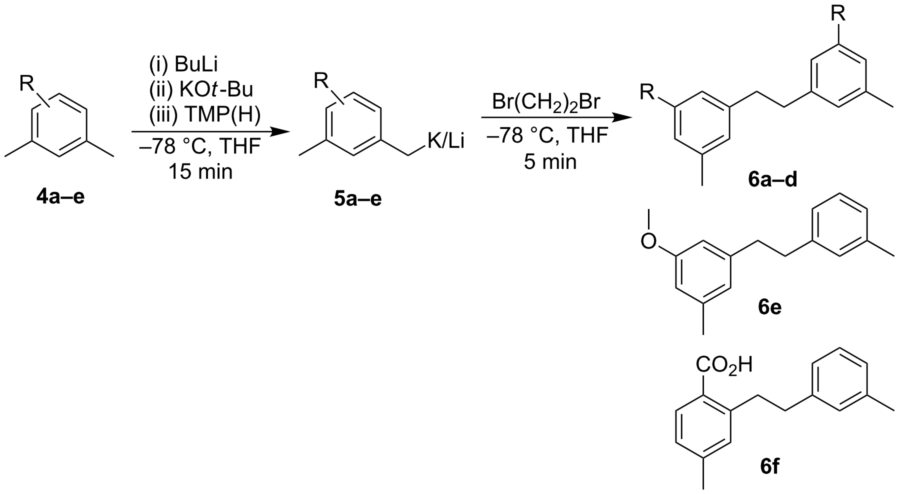
Sequential treatment of **4a–d** with BuLi, KO*t*-Bu and TMP(H) at −78 °C followed by the oxidant 1,2-dibromoethane [25] gave good to excellent yields of the targeted homo-dimer products **6a–d** (Table 1, entries 1–4). It was also possible to form a "mixed dimer" by the reaction of **4a** and **4c** together, which gave **6e**, containing one *m*-OCH_3 substituted aryl ring, in a 22% yield (Table 1, entry 5) following chromatography to remove the other homo-coupled products (**6a**, **6c**). A similar approach was used in a combined reaction of **4a** and **4e**, giving purified 4-methyl-2-(3-methylphenethyl)benzoic acid (**6f**) (Table 1, entry 6). This product is the result of oxidative hetero coupling of benzylic metalated xylene and 2-(methyl-metalated)-4-methylbenzoate.

To more clearly illustrate a site selective metalation of **4e** for the methyl group *ortho* to the carboxylate, this substrate was metalated using LiNK metalation conditions (using an addition equivalent of BuLi to first deprotonate the carboxylic acid) and quenched with CD_3OD. It was anticipated that under our low temperature yet thermodynamically controlled conditions the selective site of metalation should be the more acidic 2-methyl position [26]. This was confirmed by ^2H NMR, which showed that incorporated deuterium was above 90% in the 2-methyl position with less than 10% in the 4-methyl group and no detectable aryl deuteration (Figure 2).

A similar experiment was carried out for the even more complex hetero-dimer substrate **6f**, in which a selective di-benzylic metalation of the two different methyl positions was attempted. Treatment of **6f** with three equivalents of BuLi (one to deprotonate the carboxylic acid) and two equivalents of KO*t*-Bu/TMP(H) followed by deuteration gave the di-deuterated product D_2-**6f**. ^2H NMR analysis showed no aryl or bridging methylene deuteration, with deuterium incorporated only into the two non-equivalent benzylic methyl positions (Figure 3).

With the benzylic metalation confirmed, the second step to complete the [2.2]metacyclophane synthesis required identical conditions to the first to provide the di-benzylic metalated derivatives **7** (Table 2)**.** We anticipated that an intramolecular ring closing by oxidative coupling would provide the desired

Table 1: Oxidative coupling of benzylic metalated xylenes **4**.



Entry	Substrate	R	Product	Yield %
1	**4a**	H	**6a**	91
2	**4b**	CH_3	**6b**	72
3	**4c**	OCH_3	**6c**	92
4	**4d**	$N(CH_3)_2$	**6d**	49
5	**4a**/**4c**	OCH_3/H	**6e**	22[a]
6	**4a**/**4e**	CO_2H/H	**6f**	13[b]

[a] **6a** and **6c** also obtained in 14% and 49% yields respectively.
[b] **6a** and dimer of **4e** also obtained in 11% and 62% yields respectively.

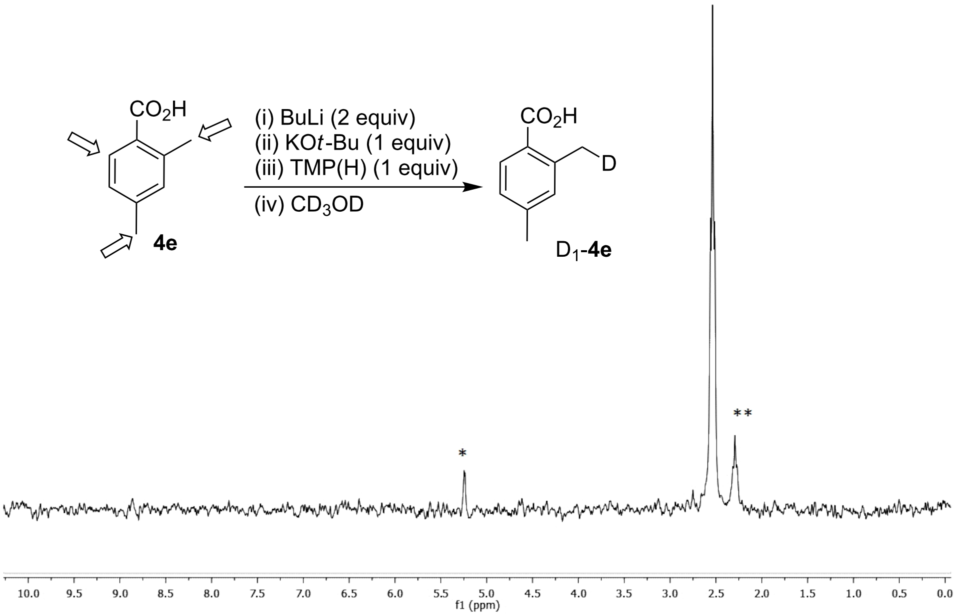


Figure 2: Metalation selectivity for **4e** (arrows indicate potential metalation sites). ^{2}H NMR spectrum in CH_2Cl_2. *CD_2Cl_2. **2-Methyl-4-D-methylbenzoic acid.

cyclophane product in addition to open chain oligomers or larger ring systems.

Substrates **6a**–**e** were treated with two equivalents of BuLi/KO*t*-Bu/TMP(H) to generate the corresponding dianions **7a**–**e**, which upon oxidative coupling gave the corresponding metacyclophanes **8a**–**e**. This provided unsubstituted cyclophane **8a** in 40% yield and 5,13-disubstituted derivatives **8b**–**d**, containing CH_3, OCH_3 and $N(CH_3)_2$ substituents respectively, in comparable yields (Table 2, entries 1–4). In addition, the mono-

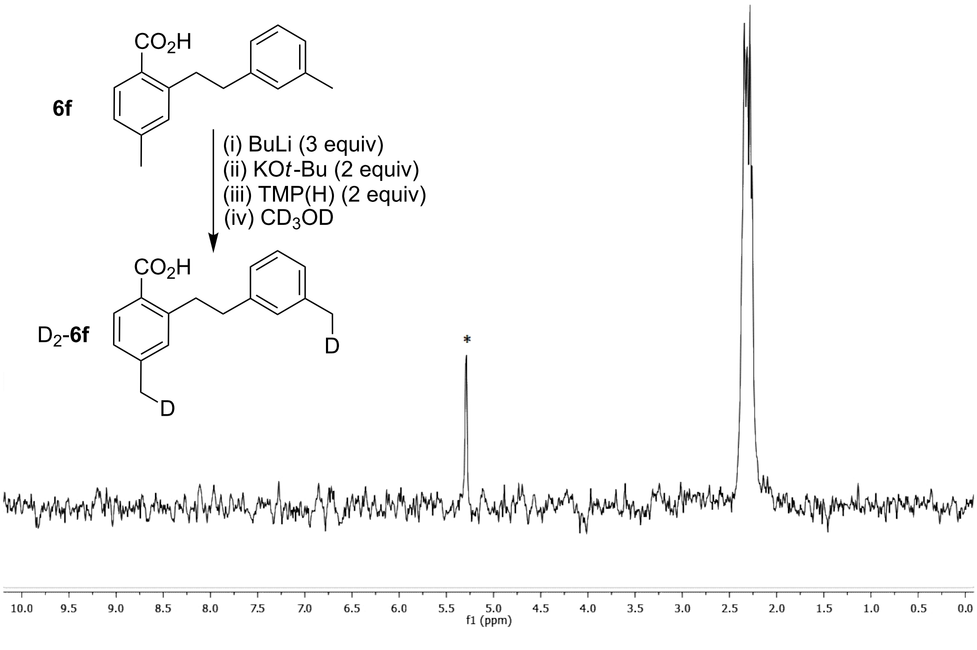
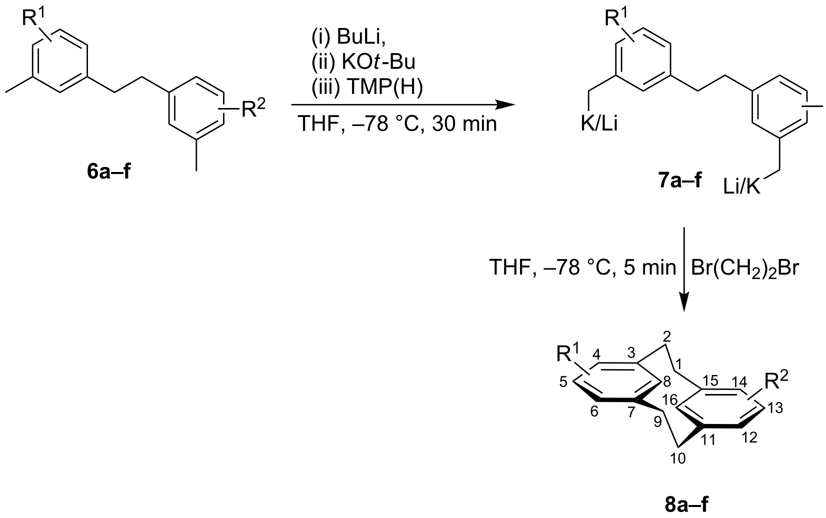


Figure 3: Di-metalation selectivity for **6f**. ^{2}H NMR spectrum in CH_2Cl_2. *CD_2Cl_2.

Table 2: Metalation/oxidative coupling to [2.2]metacyclophanes.



Entry	Substrate	R^1/R^2	Position	Product	Yield %
1	**6a**	H/H	—	**8a**	40
2	**6b**	CH_3/CH_3	5,13	**8b**	54
3	**6c**	OCH_3/OCH_3	5,13	**8c**	33
4	**6d**	$N(CH_3)_2/N(CH_3)_2$	5,13	**8d**	43
5	**6e**	OCH_3/H	5	**8e**	42
6	**6f**	CO_2H/H	4	**8f**	39

methoxy substituted derivative **6e** was effectively ring closed under our reaction conditions to yield **8e** in a 42% yield. In each case, the majority of the remaining material was oligomeric in nature, although it was not characterised. Substrate **6f** offered the potential to generate the planar chiral 4-carboxylic acid substituted metacyclophane **8f**. This was readily achieved in a 39% yield, with the characteristic NMR aromatic proton signals for C(H)-8/16 observed at 4.21 and 4.18 ppm. The efficient two step synthesis of a C(4)-substituted planar chiral **8f** was achieved from inexpensive substrates, under identical reagent conditions for both steps. This compares favourably to the previously reported elaborate seven step synthesis, which was required due to the difficulties of incorporating substituents at the C(4) position after metacyclophane synthesis [27,28]. The resolution of **8f** by salt formation with (+)-1-phenylethylamine [27] has previously been accomplished.

The stepwise *anti* conformation of the metacyclophane **8c** was confirmed by single crystal X-ray analysis. Cyclophane **8c** crystallised by the slow room temperature evaporation of a diethyl ether solution, into the monoclinic space group $P2_1/n$ as shown in Figure 4. **8c** contains an inversion centre with the co-planar aromatic rings bent into shallow boat forms with an angle of 8.9(1)° from planarity. The intra-annular distance as measured from C(8) to C(16) is as expected for [2.2]metacyclophanes at 2.66(1) Å [29].

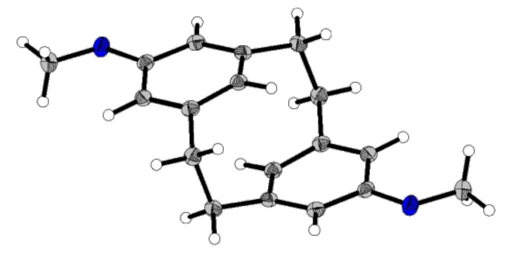


Figure 4: X-Ray structure of **8c** with thermal ellipsoids drawn at 50% probability level.

Conclusion

A new two-step general approach to [2.2]metacyclophane synthesis was described from substituted *m*-xylenes. Our strategy employs a selective benzylic metalation and oxidative C–C bond formation for both synthetic operations under LiNK metalation conditions. The synthetic ease of this approach compares favourably with previously reported methods and allows for ready access to potentially useful planar chiral derivatives. Expansion of this strategy to other chiral cyclophane architectures is ongoing and will be reported in due course. Additional synthetic applications of LiNK metalation conditions are also under development.

Supporting Information

Supporting Information File 1

All experimental details, ^{1}H and ^{13}C NMR spectra for compounds **6a–f** and **8a–f** and X-ray crystallographic data for **8c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-145-S1.pdf]

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Combined directed *ortho*-zincation and palladium-catalyzed strategies: Synthesis of 4,n-dimethoxy-substituted benzo[*b*]furans

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Abstract

A new route to regioselectively dialkoxy-functionalized benzo[*b*]furan derivatives has been developed from 3-halo-2-iodoanisoles bearing an additional methoxy group, which have been accessed through an *ortho*-zincation/iodination reaction. Two palladium-catalyzed processes, namely a Sonogashira coupling followed by a tandem hydroxylation/cyclization sequence, give rise to new and interesting dimethoxy-substituted benzo[*b*]furans.

Introduction

The directed *ortho*-metallation (D*o*M) reaction has been widely used as a powerful and efficient method for regioselective functionalization of aromatic compounds and different directing groups have been used to facilitate the deprotonation reaction [1-5]. Various strong bases such as alkyl lithiums and their derivatives (for instance, TMEDA-activated complexes [6] and heavier alkali metal *tert*-butoxide-complexed alkyl lithium reagents, known as superbases and introduced by Schlosser [7]), as well as lithium dialkylamides, have usually been employed to perform deprotonative metallations. Whereas the use of these strong bases has several limitations regarding the presence of certain functional groups (mainly carboxylic acid derivatives and halogens), the introduction in the last years of new organometallic "ate" complexes [8,9], which combine an alkali metal with either magnesium, zinc, aluminium, or copper, has allowed more selective metallation reactions. The milder reaction conditions required make these deprotonation reactions tolerant to the coexistence of a wider range of functional groups. In this field, the work of Kondo and Uchiyama is remarkable as they described highly chemo- and regioselective deprotonative zincation [10-12], alumination [13], and cupration [14] reactions of some functionalized aromatic and heteroaromatic compounds, as well as of *meta*-functionalized haloaromatics. In particular, the alkali metal mediated zincation reactions have turned out to be very useful processes and the structures and reaction pathways of TMP-zincates (TMP = 2,2,6,6-tetramethylpiperidine) have been studied in detail [15-19].

On the other hand, benzo[*b*]furan is a basic skeleton found in a variety of significant natural products [20], and some derivatives are also used as organic materials, due to their optical and electronic properties [21]. Thus, many synthetic efforts have been devoted to the synthesis of this type of compound [22,23]. In particular, several benzo[*b*]furan derivatives with oxygen-bearing substituents, such as hydroxy, or alkoxy, at the benzene moiety are known to be biologically active compounds [24-28] (Figure 1).

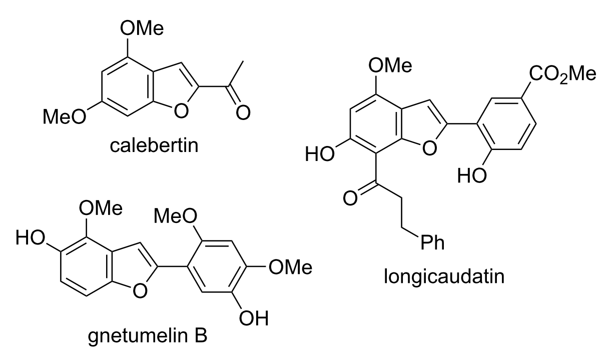
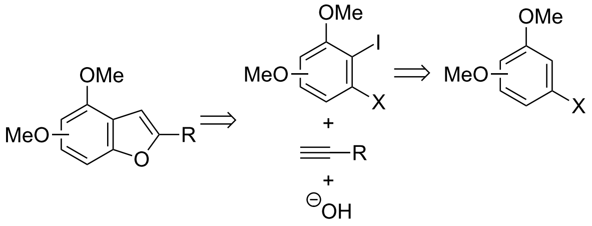


Figure 1: Some representative dihydroxybenzofuran derived natural products.

Among the various approaches developed for the synthesis of the benzofuran ring system, the cyclodehydration of α-aryloxy ketones [29], the Claisen rearrangement of an allyl aryl ether followed by Pd-catalyzed intramolecular oxidative cyclization [30], and the tandem Sonogashira coupling/heterocyclization of 2-halophenols with terminal alkynes [31], are some of the most used. However, their application to the synthesis of 4-substituted benzo[*b*]furans is especially challenging, because the *meta*-substituted starting materials tend to cyclize at the less hindered *ortho*-position, leading to the formation of 6-substituted heterocycles or a mixture of 6- and 4-substituted ones [32].

The D*o*M strategy, when linked with different cross-coupling Pd-catalyzed reactions, could provide a superior approach for the construction of polysubstituted aromatic and heteroaromatic compounds [33-38]. In this context, we studied the *o*-lithiation of 3-halophenols and the resulting 2,3-difunctionalized phenol derivatives were applied to the synthesis of 4-functionalized benzo[*b*]furans [39], 4- or 7-alkoxyindoles [40], and 7-oxy-substituted benzo[*b*]thiophenes [41] by employing Pd-catalyzed cross-coupling reactions or halocyclization processes. Following our interest in the development of strategies for the synthesis of functionalized benzo[*b*]furan derivatives [39], we envisaged that 4,n-dimethoxybenzo[*b*]furans could be regioselectively synthesized from 3-halo-2-iodoanisoles bearing an additional methoxy group, by combining two palladium-catalyzed processes, that is a selective Sonogashira coupling and a tandem hydroxylation/heterocyclization reaction. The required *o*-dihaloanisole derivatives could be prepared by a selective *ortho*-metallation reaction and subsequent electrophilic quenching with iodine (Scheme 1).

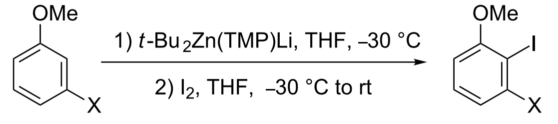


Scheme 1: Retrosynthetic analysis of 4,n-dimethoxy-substituted benzo[*b*]furans.

Results and Discussion

As established in our proposed retrosynthetic analysis (Scheme 1), we needed to develop a convenient synthesis of 3-halo-2-iodoanisoles bearing an additional methoxy group. Taking advantage of the deprotonative *ortho*-zincation of *meta*-functionalized haloaromatics by using TMP-zincates, described by Uchiyama and co-workers [11,12], we previously developed efficient syntheses of 3-chloro-2-iodoanisole (**2a**) and 3-bromo-2-iodoanisole (**2b**) from the corresponding 3-haloanisoles **1**, through their treatment with lithium di-*tert*-butyltetramethylpiperidinozincate, followed by electrophilic trapping of the intermediate arylzincate with iodine (Scheme 2) [40].

Thus, we decided to test this deprotonative metallation on the commercially available dimethoxyhalobenzene derivatives **3**

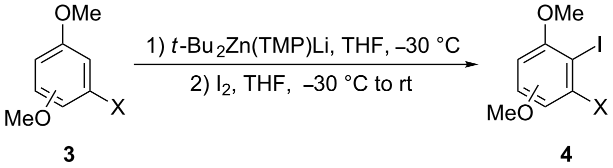


1a: X = Cl
b: X = Br

2a: X = Cl (84%)
b: X = Br (91%)

Scheme 2: Deprotonative zincation of 3-haloanisoles **1**.

Table 1: Synthesis of methoxy-substituted 3-halo-2-iodoanisoles **4**.



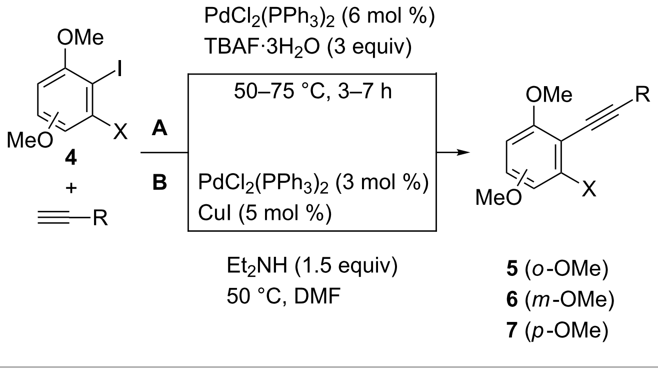
Entry	Starting material	X	OMe^a	Product	Yield (%)^b
1	**3a**	Cl	*ortho*	**4a**	70
2	**3b**	Br	*ortho*	**4b**	73
3	**3c**	Cl	*meta*	**4c**	88
4	**3d**	Br	*meta*	**4d**	75
5	**3e**	Cl	*para*	**4e**	78
6	**3f**	Br	*para*	**4f**	80

[a]Position of the additional methoxy group relative to the existing one. [b]Isolated yield based on the starting material **3**.

with the same *t*-Bu$_2$Zn(TMP)Li, easily prepared by reaction of preformed di-*tert*-butylzinc with lithium tetramethylpiperidide. Under these reaction conditions the zincation reactions took place regioselectively and, after treatment with iodine, afforded the corresponding 3-halo-2-iodoanisole derivatives **4** in good yields (Table 1). It is interesting to note that substrates **3c** and **3d** bearing the two methoxy groups in a *meta* relationship selectively undergo metalation at the position between the methoxy and the halide groups, irrespective of the nature of the halogen atom (chloro or bromo) (Table 1, entries 3 and 4).

Having an efficient protocol for the synthesis of dimethoxyhaloiodobenzene derivatives **4**, and with the retrosynthetic analysis outlined in Scheme 1 in mind, we tackled the selective introduction of an alkynyl moiety at the iodinated position. The presence of two different halogen atoms in compounds **4** implies that a selective Sonogashira coupling reaction should occur (Table 2). This has been achieved in two different ways. Considering the steric hindrance of the required position (*o*,*o*-disubstituted) we employed a copper- and solvent-free methodology for the Sonogashira coupling that uses tetrabutylammo-

Table 2: Synthesis of dimethoxy-substituted *o*-alkynylhaloarenes **5**–**7**.



Entry	Starting material	X	OMe^a	R	Product	Method^b	Yield (%)^c
1	**4a**	Cl	*ortho*	*n*-Bu	**5a**	A	65
2	**4a**	Cl	*ortho*	*c*-C_6H_9^{d}	**5b**	A	79
3	**4b**	Br	*ortho*	*n*-C_6H_{13}	**5c**	A	91
4	**4b**	Br	*ortho*	*n*-C_6H_{13}	**5c**	B	90
5	**4b**	Br	*ortho*	Ph	**5d**	A	83
6	**4b**	Br	*ortho*	Ph	**5d**	B	87

Table 2: Synthesis of dimethoxy-substituted *o*-alkynylhaloarenes **5**–**7**. (continued)

7	**4c**	Cl	*meta*	*n*-Bu	**6a**	A	57
8	**4c**	Cl	*meta*	*c*-C_6H_9[d]	**6b**	A	69
9	**4d**	Br	*meta*	*n*-C_5H_{11}	**6c**	A	63
10	**4d**	Br	*meta*	*n*-C_5H_{11}	**6c**	B	79
11	**4d**	Br	*meta*	Ph	**6d**	A	52
12	**4d**	Br	*meta*	Ph	**6d**	B	80
13	**4d**	Br	*meta*	4-MeC_6H_4	**6e**	A	75
14	**4e**	Cl	*para*	*n*-Bu	**7a**	A	69
15	**4f**	Br	*para*	*n*-C_5H_{11}	**7b**	A	55
16	**4f**	Br	*para*	*n*-C_5H_{11}	**7b**	B	95
17	**4f**	Br	*para*	Ph	**7c**	A	79
18	**4f**	Br	*para*	Ph	**7c**	B	92
19	**4f**	Br	*para*	3-FC_6H_4	**7d**	A	93

[a]Position of the additional methoxy group referred to the existing one. [b]Method A: alkyne (1.5–2 equiv), $PdCl_2(PPh_3)_2$ (6 mol %), TBAF·$3H_2O$ (3 equiv), 50–60 °C. Method B: alkyne (1.2 equiv), $PdCl_2(PPh_3)_2$ (3 mol %), CuI (5 mol %), Et_2NH (1.5 equiv), DMF, 50 °C. [c]Isolated yield based on the starting material **4**. [d]1-Cyclohexenyl.

nium fluoride as base [42] (Table 2, method A). Subsequently, we checked that the selective coupling could be carried out under standard Pd–Cu catalysis by controlling the reaction temperature [43,44] (Table 2, method B).

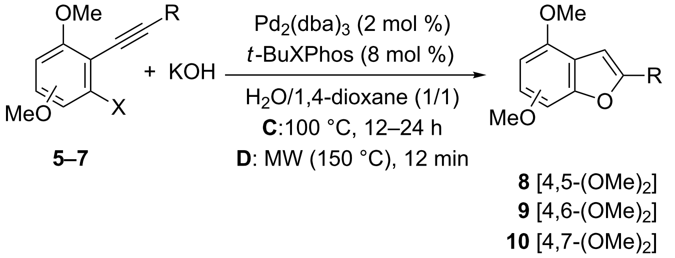
By either of these procedures, A or B, *o*-alkynylhaloarenes **5**–**7** were prepared usually in high yields from the corresponding dimethoxyhaloiodobenzenes **4** (Table 2). Starting from chloroiodo derivatives **4a,c** and **e** good yields were obtained for the corresponding coupled products **5**–**7** by using the Pd/TBAF method A, with no significant side-products (Table 2, entries 1,2,7,8 and 14). However, under these conditions bromine-containing compounds **4b,d** and **f** afforded variable amounts of dialkynylation products in some cases, and so the Pd/Cu catalyzed procedure B gave rise to better selectivities and yields of the desired alkynes **5**–**7** (Table 2, entries 4,6,10,12,16 and 18).

According to our retrosynthetic analysis (Scheme 1), the final step to achieve the benzofuran derivatives should be the incorporation of the hydroxy group followed by in situ heterocyclization. In recent years, the direct hydroxylation of aryl halides has been developed by several groups by using palladium- or copper-catalyzed protocols. Whereas the reactions under copper catalysis work well for aryl iodides [45-48], the palladium-catalyzed hydroxylation also takes place with aryl bromides and chlorides [49-51]. Thus, in our case we employed the Pd-catalyzed Buchwald protocol [49] in an attempt to synthesise the desired dimethoxybenzo[*b*]furan derivatives. Thus, reaction of the previously prepared *o*-haloaryl alkynes **5**–**7** with KOH, in the presence of catalytic amounts of $Pd_2(dba)_3$ and *t*-BuXPhos (2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl) at 100 °C in a 1:1 mixture of H_2O:1,4-dioxane, gave rise to the corresponding benzo[*b*]furan derivatives **8**–**10** in moderate to good yields (Table 3, method C). In general, slightly better results were obtained starting from aryl bromides instead of aryl chlorides. In addition, we also observed better yields for the corresponding benzofuran derivatives **9** (Table 3, entries 5–9) derived from the starting *o*-alkynylhalobenzene derivatives **6**, bearing the two methoxy groups in a 3,5-relationship relative to the halide. Moreover, because of the extended reaction times needed for complete consumption of the starting materials, we developed an alternative protocol under microwave irradiation that shortens the time required for the coupling to a few minutes (method D), and the final products were obtained in similar yields to those obtained by the conventional coupling method C.

Conclusion

We have developed a synthetic route to access regioselectively functionalized 4,n-dimethoxybenzo[*b*]furans through combined directed *ortho*-metallation (DoM)/palladium-catalyzed reactions. The deprotonative *ortho*-zincation of *meta*-functionalized haloanisoles bearing an additional methoxy group, followed by electrophilic quenching with iodine allows the regioselective and straightforward synthesis of highly functionalized dihalodimethoxybenzene derivatives. A subsequent selective Sonogashira coupling with terminal alkynes, followed by direct hydroxylation with KOH of the resulting *o*-haloaryl alkyne and in situ heterocyclization, afforded the benzo[*b*]furan derivatives. In addition, we have developed a new procedure for the Pd-catalyzed hydroxylation reaction that allows the coupling to take place within in a few minutes.

Table 3: Synthesis of dimethoxy-substituted benzo[*b*]furans **8**–**10**.



Entry	Starting material	X	R	Product	OMe[a]	Method[b]	Yield (%)
1	**5a**	Cl	*n*-Bu	**8a**	4,5-$(MeO)_2$	D	55
2	**5b**	Cl	*c*-C_6H_9[c]	**8b**	4,5-$(MeO)_2$	C	57
3	**5c**	Br	*n*-C_6H_{13}	**8c**	4,5-$(MeO)_2$	D	55
4	**5d**	Br	Ph	**8d**	4,5-$(MeO)_2$	C	50
5	**6a**	Cl	*n*-Bu	**9a**	4,6-$(MeO)_2$	C	62
6	**6b**	Cl	*c*-C_6H_9[c]	**9b**	4,6-$(MeO)_2$	C	73
7	**6c**	Br	*n*-C_5H_{11}	**9c**	4,6-$(MeO)_2$	C	70
8	**6d**	Br	Ph	**9d**	4,6-$(MeO)_2$	C	81
9	**6e**	Br	4-MeC_6H_4	**9e**	4,6-$(MeO)_2$	C	75
10	**7a**	Cl	*n*-Bu	**10a**	4,7-$(MeO)_2$	C	60
11	**7b**	Br	*n*-C_5H_{11}	**10b**	4,7-$(MeO)_2$	C	64
12	**7c**	Br	Ph	**10c**	4,7-$(MeO)_2$	D	71
13	**7d**	Br	3-FC_6H_4	**10d**	4,7-$(MeO)_2$	D	65

[a]Position of the methoxy groups referred to benzo[*b*]furan moiety. [b]Method C: conventional heating (100 °C, overnight). Method D: MW (50 W, 150 °C, 12 min). [c]1-Cyclohexenyl.

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. Copies of ^1H NMR and ^{13}C NMR spectra for new compounds.

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-146-S1.pdf]

Supporting Information File 2

NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-146-S2.pdf]

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Functionalization of heterocyclic compounds using polyfunctional magnesium and zinc reagents

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Review

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Abstract

In this review we summarize the most important procedures for the preparation of functionalized organzinc and organomagnesium reagents. In addition, new methods for the preparation of polyfunctional aryl- and heteroaryl zinc- and magnesium compounds, as well as new Pd-catalyzed cross-coupling reactions, are reported herein. Experimental details are given for the most important reactions in the Supporting Information File 1 of this article.

Introduction

The functionalization of heterocyclic scaffolds is an important task in current pharmaceutical research. In this review article, we describe the approaches to this problem that use functionalized magnesium and zinc heterocyclic intermediates. Some typical experimental procedures are indicated in each case for the most important methods. New Pd-catalyzed cross-coupling procedures are also presented.

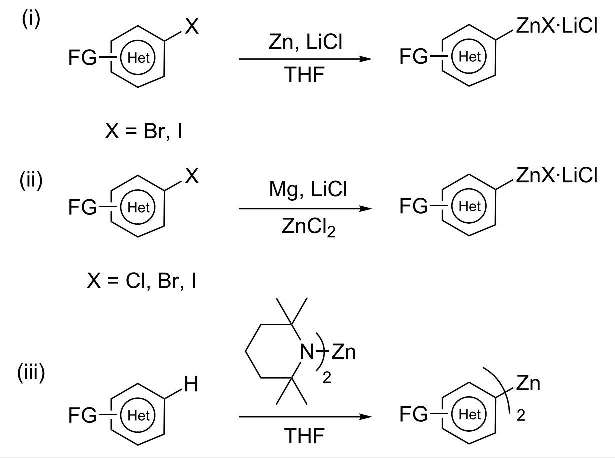
Review

1 Preparation of heterocyclic zinc reagents

Organozinc compounds [1-3] are important synthetic intermediates as they are compatible with a broad range of functional groups. The reactivity of a carbon–zinc bond is quite low, and therefore, reactions with organic electrophiles often require the use of transition metal catalysts. The preparation of aryl and heteroaryl zinc derivatives is conveniently achieved by three general procedures:

- the direct insertion of zinc dust to aryl or heteroaryl iodides or bromides;
- the direct insertion of magnesium in the presence of Zn(II) salts to aryl or heteroaryl halides;
- the metalation of aryl or heteroaryl derivatives with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$.

These three methods, developed recently in our laboratories, provide access to numerous heterocyclic zinc reagents (Scheme 1).



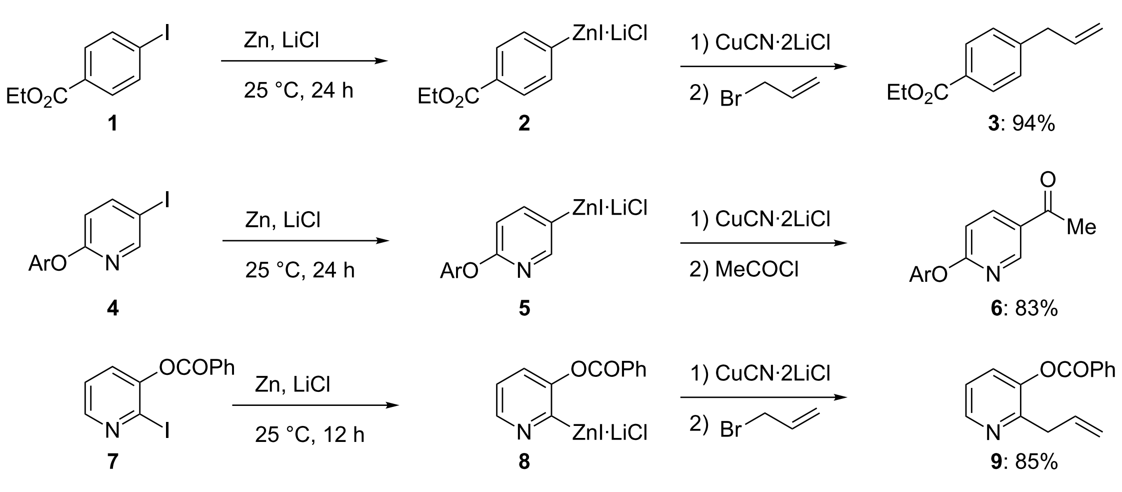
Scheme 1: Preparation of polyfunctional heteroarylzinc reagents.

1.1 The direct insertion of zinc in the presence of LiCl

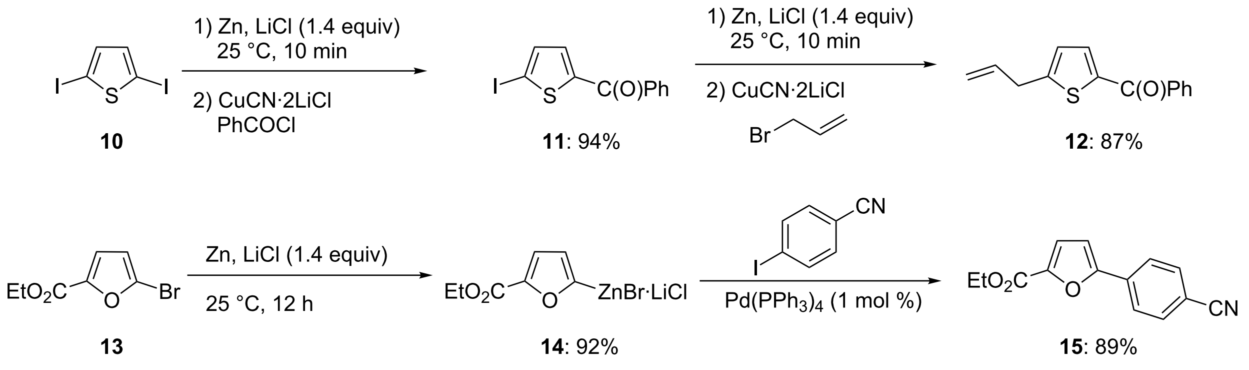
Although the direct insertion of zinc dust to alkyl iodides proceeds readily, the insertion to aryl iodides is very slow in THF and requires the use of polar solvents [4] or highly activated zinc [5]. Recently, we found that the presence of LiCl greatly facilitates the insertion of zinc to aryl iodides [6]. Thus, the insertion of zinc dust (activated with 1,2-dibromoethane and Me_3SiCl) to ethyl 4-iodobenzoate (**1**) at 70 °C provides less than 5% of zinc reagent **2** after a reaction time of 24 h. On the other hand, in the presence of one equivalent of LiCl, the insertion of zinc is completed within 24 h at 25 °C. After the addition of a catalytic amount of CuCN·2LiCl [7], the arylzinc intermediate is allylated with allyl bromide providing the ester **3** in 94% isolated yield (Scheme 2) [6].

This method can be extended to a broad variety of functionalized heterocyclic iodides such as the pyridines **4** and **7**. The corresponding zinc reagents **5** and **8** are obtained at 25 °C in quantitative yield. The allylation of pyridylzinc derivative **8** with allyl bromide provides pyridine **9** in 85% yield [6]. Interestingly, a diiodide, such as 2,5-diiodothiophene (**10**) reacts selectively with Zn and LiCl to provide the iodothienyl ketone **11** in 94% yield after benzoylation. Subsequent treatment of **11** with a second amount of Zn and LiCl (1.4 equiv) provides a new intermediate zinc reagent within 10 min, which after allylation provides the 2,5-disubstituted thiophene **12** in 87% yield (Scheme 3) [6]. The insertion reaction proceeds best with aryl and heteroaryl iodides, however, the presence of electron-withdrawing substituents greatly accelerates the zinc insertion rate and electron-poor-heteroaryl bromides, such as the bromofuran **13**, react smoothly with Zn and LiCl to furnish the furylzinc reagent **14** within 12 h at 25 °C, which after Pd-catalyzed cross-coupling (Negishi reaction) affords the 5-arylated furan **15** in 89% yield.

Interestingly, a high chemoselectivity is observed with several heterocyclic dihalides [8,9]. Thus, the tribromopyrimidine **16** provides only the 4-zincated pyrimidine **17**. After allylation, the expected allylated pyrimidine **18** is obtained in 63% yield. Also, the dibromothiazole **19** allows insertion of zinc only into the most labile C–Br bond (in position 2) leading to the zincated thiazole **20**. After Negishi cross-coupling [10-12], the 2-arylated thiazole **21** is obtained in 85% yield. Polar func-



Scheme 2: LiCl-mediated insertion of zinc dust to aryl and heteroaryl iodides.

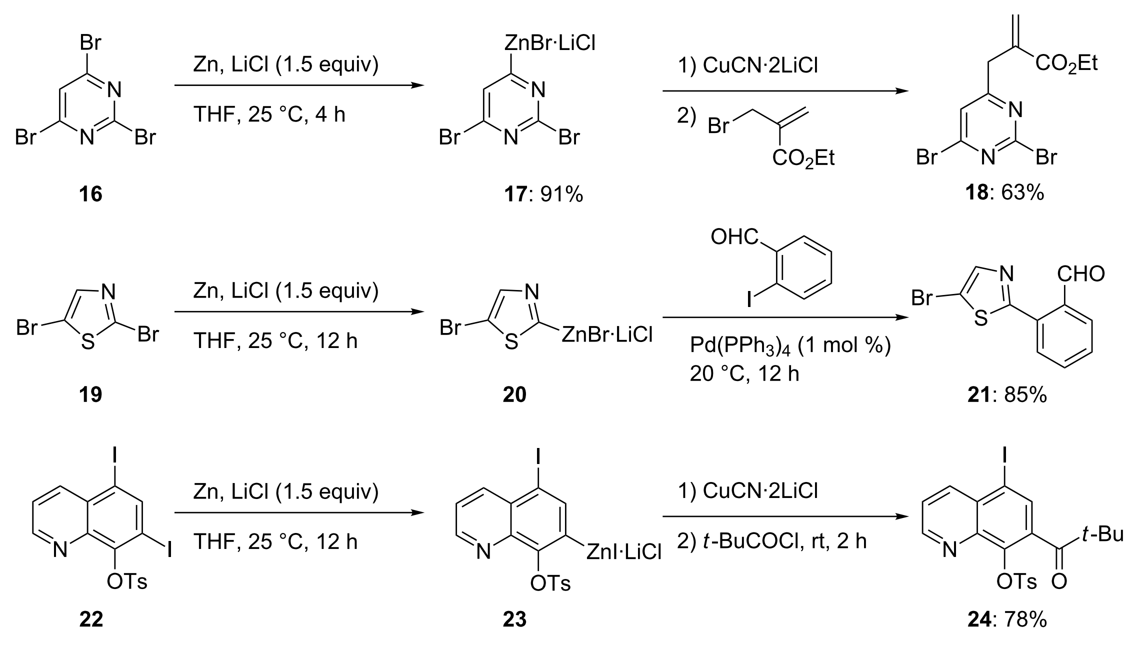


Scheme 3: Selective insertions of Zn in the presence of LiCl.

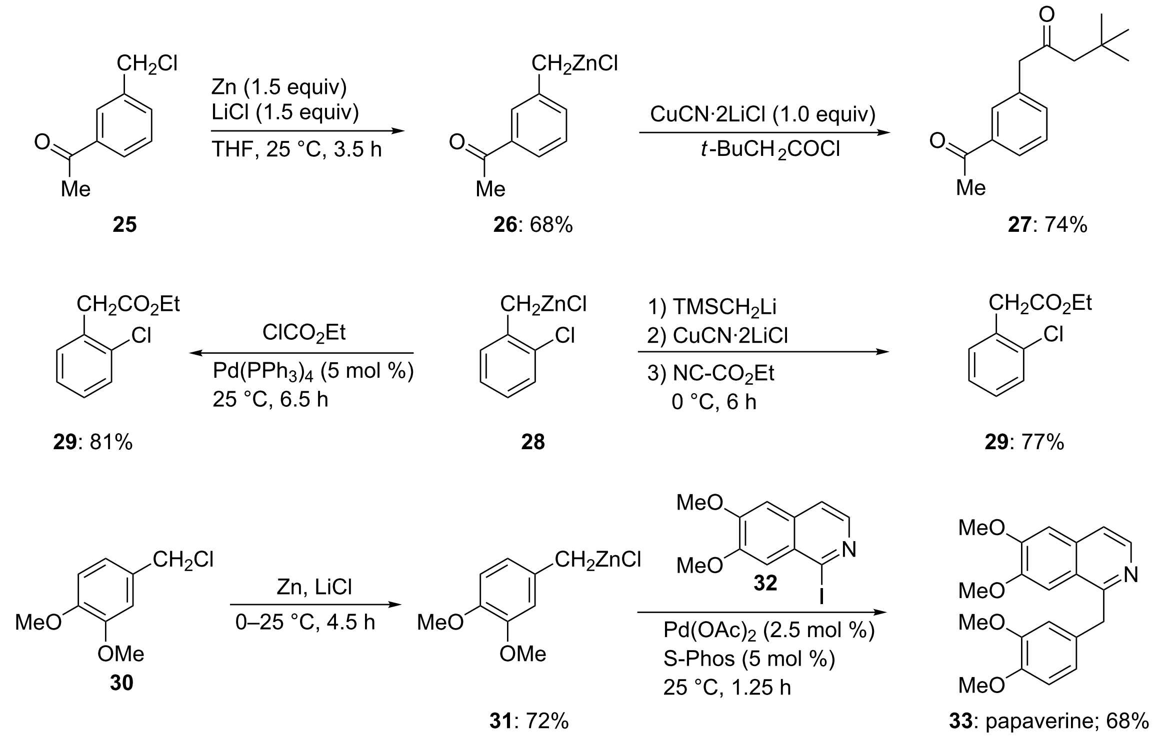
tional groups, such as a tosyloxy-group are able to direct the zincation. Thus, the diiodoquinoline **22** is regioselectively zincated (25 °C, 12 h) to intermediate **23** leading to the polyfunctional quinoline **24** in 78% yield after copper(I)-mediated acylation (Scheme 4 and Supporting Information File 1, Procedure 1) [8]. This regioselectivity is explained by the polar and electron-poor nature of the tosyloxy group, which leads to a strong electron-withdrawing effect and accelerates the insertion of zinc into the neighboring C–I bond. The presence of LiCl amplifies this effect through coordination to the tosyloxy group and to the *ortho*-iodide, and therefore facilitates the cleavage of this carbon–iodide bond.

This method has been extended to the preparation of benzylic zinc reagents [13]. A remarkable chemoselectivity is observed and functional groups, such as an acetyl group, are perfectly compatible with such synthesis. Thus, the reaction of the benzylic chloride **25** with zinc dust (1.5 equiv) and LiCl (1.5 equiv) in THF at 25 °C for 3.5 h provides the corresponding zinc reagent **26** in 68% yield. Its half-life at 25 °C is approximately two days. The copper(I)-mediated acylation of **26** provides the expected diketone **27** in 74% yield (Scheme 5) [13,14].

A broad range of functional groups are tolerated, and homocoupling products account for less than 5% of the total. These benzylic zinc reagents give access to biologically important phenylacetic acids. Thus, the treatment of the chloro-substituted benzylic zinc compound **28** with $ClCO_2Et$ in the presence of $Pd(PPh_3)_4$ (5 mol %) furnishes the phenylacetic derivative **29**



Scheme 4: Chemoselective insertion of zinc in the presence of LiCl.

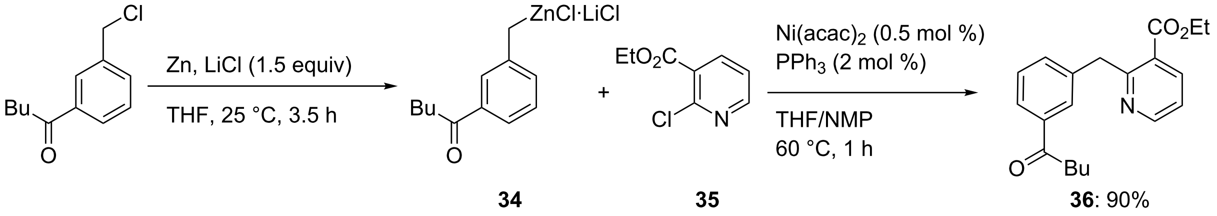


Scheme 5: Preparation and reactions of benzylic zinc reagents.

in 81% yield. Alternatively, a copper (I)-mediated reaction with NC-CO_2Et provides the same product in 77% yield when a dummy ligand is added (Scheme 5) [13]. Electron-rich benzylic chlorides, such as **30** are also readily converted to the desired zinc reagents **31**. The Pd-catalyzed cross-coupling of **31** with the iodoquinoline **32** and with S-Phos as ligand [15-17] provides the alkaloid papaverine (**33**) in 68% yield (Scheme 5) [13]. Ni-catalyzed cross-couplings can also be realized [14]. Thus, the reaction of the benzylic zinc reagent **34**, obtained by direct zinc insertion in the presence of LiCl, with the chloropyridine **35** in the presence of Ni(acac)$_2$ (0.5 mol %) and PPh_3 (2 mol %) affords the polyfunctional pyridine **36** in 90% yield (Scheme 6 and Supporting Information File 1, Procedure 2) [14,18,19].

1.2 The direct insertion of magnesium in the presence of $ZnCl_2$: A new preparation of unsaturated zinc reagents bearing sensitive functionalities

Although the LiCl-mediated zinc insertion represents a major preparative advance for the synthesis of polyfunctional zinc reagents, this method has an intrinsic limitation due to the use of zinc as a reducing agent. Zinc has only moderate reducing properties, therefore its insertion into organic halides only proceeds smoothly in the case of aryl iodides and electron-poor substituted aryl bromides. The use of highly reactive zinc (Rieke-zinc) [20,21] solves the problem only partially. It is expensive and most aryl or heteroaryl chlorides do not react. Therefore, we used a stronger reducing reagent, magnesium. Magnesium turnings readily insert into a variety of aryl chlo-

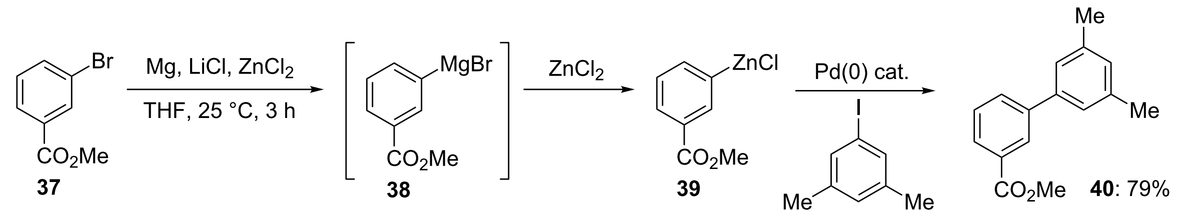


Scheme 6: Ni-catalyzed cross-coupling of benzylic zinc reagent **34** with ethyl 2-chloronicotinate.

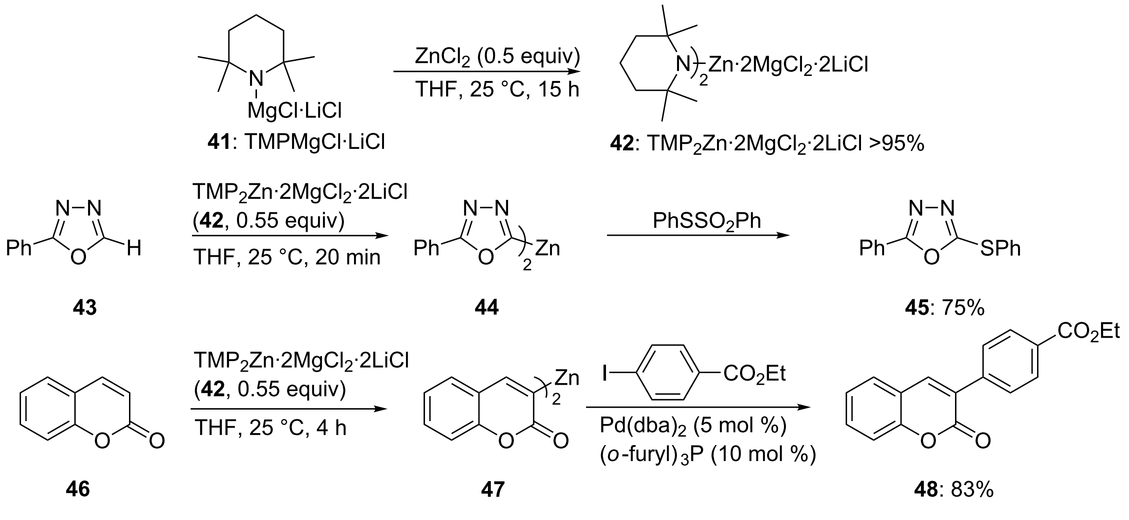
rides or bromides in the presence of LiCl. However, arylmagnesium reagents are compatible with fewer functional groups. Thus, methyl esters react rapidly with arylmagnesium reagents at 0 °C. In order to solve this problem, we have performed a Barbier-type preparation of aryl and heteroaryl zinc reagents by treating the aryl bromide or chloride with magnesium turnings in the presence of zinc chloride and LiCl. Under these conditions, the relatively unreactive aryl bromides and chlorides readily react. Furthermore, sensitive functionalities are tolerated since the reactive arylmagnesium species generated is immediately trapped with zinc chloride (Scheme 7) [22]. Thus, methyl 3-bromobenzoate (**37**) reacts with magnesium powder in the presence of LiCl (1.5 equiv) and $ZnCl_2$ (1.1 equiv) to provide the intermediate magnesium species **38**, which is immediately trapped with $ZnCl_2$ leading to the zinc reagent **39** in high yields. Subsequent Pd-catalyzed cross-coupling of **39** with an aryl iodide provides the cross-coupling product **40** in 79% yield (Scheme 7) [22].

1.3 Preparation of heteroaryl zinc reagents by direct zincation of heterocyclic compounds using the new zinc base $TMP_2Zn·2MgCl_2·2LiCl$ (**42**)

The preparation of zinc reagents by a directed deprotonation was of limited use as no soluble zinc base was available [23,24]. We found that the treatment of commercially available TMPMgCl·LiCl (**41**) [25-27] with $ZnCl_2$ (0.5 equiv) at 25 °C provides the new base $TMP_2Zn·2MgCl_2·2LiCl$ (**42**) [28]. All three metals Zn, Mg and Li are important in this mixed base [29]. The role of LiCl is to increase the solubility of the base, the role of $MgCl_2$ is to increase its reactivity and the role of zinc is essential since it confers to this base an exceptional chemoselectivity (Scheme 8). Thus, the 1,3,4-oxadiazole **43** is readily converted to the zinc reagent **44** by the reaction with $TMP_2Zn·2MgCl_2·2LiCl$ (**42**, 0.55 equiv; 25 °C, 20 min). It should be noted that both TMP-moieties are used and that no fragmentation of this sensitive heterocycle is observed, as is the case for the corresponding Mg- and Li-derivatives.



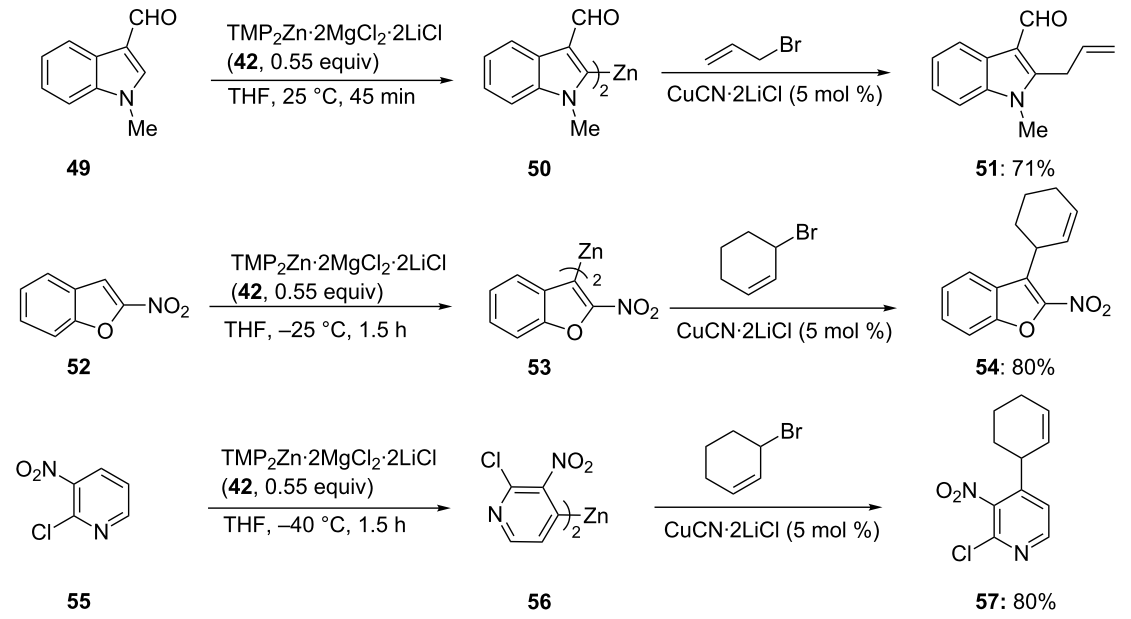
Scheme 7: In situ generation of arylzinc reagents using Mg in the presence of LiCl and $ZnCl_2$.



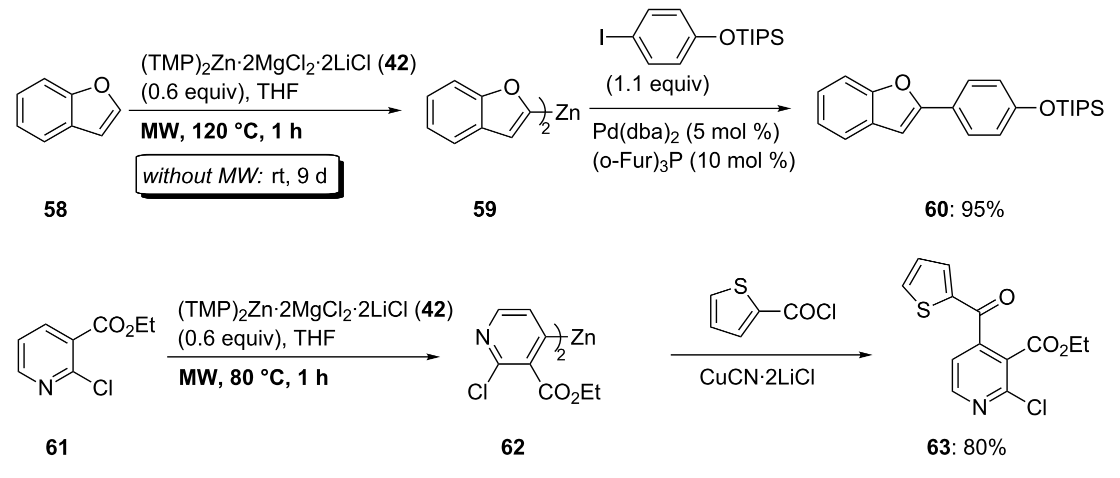
Scheme 8: Zincation of heterocycles with TMP_2Zn (**42**).

After a reaction of the heterocyclic zinc reagent **44** with $PhSO_2SPh$ the corresponding thio-derivative **45** is obtained in 75% yield. Coumarine (**46**) can be directed zincated leading to the zinc reagent **47**. After a Negishi cross-coupling with an aromatic iodide, the substituted coumarine **48** is obtained in 83% yield (Scheme 8 and Supporting Information File 1, Procedure 3) [28]. This procedure tolerates most of the important functional groups in organic chemistry. Thus, the zincation of the formyl-substituted indole **49** is complete within 45 min at 25 °C leading to the zinc reagent **50**. After allylation, the 2,3-disubstituted indole **51** is obtained in 71% yield (Scheme 9). Similarly, 2-nitrobenzofuran (**52**) is zincated without reacting with the nitro group, leading to the nitro-substituted zinc reagent **53**. After allylation, the benzofuran **54** is obtained in 80% yield. The polyfunctional pyridine **55** is zincated with $TMP_2Zn·2MgCl_2·2LiCl$ (**42**) leading to the zinc reagent **56**. Subsequent allylation furnishes the trisubstituted pyridine **57** in 80% yield (Scheme 9) [28].

In some cases, the zincation using $TMP_2Zn·2MgCl_2·2LiCl$ (**42**) is slow and requires long reaction times. This is the case for benzofuran (**58**), which requires 9 days at 25 °C for a complete zincation in position 2 leading to **59**. The reaction time can be dramatically decreased by means of microwave irradiation. Under these conditions, the zincation is complete within 1 h at 120 °C (Scheme 10). Similarly, the functionalized pyridine **61**



Scheme 9: Preparation of highly functionalized zincated heterocycles using $TMP_2Zn·2MgCl_2·2LiCl$ (**42**).



Scheme 10: Microwave-accelerated zincation of heterocycles using $TMP_2Zn·2MgCl_2·2LiCl$ (**42**).

is zincated within 1 h at 80 °C under microwave irradiation leading to **62**. The success of this procedure is a result of the high thermal stability of organozinc reagents. A Pd-catalyzed cross-coupling of **59** or a copper(I)-mediated acylation of **62** affords the products **60** and **63** in 80–95% yield (Scheme 10 and Supporting Information File 1, Procedure 4) [30].

2 Preparation of heterocyclic magnesium reagents

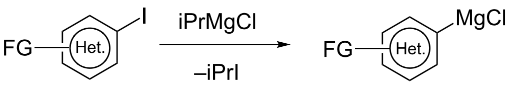
Unexpectedly, recent research work from our laboratories showed that the preparation of heteroarylmagnesium reagents is compatible with numerous functional groups [31-33]. There are three important synthetic methods for the preparation of polyfunctional heteroarylmagnesium reagents:

1. the bromine- (or iodine-) magnesium exchange reaction;
2. the direct insertion of magnesium turnings in the presence of LiCl;
3. the direct magneziation of heterocycles using TMPMgCl·LiCl (**41**).

Due to the higher polarity of the carbon–magnesium bond, these heterocyclic organometallics are significantly more reactive than the corresponding zinc reagents. This makes their preparation especially important.

2.1 The preparation of heterocyclic magnesium reagents through a bromine- (or iodine-) magnesium exchange

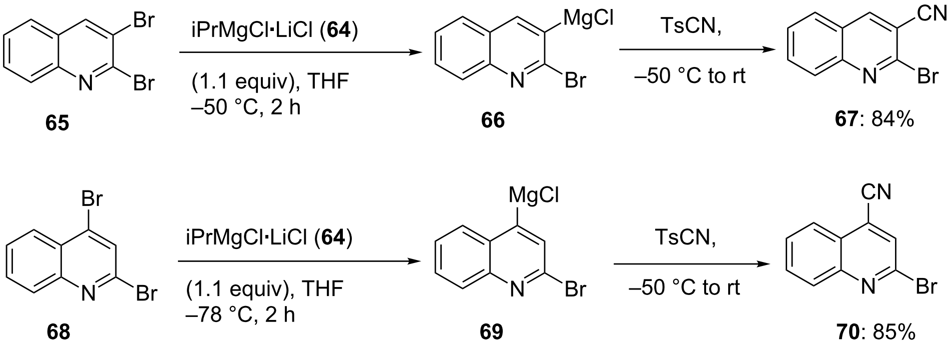
Compared to the halogen/lithium exchange, discovered in 1939 by Wittig and Gilman, the halogen/magnesium exchange is much slower. Whereas aryl and electron-poor unsaturated iodides readily react with iPrMgCl and undergo a metal-metathesis to provide the more stable heteroarylmagnesium reagent (Scheme 11) [34], the reaction of aryl and heteroaryl bromides is slow when iPrMgCl is used as an exchange reagent.



Scheme 11: The I/Mg-exchange as a metal-metathesis reaction.

However, with the aid of the mixed Li/Mg-reagent iPrMgCl·LiCl (**64**), an efficient exchange reaction is also effective with a wide range of aryl and heteroaryl bromides [31-33,35]. This reagent (**64**) is commercially available as an approx. 1 M THF solution from Chemetall GmbH [27]. Recently, we have applied this exchange reaction for the regioselective functionalization of quinolines. Thus, the 2,3-dibromoquinoline (**65**) is regioselectively converted to the 3-magnesiated quinoline derivative **66**. Using the same exchange reagent, iPrMgCl·LiCl (**64**) and 2,4-dibromoquinoline (**68**), it is now possible to obtain the 4-magnesiated quinoline **69**. All these magnesiations proceed at low temperature (−50 °C to −78 °C) and are complete within 2 h reaction time. After reaction with TsCN, the corresponding nitriles **67** and **70** were obtained in 84–85% yield (Scheme 12 and Supporting Information File 1, Procedure 5) [36].

The rate of the Br/Mg-exchange depends on the electronic density of the heterocyclic rings. The electron-poor ring systems undergo considerably faster Br/Mg-exchange reactions than do heterocyclic ring systems bearing electron-rich substituents [31-35]. Therefore, in order to achieve a regioselective exchange with the very electron-poor tribromoquinoline **73**, it was necessary to reduce the reactivity of the exchange reagent and thus, to switch from iPrMgCl·LiCl (**64**) to the less reactive mesitylmagnesium reagent MesMgCl·LiCl (**71**). This reagent is readily prepared by the reaction of mesityl bromide with magnesium turnings in the presence of LiCl (25 °C, 12 h; Scheme 13) [36]. The lower reactivity of **71** allows a perfectly regioselective exchange reaction of **73**, to afford the 3-magnesi-



Scheme 12: Regioselective Br/Mg-exchange of dibromoquinolines **65** and **68**.

ated quinoline **74** only. A differentiation between the reactivity of a 3-bromo- and a 4-bromo-substituted quinoline is more difficult and even the use of the less reactive exchange reagent MesMgBr·LiCl is not satisfactory. This reactivity can be further tuned: First by preparing the dimesitylmagnesium reagent $Mes_2Mg·2LiBr$ (which has a higher reactivity than **71**) and then by adding a complexation reagent, such as TMEDA (1 equiv), which considerably lowers the reactivity [37,38]. The new resulting reagent $Mes_2Mg·2LiBr·TMEDA$ (**72**) now reacts smoothly with 3,4-dibromoquinoline (**76**) providing selectively the 3-magnesiated 4-bromoquinoline **77**. The quenching of **74** and **77** with TsCN and $PhSO_2SMe$, respectively, leads to the regioselectively functionalized quinolines **75** and **78** in 79–88% yield (Scheme 13) [36].

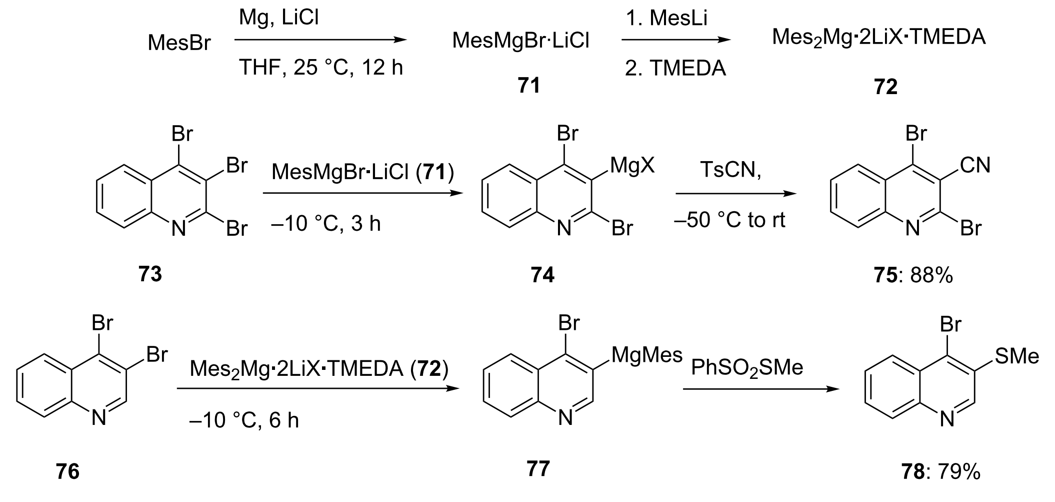
This fine tuning is usually not necessary and numerous Br/Mg-exchange reactions making use of the commercially available reagent iPrMgCl·LiCl (**64**) have been reported in the literature [31-34,39].

The use of iPrMgCl·LiCl also proves to be very practical for the generation of polyfunctional alkenylmagnesium reagents, which react only slowly with iPrMgCl [40,41], as well as for the preparation of arylmagnesium reagents bearing sensitive functionalities, such as triazene. Thus, aryl iodide **79** is treated with iPrMgCl·LiCl (**64**) at −40 °C for 1 h leading to an intermediate magnesium reagent, which after transmetalation to the corresponding zinc reagent using $ZnBr_2$ provides, after Negishi cross-coupling reaction with the bromoquinoline **80**, the polyfunctinal triazene **81** in 75% yield. The conversion of the triazene functionality to an azide group is readily achieved by treating **81** with $NaN_3/BF_3·OEt_2$-CF_3CO_2H in CH_2Cl_2 leading to the aryl azide **82** in 78% yield. Heating of **82** in mesitylene at reflux for 6 h provides ellipticine **83**, a potent antitumor agent in 57% yield (Scheme 14) [42].

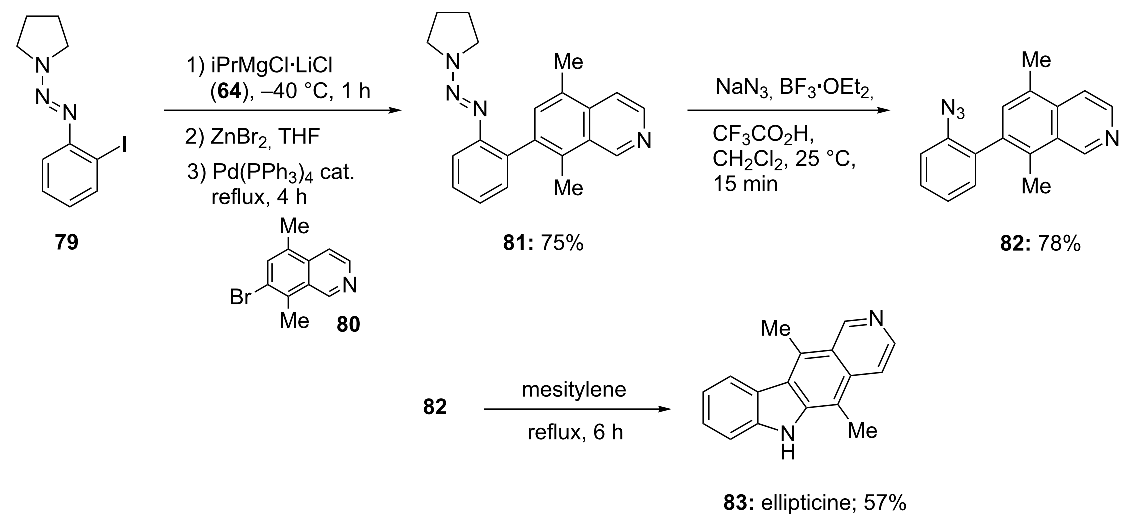
The structural variations of pyrimidines and purines are very important for the design of antiviral agents. The amination of this class of heterocycles is of particular importance. Recently, we developed an oxidative amination procedure for lithium derivatives using chloranil as oxidation agent [43]. We applied this procedure in the preparation of a CDK inhibitor, purvalanol A (**84**). Thus, an I/Mg-exchange on the purine **85** with iPrMgCl·LiCl (**64**), followed by the transmetalation to the corresponding copper derivative with CuCl·2LiCl, and the addition of the lithiated aniline derivative **86**, furnishes the amidocuprate **87**. In the presence of chloranil amidocuprate **87** undergoes an oxidative coupling providing the adenine derivative **88** in 71% yield. A treatment with D-valinol (**89**) affords the desired CDK inhibitor, purvalanol A (**84**) in 65% yield (Scheme 15) [44].

2.2 The preparation of polyfunctional heterocyclic magnesium reagents by the insertion of Mg in the presence of LiCl

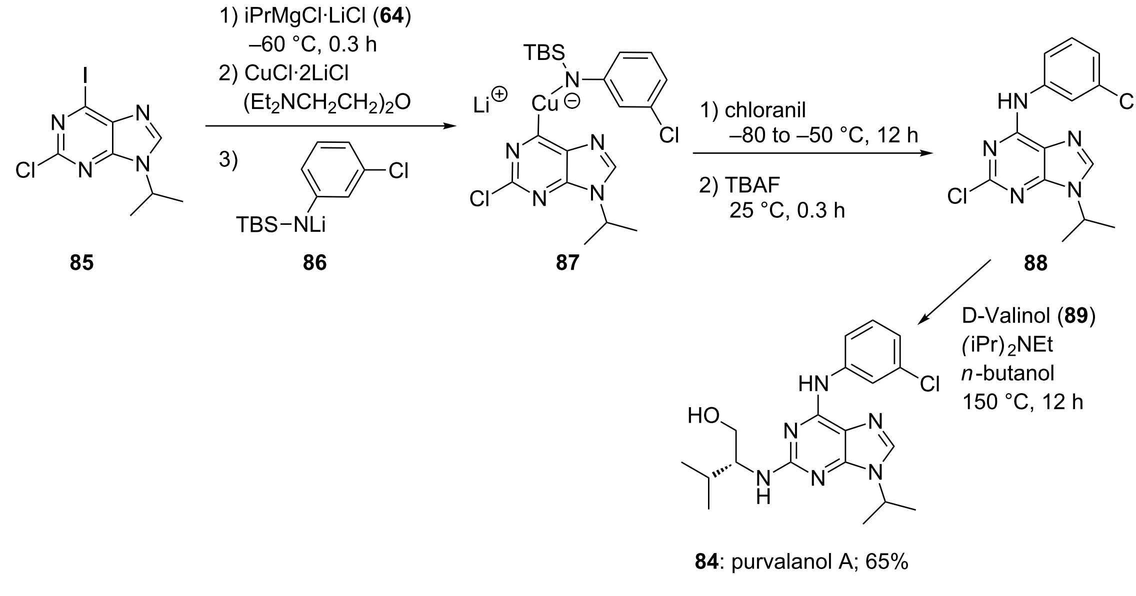
The presence of LiCl facilitates greatly the insertion of many metals into carbon-halogen bonds and avoids the use of expensive activated forms of Mg, such as “Rieke-magnesium”. This property of LiCl for accelerating the insertion of Mg to organic halides has found numerous applications in the preparation of new polyfunctional arylmagnesium reagents. Thus, the rapid reaction of Mg/LiCl with aryl bromides **90**, **93** and **96** allows an expeditive synthesis of the new arylmagnesium derivatives **91**, **94** and **97**. Quenching with typical electrophiles provides the expected products **92**, **95** and **98** in 76–95% yield (Scheme 16) [22,45].



Scheme 13: Improved reagents for the regioselective Br/Mg-exchange on bromoquinolines.



Scheme 14: Synthesis of ellipticine (**83**) using an I/Mg-exchange reaction.

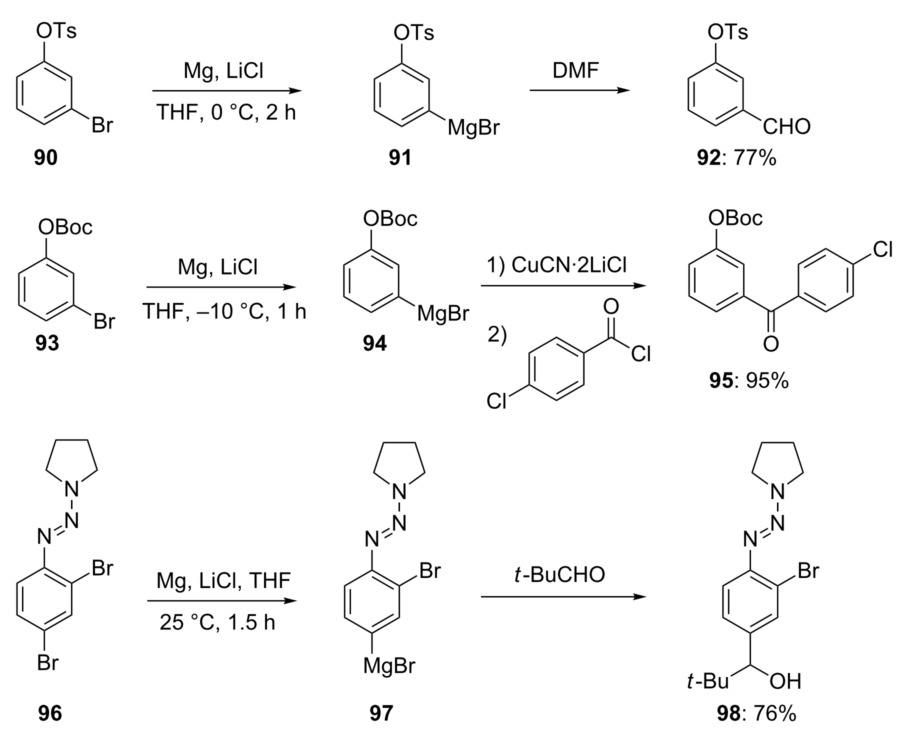


Scheme 15: An oxidative amination leading to the biologically active adenine, purvalanol A (**84**).

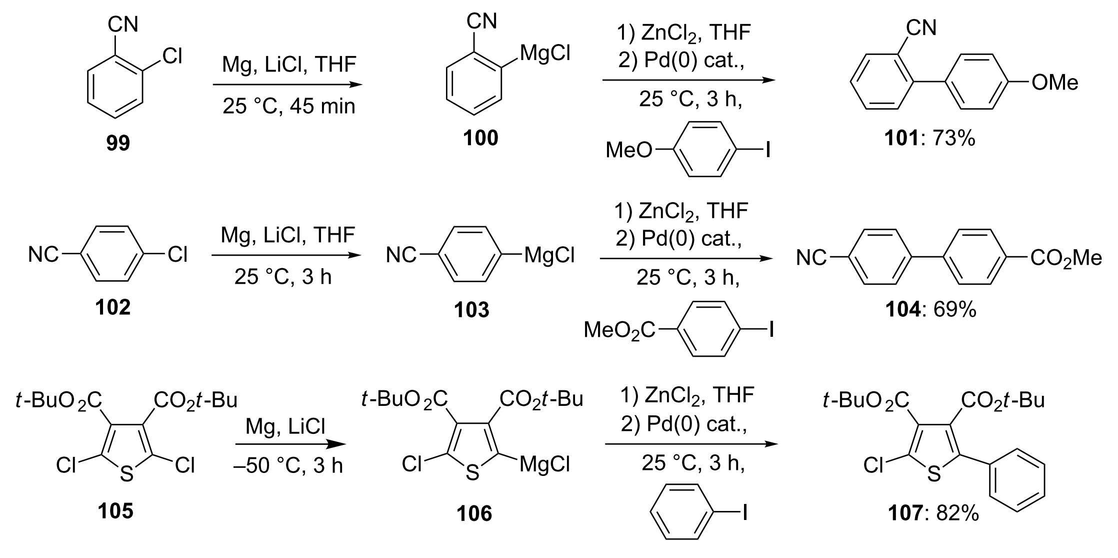
Remarkably, this insertion proceeds also with readily available and inexpensive aryl and heteroaryl chlorides, such as **99**, **102** and **105**, providing the functionalized magnesium reagents **100**, **103** and **106** under mild conditions. The cross-coupling reaction of these Grignard reagents and transmetalation to zinc organometallics with $ZnCl_2$ affords the expected products **101**, **104** and **107** in 69–82% (Scheme 17 and Supporting Information File 1, Procedure 6) [9,22].

2.3 Preparation of polyfunctional heterocyclic magnesium reagents by directed magnesation using TMPMgCl·LiCl (41) or $TMP_2Mg·2LiCl$ (129)

The directed magnesiation of aromatic substrates using TMPMgCl·LiCl (**41**) constitutes an economical preparation of a range of functionalized arylmagnesium compounds [25,26]. Sensitive heterocycles such as pyrimidines can be readily magnesiated with commercially available TMPMgCl·LiCl (**41**)



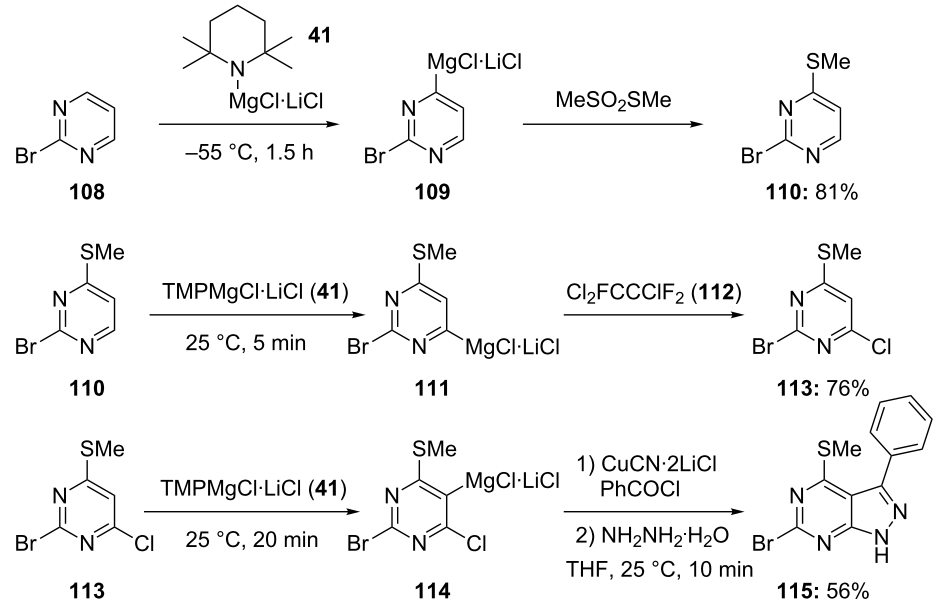
Scheme 16: Preparation of polyfunctional arylmagnesium reagents using Mg in the presence of LiCl.



Scheme 17: Preparation of polyfunctional magnesium reagents starting from organic chlorides.

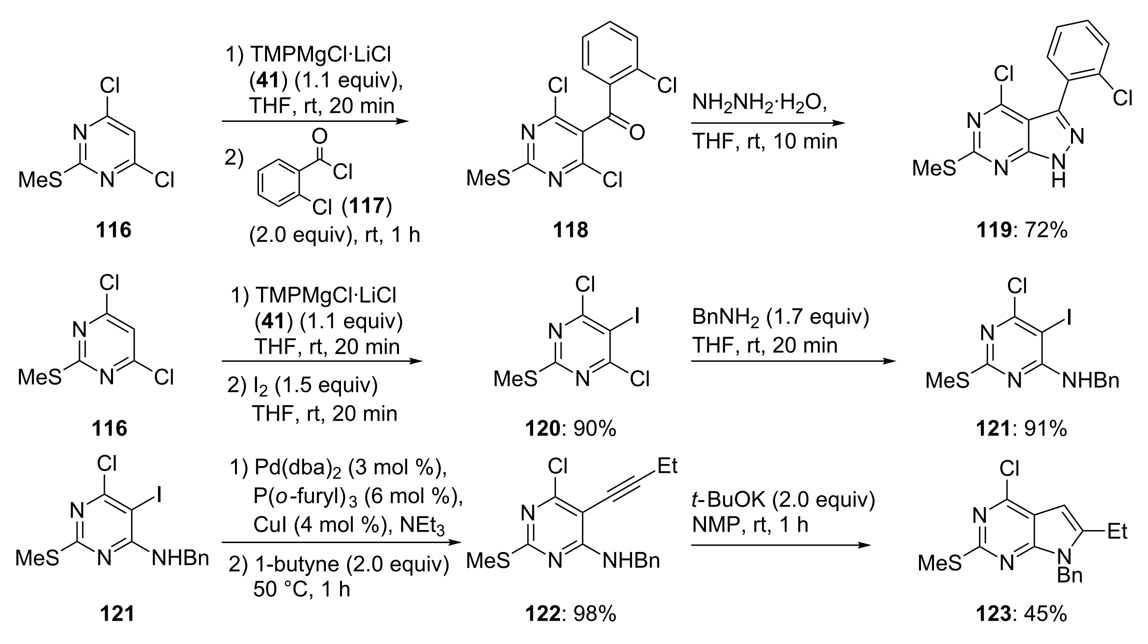
[27]. Thus, electron-poor 2-bromopyrimidine (**108**) is converted within 1.5 h at −55 °C in the presence of TMPMgCl·LiCl (**41**) to the corresponding magnesium reagent **109**. A low reaction temperature is required in this case, since the sensitive heterocycle **108** undergoes ring addition reactions at temperatures above −30 °C. Quenching of the 4-magnesiated pyrimidine **109** with $MeSO_2SMe$ provides the thiomethyl derivative **110** in 81% yield (Scheme 18 and Supporting Information File 1, Procedure 7) [46].

The presence of a thiomethyl substituent considerably increases the electron density of this pyrimidine and the addition of a



Scheme 18: Selective multiple magnesiation of the pyrimidine ring.

Grignard reagent to this heterocycle can no longer occur. Therefore, a subsequent magnesiation of **110** with TMPMgCl·LiCl (1.0 equiv) can be performed at 25 °C. After 5 min reaction time at this temperature, the resulting 6-magnesiated pyrimidine **111** is obtained quantitatively. Quenching of **111** with $Cl_2FCCClF_2$ (**112**) provides the trisubstituted pyrimidine **113** in 76% yield. A final functionalization in position 5 is readily achieved by treating **113** with a further equivalent of TMPMgCl·LiCl (**41**, 25 °C, 20 min) providing the 5-magnesiated pyrimidine **114**. Quenching with benzoyl chloride furnishes the expected unsaturated ketone, which by treatment with hydrazine (NH_2-NH_2·H_2O, THF, 25 °C, 10 min) leads to the pyrazolopyrimidine **115** in 56% overall yield (Scheme 18) [46]. A similar approach has been used to prepare the p38 kinase inhibitor **119** in 72% overall yield, as well as the sPLA2 inhibitor **123**, in a short reaction sequence (Scheme 19) [46].



Scheme 19: Synthesis of a p38 kinase inhibitor **119** and of a sPLA2 inhibitor **123**.

Using TMPMgCl·LiCl (**41**), it is possible to prepare fully substituted indoles, such as **128** (Scheme 20) [47]. Thus, starting from the aniline **124**, an *ortho*-directed chlorination with *N*-chlorosuccinimide at 90 °C followed by an iodination with iodine and Ag_2SO_4 furnishes the tetrasubstituted aniline **125**. Protection of the free amino-group followed by a Negishi-reaction provides the scaffold **126** in 80% yield (Scheme 20).

Successive magnesiations at the positions 5 and 3 of the tetrasubstituted anilines **126** with TMPMgCl·LiCl (**41**) can be performed. The strongly electron-withdrawing properties of the chloro-substituent favor a metalation at position 5. After the addition of pivaldehyde, the subsequent addition of a second equivalent of TMPMgCl·LiCl (**41**; −30 °C, 1.5 h) allows now a magnesiation in position 3. Quenching with TsCN and deprotection of the silylated aniline with KF and HCl furnishes the hexa-substituted aniline **127** in 76% overall yield. Potassium hydride mediated ring closure in NMP [48] affords the desired indole **128** in 96% yield (Scheme 20) [47].

In some cases, TMPMgCl·2LiCl (**41**) is not reactive enough to achieve a magnesiation in a reasonable time frame. We therefore prepared a more reactive bis-TMP base, $TMP_2Mg·2LiCl$ (**129**), by mixing TMPLi with the commercially available base **41** [49]. The metalation temperature using such a base is low enough that functional groups such as a Boc-group or an aryl ketone are readily tolerated. Thus, the Boc-substituted benzophenone **130** reacts with $TMP_2Mg·2LiCl$ (1.1 equiv, −20 °C, 4 h) providing the expected aryl magnesium amide **131**, which after a copper-mediated benzoylation leads to the 1,2,3-trisubstituted diketone **132** in 72% yield. This reagent allows a smooth functionalization of heterocycles such as the dicarbethoxypyridine **133**, which is readily magnesiated with the base **129** at −40 °C within 3 h, leading to **134**. After a Negishi cross-coupling reaction with an aromatic iodide, the 2-functionalized pyridine **135** is obtained in 73% yield (Scheme 21, Procedure 8) [49].

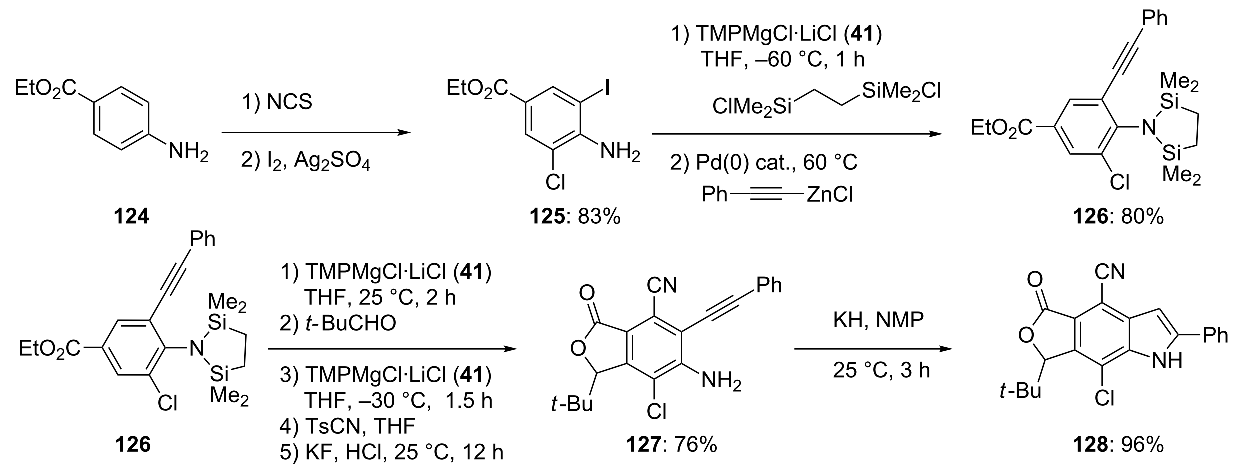
3 New Pd- and Ni-cross-coupling procedures

Although numerous cross-coupling methods have been recently described in the literature [50-52], there is still the need for new convenient procedures. We would like to focus on the chemoselectivity problem in cross-couplings in this short section and report two protocols recently developed in our laboratories:

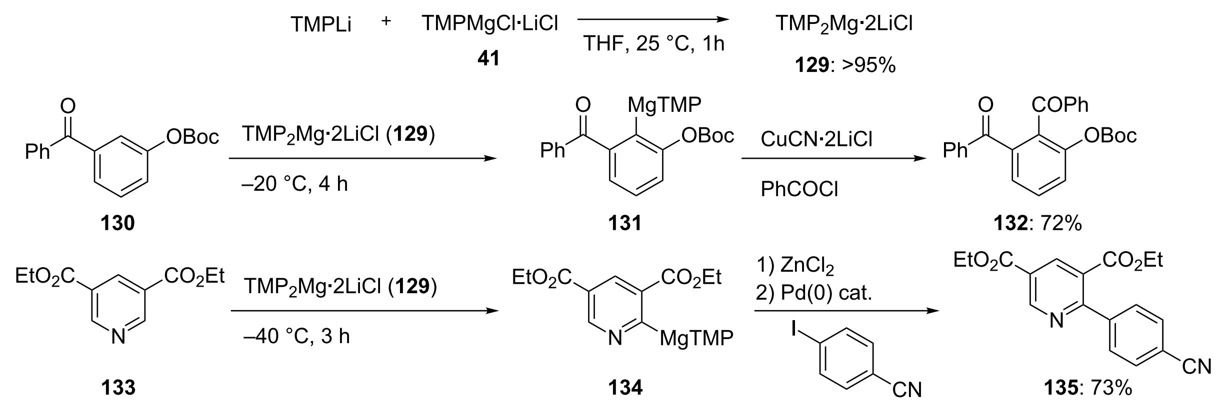
1. A chemoselective Negishi cross-coupling protocol tolerating acidic hydrogen atoms.
2. A chemoselective Kumada cross-coupling based on a new radical mechanism.

3.1 Chemoselective Negishi cross-coupling using substrates bearing acidic hydrogen atoms

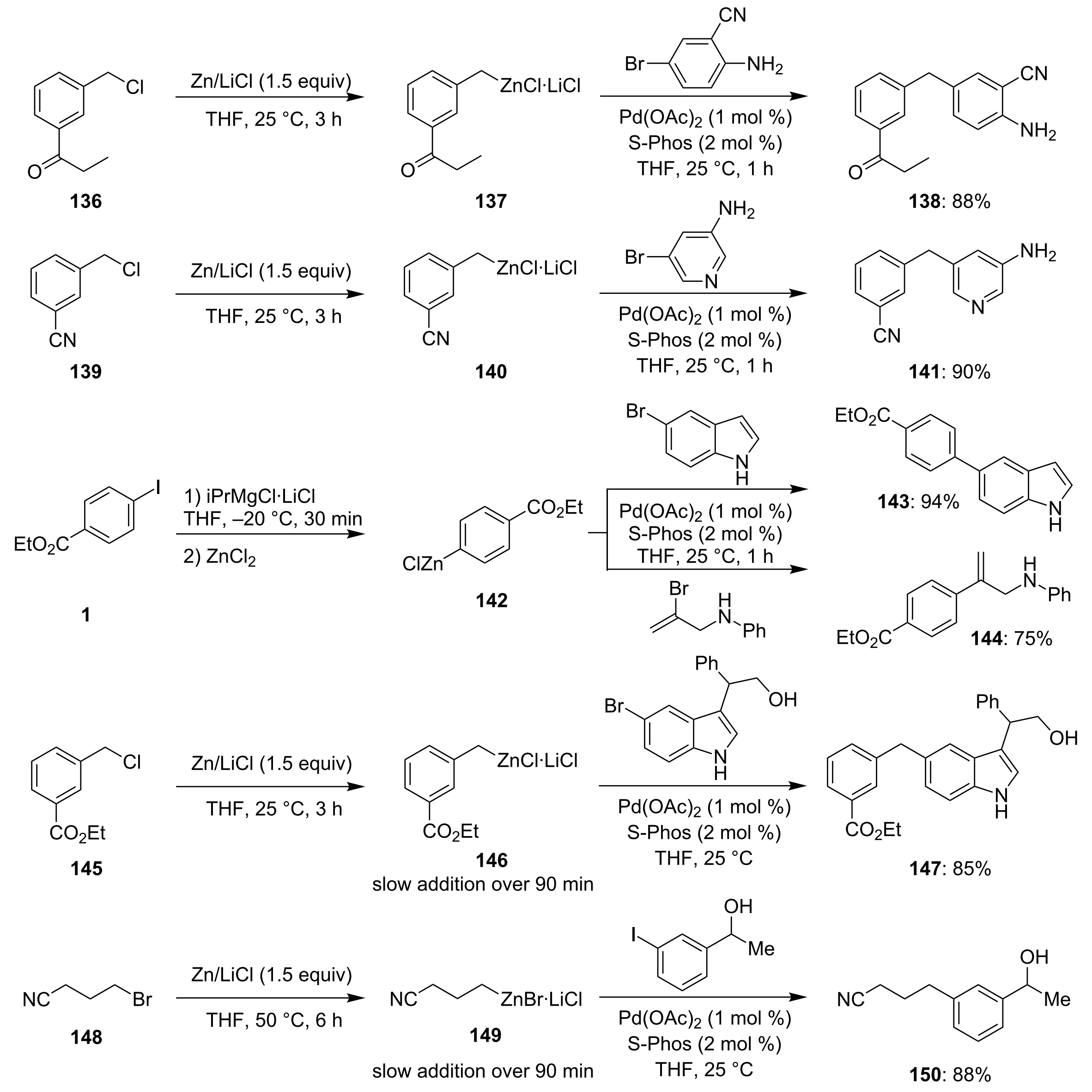
The ability to perform cross-couplings is certainly one of the most versatile functions of heterocyclic zinc intermediates. Recently, we have shown that $NiCl_2$ (0.05 mol %) constitutes an economical method for performing Negishi cross-couplings [18,19], however, it does not solve the problem of the moderate chemoselectivity of organozinc reagents towards substrates bearing acidic hydrogen atoms, such as N–H and O–H bonds. This is an important limitation of the Negishi cross-coupling, especially compared to the Suzuki cross-coupling based on boronic acid derivatives, which are much more tolerant toward acidic NH- and OH-groups. In the course of our studies, we found that by using an active catalyst system, such as S-Phos, developed by S. L. Buchwald [15-17], a smooth cross-coupling can be achieved between benzylic, aromatic and alkyl zinc reagents with substrates bearing an NH- or an OH-group (Scheme 22) [53,54].



Scheme 20: Synthesis of highly substituted indoles of type **128**.



Scheme 21: Efficient magnesiations of polyfunctional aromatics and heterocycles using $TMP_2Mg·2LiCl$ (**129**).



Scheme 22: Negishi cross-coupling in the presence of substrates bearing an NH- or an OH-group.

Remarkably, this reaction protocol was extended to substrates bearing an α-aminoester moiety, such as **152** providing the cross-coupling product **153** in 85% yield (Scheme 23 and Supporting Information File 1, Procedure 9) [54].

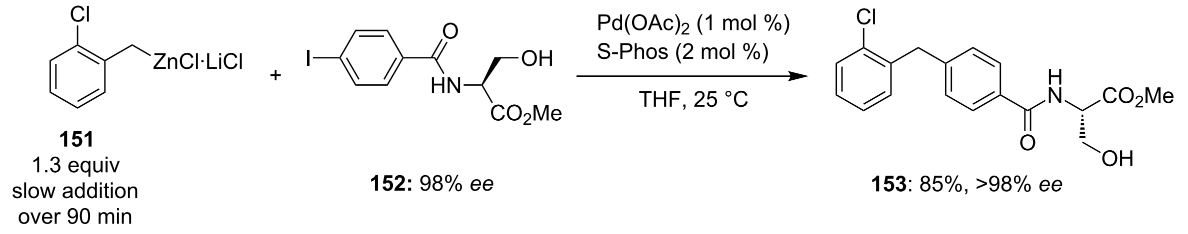
3.2 Radical catalyzed Kumada chemoselective cross-coupling

As aryl- and heteroarylmagnesium reagents are readily available, it would be highly desirable if cross-couplings could be directly realized using these organometallics without the need of further transmetalation to zinc, boron or other metals. However, the disadvantage of this cross-coupling, known in the literature as Kumada cross-coupling [55,56], is that it only proceeds with relatively nonfunctional molecules as the C–Mg bond can competitively attack the functional group present in the aromatic or heterocyclic electrophile instead of undergoing the desired cross-coupling. We have found that the presence of iPrI (or another alkyl iodide) catalyzes the Kumada cross-coupling reaction, such that highly reactive functional groups, such as ketones, esters or nitriles, are perfectly tolerated (Scheme 24 and Supporting Information File 1, Procedure 10) [57,58].

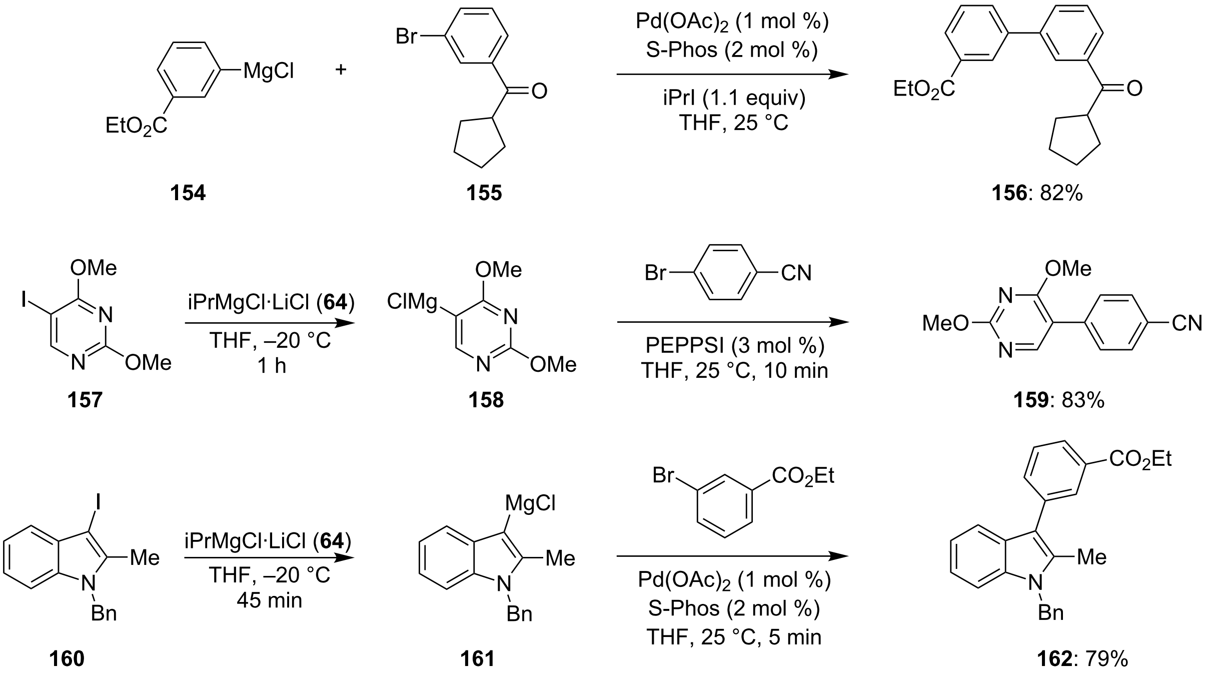
The mechanism of the reaction has been shown to be of radical nature, and it affords the cross-coupling products in very short reaction times, often less than 5 min.

4 $MgCl_2$-Enhanced reactivity of functionalized organozincs towards their addition to aldehydes, ketones and carbon dioxide

The addition reactions of organometallic reagents to ketones, aldehydes and carbon dioxide are essential transformations in organic synthesis as they provide a convenient access to various



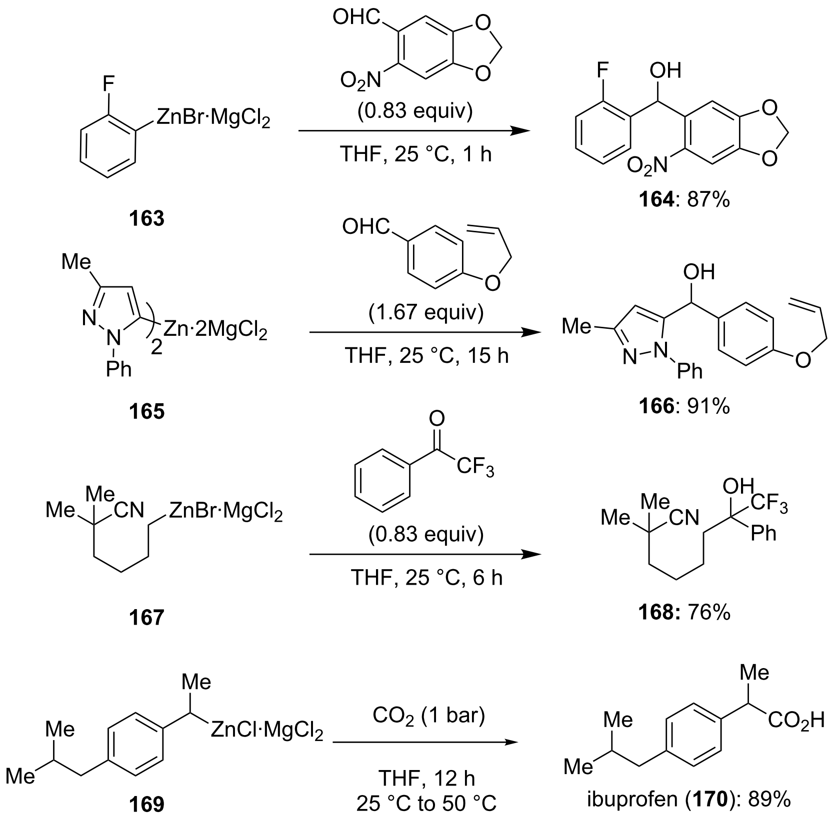
Scheme 23: Negishi cross-coupling in the presence of a serine moiety.



Scheme 24: Radical catalysis for the performance of very fast Kumada reactions.

types of alcohols or carboxylic acids. Usually, organozinc reagents only react with these types of electrophiles in the presence of catalytic amounts of transition metal salts and in a very limited scope. Recently, we showed that the cheap and nontoxic main group Lewis acid $MgCl_2$ allows smooth addition reactions of different aromatic, heteroaromatic, alkyl and benzylic zinc reagents to various carbonyl derivatives and carbon dioxide without the use of polar cosolvents (Scheme 25 and Supporting Information File 1, Procedure 11). The Lewis acid $MgCl_2$ is usually generated during the formation of the organozinc reagent by a magnesium insertion in the presence of $ZnCl_2$ (compare section 1.2) [59,60].

Thus, 2-fluorophenylzinc bromide **163** and the pyrazolylzinc chloride **165** react at room temperature with the aromatic aldehydes to provide the secondary alcohols **164** and **166** in 87–91% yield. The alkyl zinc reagent **167** adds to α,α,α-trifluoromethylacetophenone in 2 h and the corresponding alcohol **168** was isolated in 76% yield. Furthermore, the method was applied to the synthesis of the blockbuster drug ibuprofen (**170**). To achieve this, the secondary benzylic zinc reagent **169** was reacted with CO_2 gas to provide the phenylacetic acid **170** in 89% yield.



Scheme 25: $MgCl_2$-mediated addition of functionalized aromatic, heteroaromatic, alkyl and benzylic organozincs to aldehydes, ketones and carbon dioxide.

Conclusion

We have summarized the most important procedures for the preparation of functionalized organzinc and organomagnesium reagents in this short review. Although, these reagents were introduced to synthetic organic chemistry at the turn of the 20th century, they are now more than ever essential organometallic intermediates. The progress in the 5 last years in our laboratories shows that much is still unknown in this field, and that the important synthetic preparation methods developed recently will lead to a revolution in the field and considerably expand the use of these organometallics in synthesis.

Experimental

Experimental details for the most important reactions of this review are given in the Supporting Information File 1.

Supporting Information

Supporting Information File 1

Experimental section.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-147-S1.pdf]

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Bromine–lithium exchange: An efficient tool in the modular construction of biaryl ligands

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Abstract

Regioselective bromine–lithium exchange reactions on polybrominated biaryls enable the modular synthesis of various polysubstituted biphenyls such as bis(dialkylphosphino)-, bis(diarylphosphino)- and dialkyl(diaryl)phosphinobiphenyls. All permutations of substituents at the ortho positions of the biphenyls are possible. In a similar manner, one can gain access to monophosphine analogues. So far, such a process, based on the effective discrimination between bromine atoms as a function of their chemical environment, has been observed only sporadically.

Introduction

Atropisomeric biaryls are important compounds in various fields. In particular, pharmaceuticals and agrochemicals with biaryl substructures are of general interest [1]. In addition, they have widespread applications as ligands in catalysis, or in materials sciences [2]. The atropisomeric C_2-symmetric binaphthyl- or biphenyl-bridged diphosphine ligands BINAP [3], H8-BINAP [4], BIPHEMP [5], MeO-BIPHEP [6], SEGPHOS [7-9], P-Phos [10], SYNPHOS [11,12], C_n-TUNAPHOS [13] and DIFLUORPHOS [14-16] and their analogues are well known as highly efficient chiral ligands for a variety of transition metal-catalyzed asymmetric transformations. The biphenyl backbone has the advantage that substituents at the 6- and 6'-positions can affect the dihedral angle of the biphenyl backbone, one of the key factors for ligand efficiency. Both the aryl phosphorus substituents and the biphenyl backbone can be tailored in order to modify the stereoelectronic profile of a ligand.

Most frequently, biaryls are prepared through transition metal-catalyzed reactions of suitable functionalized starting materials [17-22]. Although these methods are well established, alternatives are investigated in order to avoid expensive transition metals or ligands, which are especially required for the coupling of deactivated or sterically hindered substrates.

Our group is developing new methods towards the synthesis of highly functionalized atropisomeric biphenyls [23-32]. We seek to perform their synthesis (a) in a modular way starting from a few common and easily available precursors; (b) with a high degree of structural diversity; (c) in a straightforward, short, reproducible manner; (d) in high yield and on multigram scale; and, last but not least, (e) with a restricted use of transition metals and ligands.

Polar organometallic chemistry [33-35] allows the performance of highly selective reactions. Therefore, it seemed to us the ideal tool to reaching this goal. In this context, we recently developed a novel transition metal-free aryl–aryl coupling protocol, the "ARYNE-coupling", which allows the preparation of di-, tri-, and even tetra-substituted *ortho*,*ortho*'-dibromobiphenyls [25,28,31,36-38]. These have the advantage that, by means of successive or simultaneous bromine–lithium exchanges, a huge panel of substituents can be introduced into the biphenyl backbone.

The bromine–lithium exchange reaction is certainly one of the most fundamental synthetic transformations [39]. Although this reaction was reported by C. S. Marvel in 1927 [40], G. Wittig [41] and H. Gilman [42-44] were the first to apply it in organic synthesis in the late thirties. Since then, this reaction has been considered as a mature method lacking both appeal and surprise [33], and only new applications of this reaction or mechanistic studies have been reported [30,32,33,45-55]. However, in the last few years, the halogen–metal permutation has recaptured its former role as one of the most important and versatile methods in organic synthesis. New exchange reagents, such as isopropylmagnesium chloride, its LiCl complex [53-61] and lithium tributylmagnesate [62,63], have been developed and allow reactions under noncryogenic conditions [64-66]. New access routes to synthetically challenging aryl halide precursors have been devised.

A. Alexakis et al. recently achieved a significant breakthrough. They succeeded in the desymmetrization of prochiral polybrominated [32,51] compounds by an asymmetric bromine–lithium exchange in the presence of a stoichiometric amount of chiral diamines. An enantiomeric excess of up to 63% was obtained [67]. H. Kagan et al. reported the desymmetrization of prochiral aromatic or vinylic dihalide substrates by halogen–metal exchange in the presence of a stoichiometric amount of diamines, with enantiomeric excess up to 26% [68]. Very recently, the Alexakis group achieved the catalytic bromine–lithium exchange allowing the preparation of biarylatropisomers in quantitative yields and enantiomeric excesses up to 82% [69].

Herein, we report on the preparation of C_1 analogues of the most efficient and popular C_2-symmetric biphenyl ligands. We will show that by means of regioselective bromine–lithium exchanges all possible permutations of bis(diaryldiphosphino)-, bis(dialkylphosphino)- and dialkyl(diaryl)phosphinobiphenyls become feasible. In a similar way, biphenyl-based monophosphine ligands were also obtained (Figure 1).

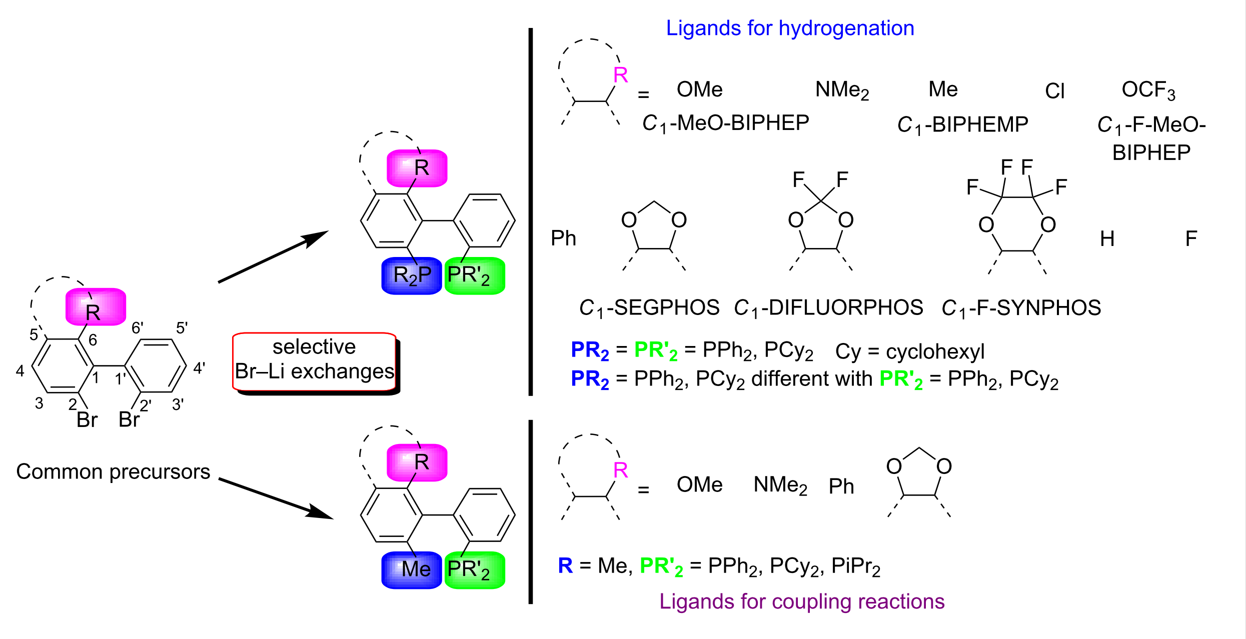


Figure 1: Modular synthesis of bis(diarylphosphino)-, bis(dialkylphosphino)- and dialkyl(diaryl)phosphinobiphenyls as well as monophosphinobiphenyls by means of polar organometallic chemistry.

Results and Discussion

Regioselective bromine–lithium exchange on polybrominated biphenyls

Our group recently reported the efficient coupling of organolithium intermediates with arynes, the so-called "ARYNE coupling" [25,31,36]. This protocol is based on the formation of a thermodynamically stable aryllithium intermediate and its subsequent reaction with a 1,2-dibromobenzene derivative. The transient benzyne adds the aryllithium derivative, followed by in situ transfer of bromine between the resulting 2-biaryllithium intermediate and another molecule of 1,2-dibromobenzene. Mono-, di- or even tetra-substituted *ortho*-bromobiaryls can be obtained on a gram scale (Figure 2).

The intriguing question is whether one bromine would be exchanged preferentially on the substrate when the bromine atoms are not activated by adjacent heteroatoms. An effective discrimination between two bromine atoms as a function of their chemical environment has so far been observed only sporadically in such processes [30,34,35,51,52,70-72].

Fortunately, the reaction occurred exclusively on the doubly halogenated ring when 2,2',6-tribromobiphenyl [28,38], obtained almost quantitatively by the ARYNE coupling protocol, was submitted to the bromine–lithium exchange reaction. When 2,2',6-tribromobiphenyl (**1a**) [28] was treated at −78 °C with BuLi and the intermediate aryllithium trapped with iodomethane, 2,2'-dibromo-6-methylbiphenyl (**1b**) was obtained in an excellent yield of 96%. Analogously, when benzenesulfonylazide was used as an electrophile, 2-azido-2',6-dibromobiphenyl was obtained. The use of lithium aluminium hydride in ether at reflux for 4.5 h gave exclusively 2-amino-2',6-dibromobiphenyl, which was submitted to a reductive methylation by means of formaldehyde and sodium cyanoborohydride. 2-*N*,*N*-Dimethylamino-2',6-dibromobiphenyl (**1c**) was obtained in an overall yield of 79% in 3 steps (Scheme 1). To introduce the methoxy group, 2,2',6-tribromobiphenyl (**1a**) was successively subjected to lithiation, borylation with fluorodimethoxyborane·diethyl ether, followed by oxidation with hydrogen peroxide and *O*-methylation with iodomethane in acetone. 2,2'-Dibromo-6-methoxybiphenyl (**1d**) was finally obtained in a very good global yield of 68% in 3 steps. Finally, we proposed to introduce the phenyl ring (**1f**, 95%) by a regioselective Suzuki–Miyaura coupling via the iodo derivative **1e**, the latter being obtained in 83% yield after trapping with iodine.

Similarly, as shown for 2,2',6-tribromobiphenyl (**1a**), when 6-substituted 2,2'-dibromobiphenyls **1b–e** were treated with just one equivalent of butyllithium in tetrahydrofuran at −78 °C, another regioselective bromine–lithium exchange occurs on the functionalized ring (Scheme 2). Trapping with iodomethane afforded the biphenyls **2** in high yield and perfect regioselectivity, except for R = Ph (**1f**) and the benzodioxole derivative (**1i**), where the regioselectivity was slightly lower (91:9 and 92:8, respectively).

M. Schlosser and J. Gorecka-Kobylinska recently reported on the relative basicities of aryllithiums bearing methoxy, chlorine, fluorine, trifluoromethyl and trifluoromethoxy substituents at the ortho, meta, and para positions. Equilibration studies of two aryllithiums of comparable basicity with the corresponding bromo- or iodoarenes allowed them to determine the "basicity" (protodelithiation) increments $\Delta\Delta G$, derived from the equilibrium constants. The authors showed that the basicity increments are linearly correlated with the relative protonation enthalpies of the corresponding aryl anions in the gas phase. Compared with "naked" aryl anions, the basicity of aryllithiums mirrors the effects of ortho, meta, and para substituents to the extent of 36%, 30%, and 25%, respectively [73].

These results explain the difference in regioselectivity of the bromine–lithium exchange, between a bromine atom residing

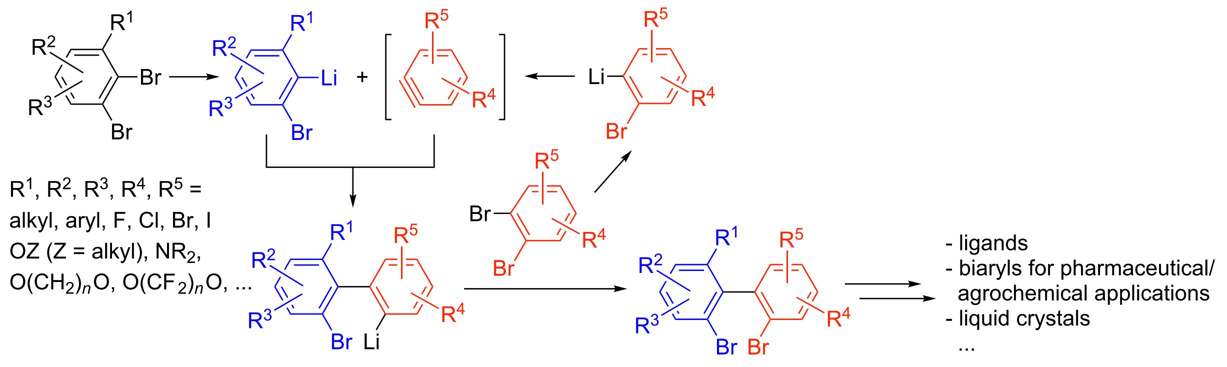
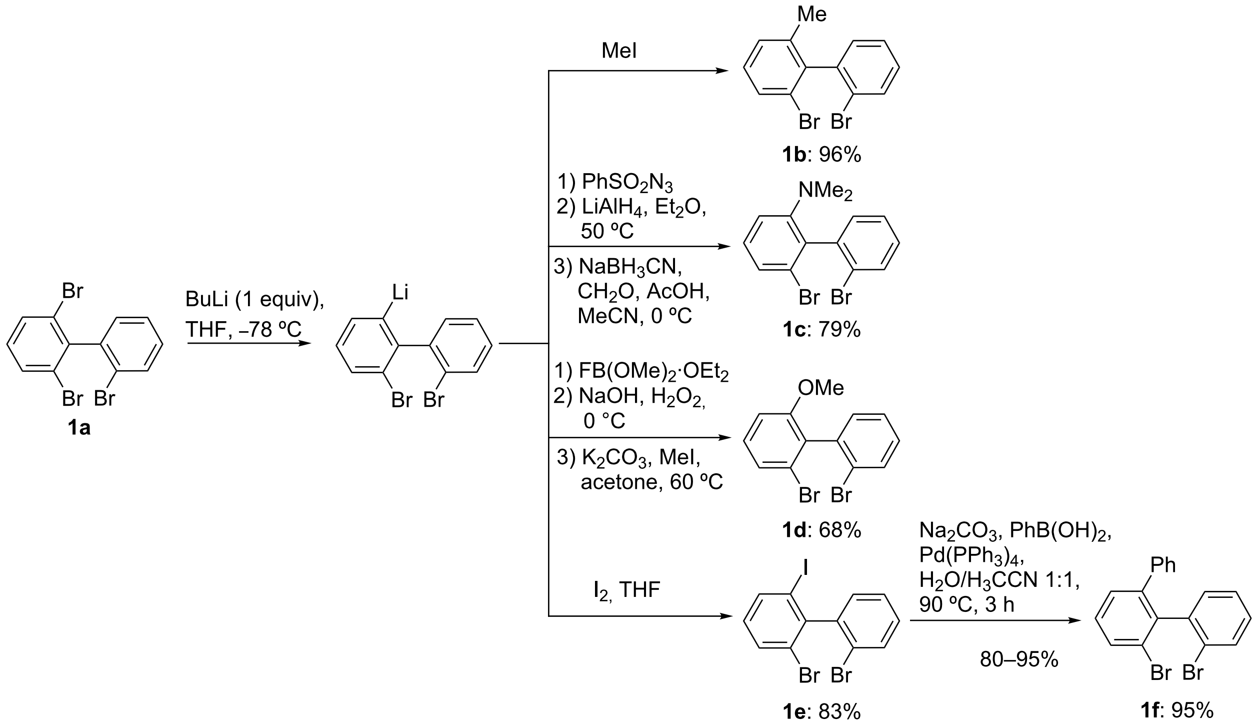
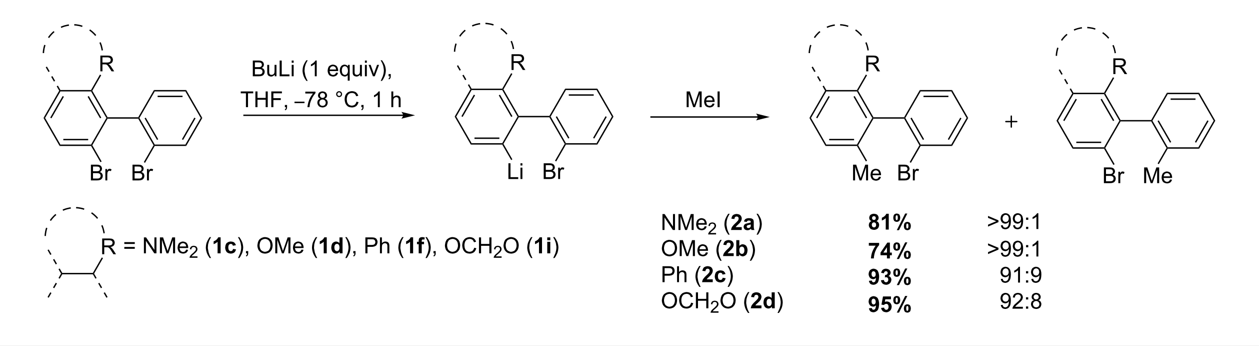


Figure 2: ARYNE coupling.



Scheme 1: Functionalization of 2,2',6-tribromobiphenyl (**1a**) by regioselective bromine–lithium exchange.



Scheme 2: Functionalization of 2,2'-dibromobiphenyls (**1b–e**) by regioselective bromine–lithium exchange.

on a phenyl ring that bears a "stabilizing" substituent at a remote meta position and a bromine atom on an "unstabilized" phenyl ring.

Biaryl mono- and diphosphines

In the following section we will show how a large family of biaryl mono- and diphosphines becomes readily accessible through these common building-blocks. The general access is depicted in Figure 3.

Biarylmonophosphines: Path A

From the methylated intermediates **2a–d**, new monophosphines became accessible in one additional step (Scheme 3). The bromine–lithium exchange was either performed with just one equivalent of butyllithium in tetrahydrofuran at −78 °C (*conditions a*) or in toluene at 0 °C (*conditions b*). After cooling to −78 °C, the lithiated intermediate was then allowed to react with a solution of $ClPCy_2$, or $ClPPh_2$ in toluene. In these cases, the monophosphines **3** were obtained in good yields (Scheme 3).

Single crystal X-ray analyses [74] of one ligand of each family (R^1 = NMe_2 (**3a**, Figure 4), OMe (**3b**, see Supporting Information File 3), Ph (**3d**, see Supporting Information File 4), OCH_2O (**3f**, see Supporting Information File 5)) were performed in order to confirm their structure. Thus, we confirmed the selectivity of the different halogen–metal exchange reactions performed throughout the synthesis.

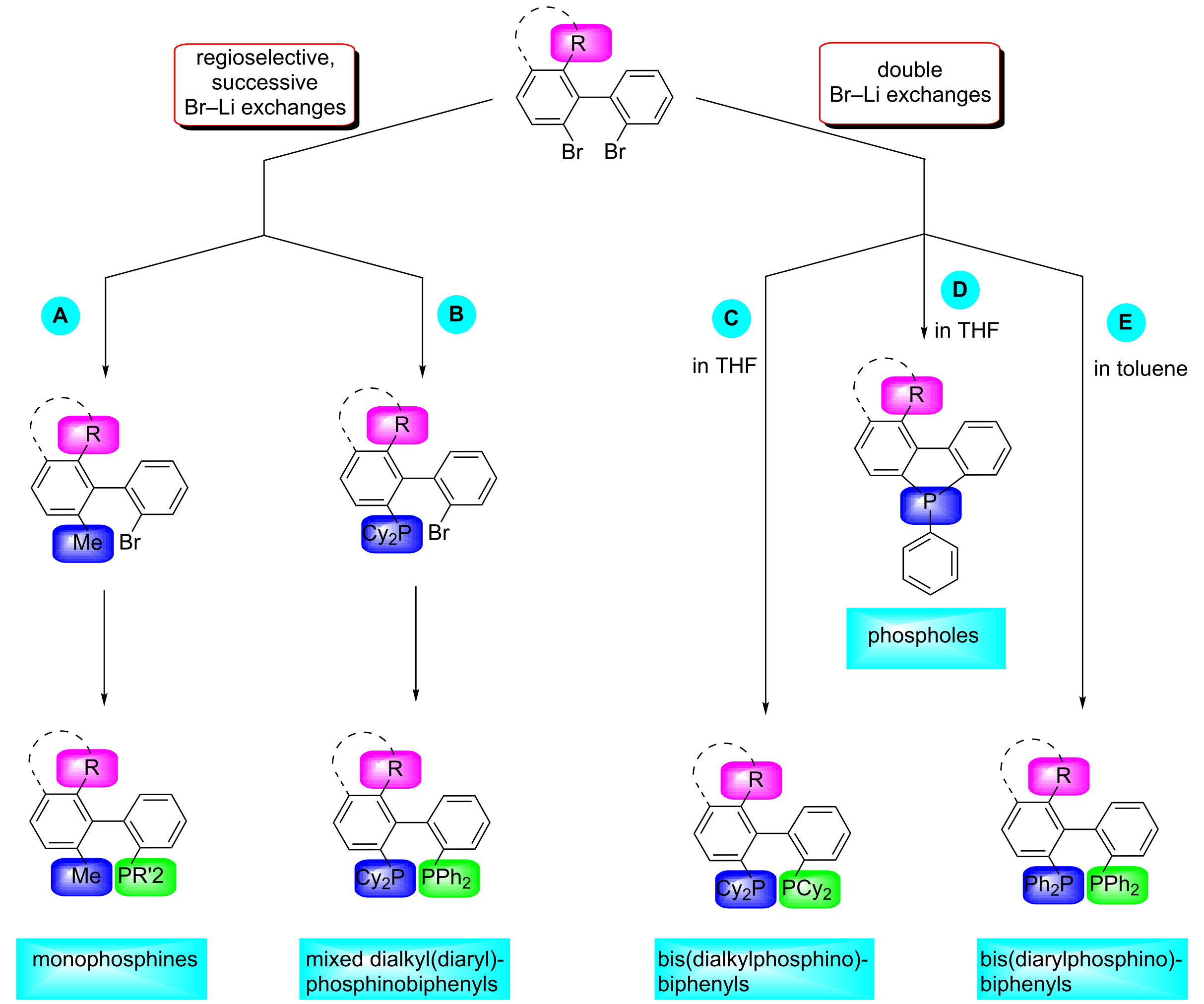
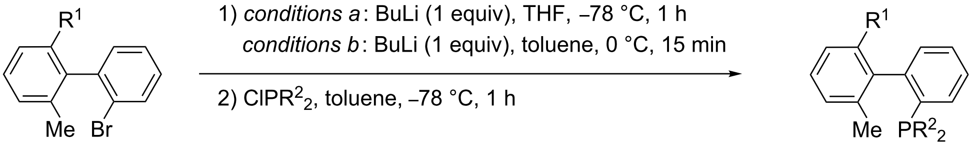


Figure 3: General access to biaryl mono- and diphosphine ligands; (Cy = cyclohexyl).



R^1 = NMe_2 (**2a**), OMe (**2b**),
Ph (**2c**), OCH_2O (**2d**)

R^1 = NMe_2, PR^2_2 = PCy_2 (**3a**): 66%
OMe, PR^2_2 = PPh_2 (**3b**): 68%
OMe, PR^2_2 = PCy_2 (**3c**): 76%
Ph, PR^2_2 = PPh_2 (**3d**): 65%
Ph, PR^2_2 = PCy_2 (**3e**): 66%
OCH_2O, PR^2_2 = PCy_2 (**3f**): 63%

Scheme 3: Synthesis of monophosphines **3**; (Cy = cyclohexyl).

Mixed dialkyl(diaryl)phosphinobiphenyls: Path B

In order to synthesize mixed diphosphines, we took advantage of the non-equivalence of the two phenyl rings towards lithiation. We started from the same dibromobiaryls **1** as before, but submitted them now to just one equivalent of butyllithium in THF. The aryllithium intermediate was then trapped with one equivalent of $ClPCy_2$. The resulting monophosphine **4** was

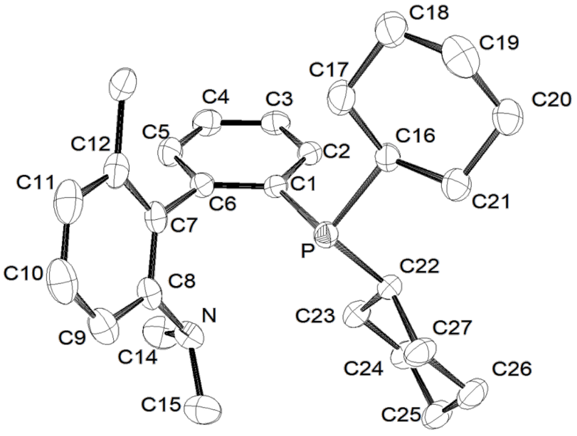
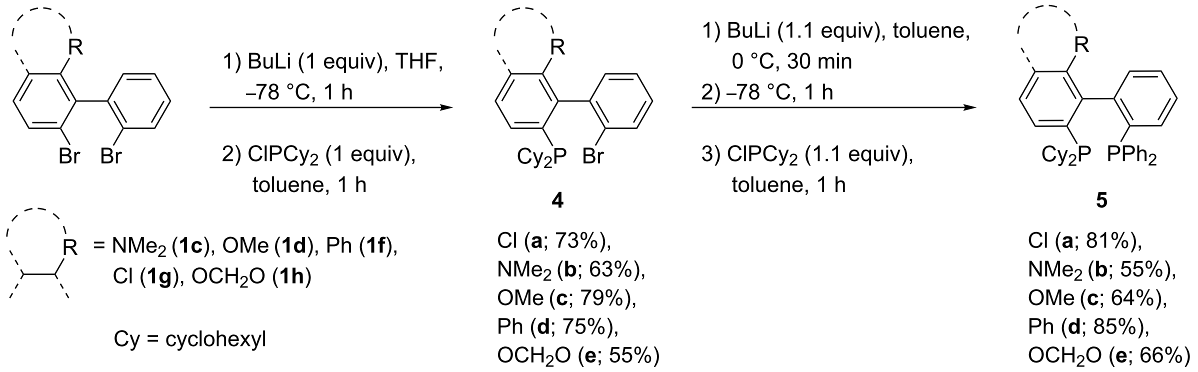


Figure 4: Molecular structure of compound **3a** (crystallized from ethyl acetate/hexane) [74].



Scheme 4: Preparation of mixed dialkyl(diaryl)phosphinobiphenyls **5** via successive bromine–lithium exchange.

isolated and then submitted to a second bromine–lithium exchange in toluene followed by addition of $ClPPh_2$ (Scheme 4). The lithiation–phosphination sequence was not substrate-dependent and reaction conditions were the same for all the different ortho substituents. In this way, pure ligands were obtained on a gram scale.

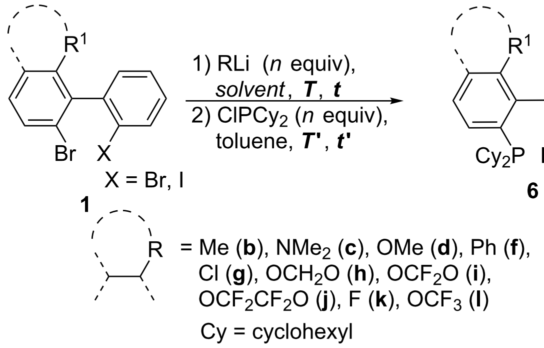
Bis(dialkyl)phosphinobiphenyls: Path C

In order to gain access to bis(dicyclohexylphosphino)biphenyls **3**, a double bromine–lithium exchange was performed on the 2,2'-dibromobiaryls **1**. A screening of the reaction conditions revealed higher yields for the double phosphination when the bromine–lithium exchange and trapping with $ClPCy_2$ were carried out in toluene rather than in THF and at higher temperature. For example, with R^1 = Me, OCF_2O, and OCF_2CF_2O, the corresponding diphosphines were obtained in a yield of 54% (in toluene) versus 12% (in THF), 53% versus 36% and 73% versus 35%, respectively (Table 1, entries 1, 2, 9, 10, 11 and 12). A series of bis(dicyclohexylphosphino)biphenyls **6** was obtained in good yield. However, we noticed lower yields for biaryls carrying α-fluorinated ether substituents, such as OCF_2O (53%; Table 1, entry 9) or OCF_3 (33%; Table 1, entry 14), in comparison with their nonfluorinated counterparts, OCH_2O (70%; Table 1, entry 8) and OMe [30] (74%; Table 1, entry 5).

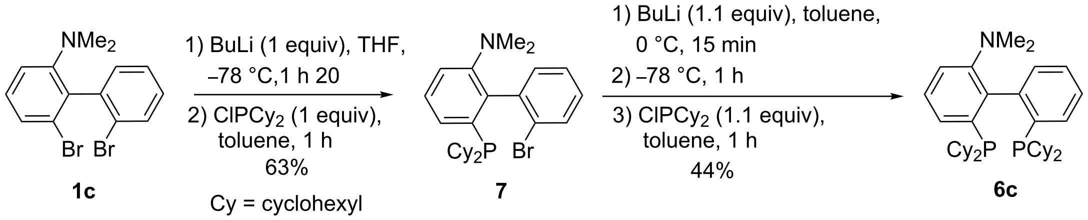
In the case of 2-*N*,*N*-dimethylamino-2',6-dibromobiphenyl (**1c**), higher yields were obtained when the double bromine–lithium exchange was realized successively instead of simultaneously. Indeed, the double phosphination in THF or toluene gave the corresponding ligand in a very poor yield (Table 1, entries 3 and 4). When the first Br–Li exchange was carried out in THF at −78 °C, followed by trapping with $ClPCy_2$, the corresponding monophosphine **7** was obtained in a good yield of 63%. The second Br–Li exchange was performed in toluene at 0 °C, affording ligand **6c** in a moderate yield of 44% after trapping with $ClPCy_2$ (Scheme 5).

Single crystal X-ray analysis of **6c** was performed (see Supporting Information File 6) [74].

Table 1: Synthesis of bis(dicyclohexylphosphino)biphenyls **6**.



Entry	R^1	X	RLi	*n*	Solvent	*T* [° C]	*t*	*T'* [°C]	*t'*	Ligand	Yield
1	Me	Br	BuLi	2	toluene	110	1 h	50	2 h	**6b**	54%
2	Me	Br	BuLi	2	THF	−78	1 h	−78	1 h	**6b**	12%
3	NMe_2	Br	*t*-BuLi	4	THF	−78	1 h	−78	1 h	**6c**	22%
4	NMe_2	Br	BuLi	2	toluene	0	15 min	−78	1 h	**6c**	30%
5	OMe [30]	Br	BuLi	2	THF	−78	1 h	−78	1 h	**6d**	74%
6	Ph	Br	*t*-BuLi	4	THF	−78	1 h	−78	1 h	**6f**	66%
7	Cl	Br	BuLi	2	THF	−78	1 h	−78	1 h	**6g**	49%
8	OCH_2O	Br	BuLi	2	toluene	110	1 h	50	2 h	**6h**	70%
9	OCF_2O	I	BuLi	3	toluene	25	1 h	25	2 h	**6i**	53%
10	OCF_2O	I	BuLi	3	THF	−78	1 h	−78	1 h	**6i**	36%
11	$O(CF_2)_2O$	I	BuLi	3	toluene	25	1 h	25	2 h	**6j**	73%
12	$O(CF_2)_2O$	I	BuLi	3	THF	−78	1 h	−78	1 h	**6j**	35%
13	F	Br	BuLi	2	THF	−78	15 min	−78	1 h	**6k**	79%
14	OCF_3	Br	BuLi	2	toluene	110	1 h	50	2 h	**6l**	33%



Scheme 5: Stepwise bromine–lithium exchange on **1c**.

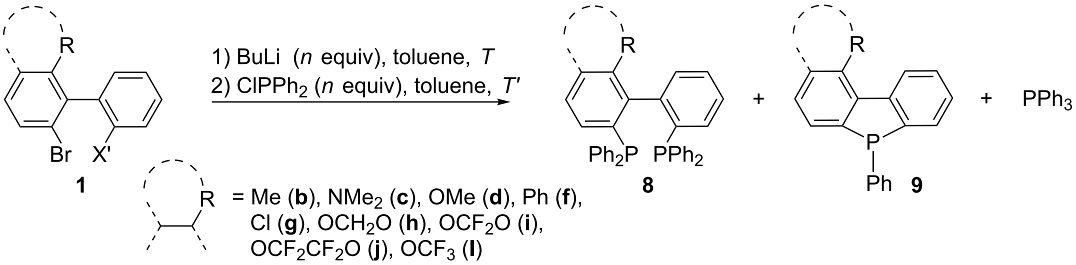
Phosphafluorenes and bis(diarylphosphino)biphenyls: Path D and E

When the *ortho,ortho*'-dibromobiphenyls **1** were submitted to a double bromine–lithium exchange in THF followed by trapping with two equivalents of $ClPPh_2$, whatever the nature of the ortho substituent (R = Me, OMe, NMe_2, Cl, OCF_3, Ph, OCH_2O, OCF_2O, OCF_2CF_2O, H, F), the formation of an intramolecular cyclization product, a dibenzophosphole, was exclusively observed. This is consistent with the observations of O. Desponds et al. [75]. However, when THF was replaced by toluene, the outcome of the reaction could be modified in favor of the 2,2'-bis(diphenylphosphino)biphenyls **8** [27] which were still contaminated with varying amounts of phosphafluorenes **9** and triphenylphosphine (Table 2).

Conclusion

In the present work, we showed how completely regioselective bromine–lithium exchange reactions on polybrominated biphenyls allow the construction of a new family of di- and monophosphine ligands. The required polybrominated biphenyls can be easily obtained through an efficient transition metal-free aryl–aryl coupling protocol developed by our group. The regioselectivity can be explained by recent equilibration studies of M. Schlosser et al. which allowed the determination

Table 2: Synthesis of bis(diphenylphosphino)biphenyls **8**.



Cpd.	R	X'	*n* [equiv]	T^{a} [°C]	$T^{\,b}$ [°C]	Yield **8**^{c}
8b	Me	Br	2	110	50	30%
8c	NMe_2	Br	2	110	50	44%
8d	OMe	Br	2	110	50	17%
8f	Ph	Br	2	110	50	24%
8g	Cl	Br	2	110	50	23%
8h	OCH_2O	Br	2	110	50	18%
8i	OCF_2O	I	3	25	25	47%
8j	OCF_2CF_2O	I	3	25	25	34%
8l	OCF_3	Br	2	110	50	10%

[a] Temperature for the halogen/metal exchange; [b] Trapping temperature; [c] Isolated yield of **8** after flash-chromatography on silica gel.

of ΔΔ*G* increments for substituents at the ortho, meta, and para positions.

Overall, the methodology presented in this study offers the possibility to consider new pathways for the synthesis of more sophisticated biaryl scaffolds. Catalytic studies as well as the control of biaryl axial chirality are currently underway and will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental details and spectroscopic data for new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-148-S1.pdf]

Supporting Information File 2

Crystal structure data for **3a**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-148-S2.pdf]

Supporting Information File 3

Crystal structure data for **3b**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-148-S3.pdf]

Supporting Information File 4

Crystal structure data for **3d**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-148-S4.pdf]

Supporting Information File 5

Crystal structure data for **3f**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-148-S5.pdf]

Supporting Information File 6

Crystal structure data for **6c**.
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Directed ortho,ortho'-dimetalation of hydrobenzoin: Rapid access to hydrobenzoin derivatives useful for asymmetric synthesis

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Full Research Paper

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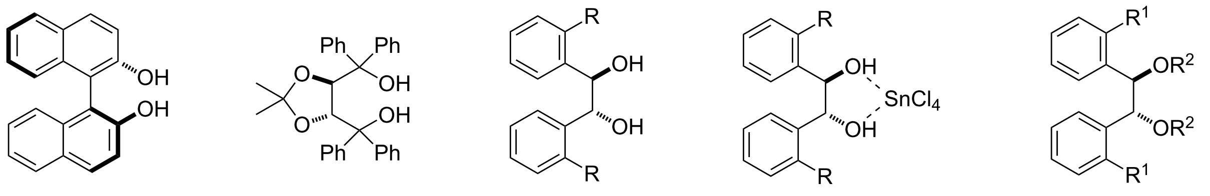
Abstract

A variety of ortho,ortho'-disubstituted hydrobenzoin derivatives are readily accessible through a directed ortho,ortho'-dimetalation strategy in which the alcohol functions in hydrobenzoin are deprotonated by *n*-BuLi and the resulting lithium benzyl alkoxides serve as directed metalation groups. The optimization and scope of this reaction are discussed, and the utility of this process is demonstrated in the one-pot preparation of a number of chiral diols as well as a short synthesis of the chiral ligand Vivol.

Introduction

The discovery of new chiral ligands and auxiliaries continues to expand the frontiers of catalytic asymmetric synthesis. In particular, C_2-symmetric diols, such as (*S*)-BINOL (**1**) [1] and (−)-TADDOL (**2**) [2] (Figure 1), have garnered considerable attention owing to the wide variety of asymmetric reactions promoted by these ligands and/or their derivatives. Although hydrobenzoin (e.g., **3**) has not been utilized to the same extent, it has also demonstrated utility as both a chiral ligand [3-8] and auxiliary [9-17]. For example, Hall reported that the hydrobenzoin·$SnCl_4$ complex **5** promotes the allylboration of hydrocinnamaldehyde with modest enantioselectivity (26% ee) [3], and a hydrobenzoin–ytterbium complex was found to catalyze asymmetric aldol/Evans–Tishchenko reactions [5]. Moreover, the hydrobenzoin dimethyl ether **7** was shown to direct the asymmetric addition of organolithium reagents to arene tricarbonylchromium complexes [7] and α,β-unsaturated aldimines [8]. Notably, derivatives of hydrobenzoin in which the aromatic rings have been functionalized in the ortho and ortho' positions often display improved diastereo- or enantioselectivity over the parent diol **3** [3,14]. For example, the addition of cyclooctyl rings to the ortho and ortho' positions of the hydrobenzoin·$SnCl_4$ complex (i.e., Vivol·$SnCl_4$ (**6**)) leads to a dramatic improvement in enantioselectivity in the allylboration of hydrocinnamaldehyde (93% ee) [3]. Unfortunately, while (*R*,*R*)- and



1 **2** **3**: R = H **4**: R = cyclooctyl (Vivol) **5**: R = H **6**: R = cyclooctyl **7**: R¹ = H, R² = CH₃ **8**: R¹ = R² = Li

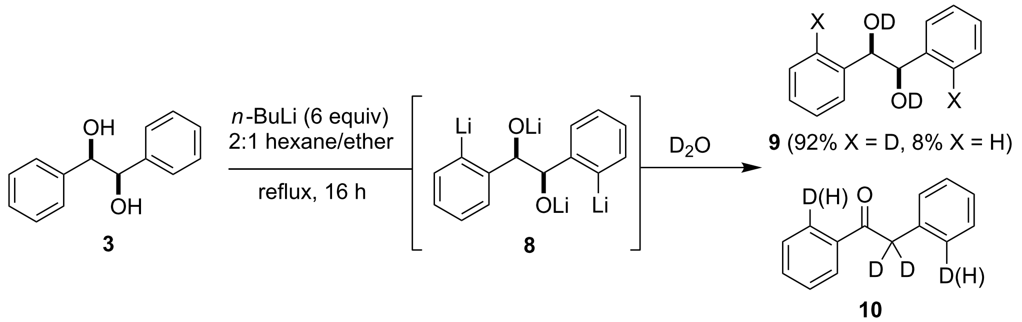
Figure 1: Chiral diols useful for asymmetric synthesis and the tetralithio intermediate **8**.

(*S*,*S*)-hydrobenzoin are relatively inexpensive [18], or can be readily prepared on kilogram-scale from *trans*-stilbene through Sharpless asymmetric dihydroxylation (SAD) [19,20], the synthesis of ortho,ortho'-functionalized derivatives of hydrobenzoin typically requires several steps that include McMurry coupling of an ortho-substituted benzaldehyde followed by I_2-catalyzed isomerization of the resulting stilbene and subsequent SAD [21,22]. Thus, while various hydrobenzoin derivatives have been reported, their multi-step synthesis, the modest enantioselectivity in the SAD step [22], the problems associated with their optical enrichment [6], and the necessary determination of optical purity for each derivative, all complicate the rapid preparation of congeneric libraries. To address these issues, we recently reported a new process for the direct functionalization of (*R*,*R*)-hydrobenzoin (**3**) [23] through a directed ortho,ortho'-dimetalation strategy in which the alcohol functions in hydrobenzoin are deprotonated by *n*-BuLi and the resulting lithium benzyl alkoxides serve as directed metalation groups (DMGs) [24-28] and facilitate formation of the tetralithio intermediate **8**. Herein, we provide a detailed account of this work as well as the application of these methods to a short synthesis of the chiral diol Vivol (**4**).

Results and Discussion

As indicated in Scheme 1, the optimized conditions for the directed ortho,ortho'-dimetalation of (*R*,*R*)-hydrobenzoin (**3**) involve the treatment of a solution of **3** under reflux with an excess (6 equiv) of *n*-BuLi, followed after 16 h by treatment with an electrophile [23]. The optimization of this process relied on a series of D_2O quenching studies and analysis of the ^1H NMR and mass spectra derived from the crude reaction products. These studies led to the eventual selection of a 2:1 mixture of hexane/ether as the most favorable reaction solvent for the formation of the tetralithio intermediate **8** [23].

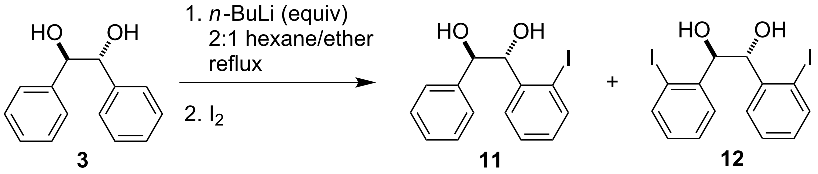
Despite the high level of deuterium incorporation (92%) observed in the reaction of the tetralithio intermediate **8** with D_2O (Scheme 1), this result was not observed for reactions with other electrophiles (see below). In addition, the products from deuterium quenching studies were often accompanied by the formation of varying amounts of the deoxybenzoin **10**, which presumably derives from reaction of an alkoxide function in **8** with D_2O, followed by deuteroxide elimination/enolate formation and subsequent reactions with D_2O. Bearing this in mind, the directed ortho,ortho'-dimetalation of hydrobenzoin was reinvestigated using I_2 as the electrophile quench. As indicated in Table 1, the use of stoichiometric (i.e., 4 equiv, entry 1) amounts of *n*-BuLi led to low isolated yields of the diiodohydrobenzoin **12**. Successively increasing the equivalents of *n*-BuLi resulted in approximate increases of 15% in the isolated yield of **12**, with a maximum yield of roughly 50% achieved when 6 equiv of *n*-BuLi were employed (entries 2 and 4). Although the use of 8 equiv of *n*-BuLi led to a slightly higher isolated yield of **12** (53%), and only 8 hours were required for



3 **8** **9** (92% X = D, 8% X = H) **10**

Scheme 1: Directed ortho,ortho'-dimetalation of (*R*,*R*)-hydrobenzoin (**3**).

Table 1: Optimization of the synthesis of the diiodohydrobenzoin **12**.



entry	*n*-BuLi [equiv]	reflux time [h]	I_2 [equiv]	ratio **11**:**12**[a]	isolated yield **12** [%]
1	4	16	5	1:1	20
2	5	16	6	1:1.7	34
3	5[b]	16	6	2.6:1[c]	8
4	6	16	7	1:5	51
5	6[d]	16	7	2:1[e]	13
6	8	16	9	1:5	53
7	8	8	12	N.D.[f]	51

[a] Ratio determined by analysis of ^{1}H NMR spectra recorded on crude reaction mixture. [b] TMEDA (5 equiv) was added prior to the addition of *n*-BuLi. [c] Hydrobenzoin (48%) was also recovered from this reaction. [d] TMEDA (6 equiv) was added prior to the addition of *n*-BuLi. [e] Hydrobenzoin (34%) was also recovered from this reaction. [f] Not determined.

the formation of the tetralithio intermediate (entries 6 and 7), the conditions identified in entry 4 require fewer equivalents of base and electrophile and were consequently selected as the optimal reaction conditions [23]. Notably, addition of TMEDA (entries 3 and 5), which would presumably assist in the disaggregation of organolithium species, failed to improve these results and in fact led to lower conversion and isolated yields of the diiodohydrobenzoin **12**.

During the evaluation of the reaction of the tetralithio intermediate **8** with I_2 (Table 1), we were surprised to find that monoiodohydrobenzoin **11** was produced in equivalent or lower yield than the diiodohydrobenzoin **12**, even at low overall conversion (e.g., Table 1, entries 1 and 2). These results suggested that the rate-limiting step in the formation of the tetralithio intermediate **8** may be the first DoM (i.e., formation of a trilithio intermediate) and that the second DoM event is relatively more rapid. To gain further insight into this process, the reaction of (*R*,*R*)-hydrobenzoin (**3**) with *n*-BuLi followed by treatment with D_2O [23] or CH_3I was monitored by mass spectrometry and ^{1}H NMR spectroscopy, respectively. As indicated in Figure 2, the results of the D_2O quenching study were in accordance with our original observation: A relatively slow removal of the first ortho proton is followed by a second, more rapid DoM event.

When the progress of the sequential ortho-metalations was monitored by quenching with CH_3I, however, the difference in rates was not as pronounced, and only in the case where the formation of the tetralithio intermediate **8** was allowed 6 hours at reflux was the proportion of mono- and dimethylhydrobenzoin (i.e., **14** and **15**) equivalent. It is notable that the differing results depicted in Figure 2 and Figure 3 may be attributed to intra- or intermolecular deprotonation of the *o*-tolyl group following reaction of the tetralithio intermediate **8** with one equiv of CH_3I, leading to the formation of misleading amounts of the monomethylhydrobenzoin **14**, or simply differing reactivity of the tetralithio intermediate with D_2O and CH_3I.

A possible explanation for the differing rates of DoM events observed during the D_2O quenching studies is depicted in Scheme 2 [29]. Thus, following the first ortho-metalation, the intermediate aryl lithium **17** (presumably in an aggregated form) may adopt a conformation in which the lithium alkoxide (DMG) and consequently the base (i.e., *n*-BuLi or its aggregates) are positioned in close proximity to the ortho proton that is to be removed. Alternatively, the intermediate aryl lithium **17** may undergo rearrangement to the six-membered heterocycle **18**, in which the cis-relationship between the distal lithium alkoxide and the unlithiated phenyl ring facilitates the second deprotonation. While the latter proposal is less likely, based on Seebach's observation that 2-phenylethanol does not undergo ortho-lithiation [30], reaction of the tetralithio intermediate **8** with dimethyldichlorosilane led to the formation of the bis(siloxane) **19** (not the 5-membered ring bis(siloxane) isomer), whose structure was unambiguously confirmed by X-ray crystallographic analysis (see Scheme 2, inset).

As indicated in Scheme 3, formation of the tetralithio intermediate **8** and subsequent reaction with various electrophiles led to synthetically useful yields of ortho-functionalized hydrobenzoin derivatives [23]. In each case, approximately 5–10% of the

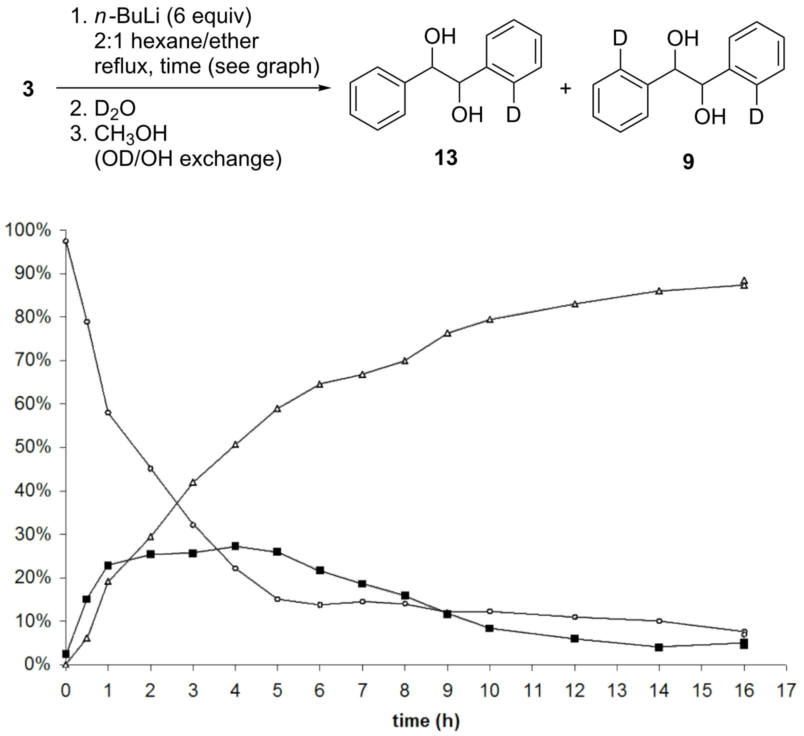


Figure 2: Percentage of (*R*,*R*)-hydrobenzoin (**3**) (○), monodeuterohydrobenzoin (**13**) (■), and dideuterohydrobenzoin (**9**) (Δ) as determined by mass spectrometry (ESI) [23].

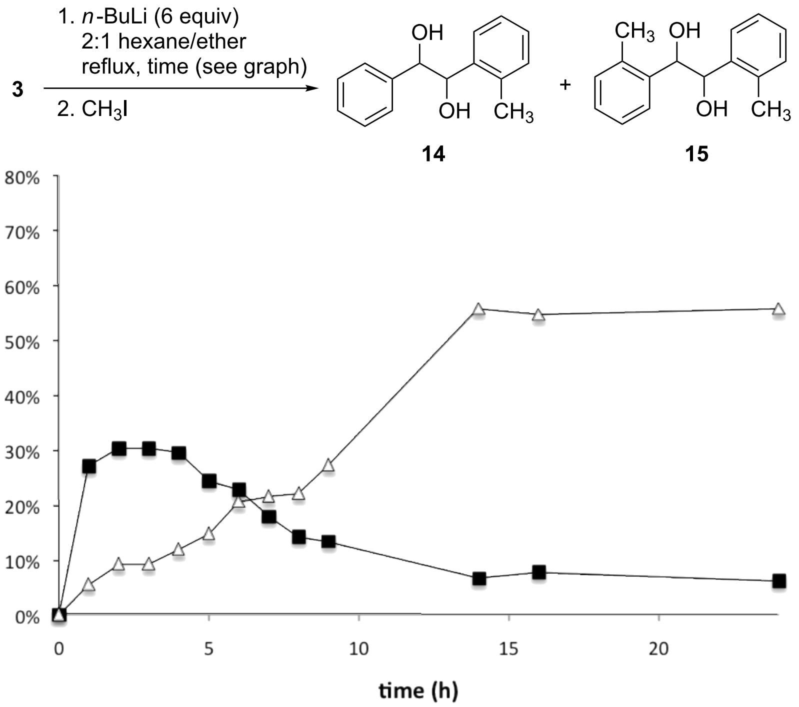
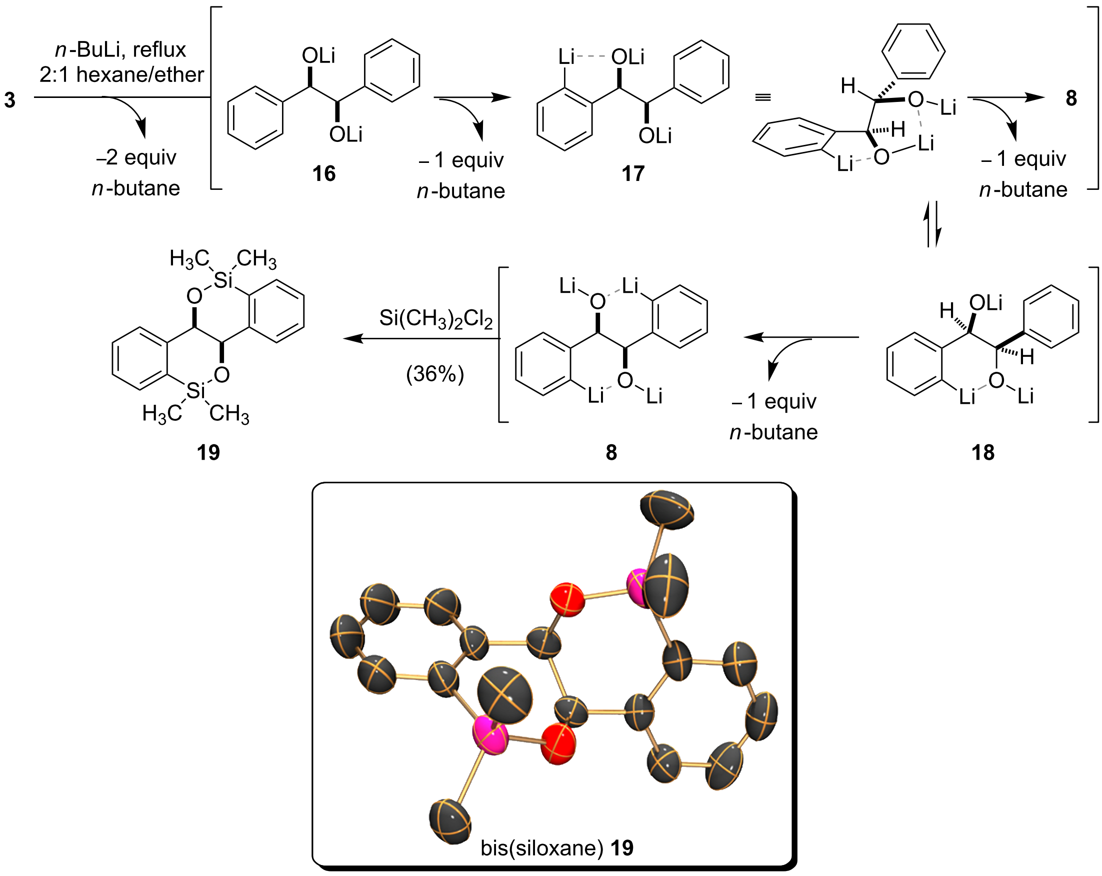
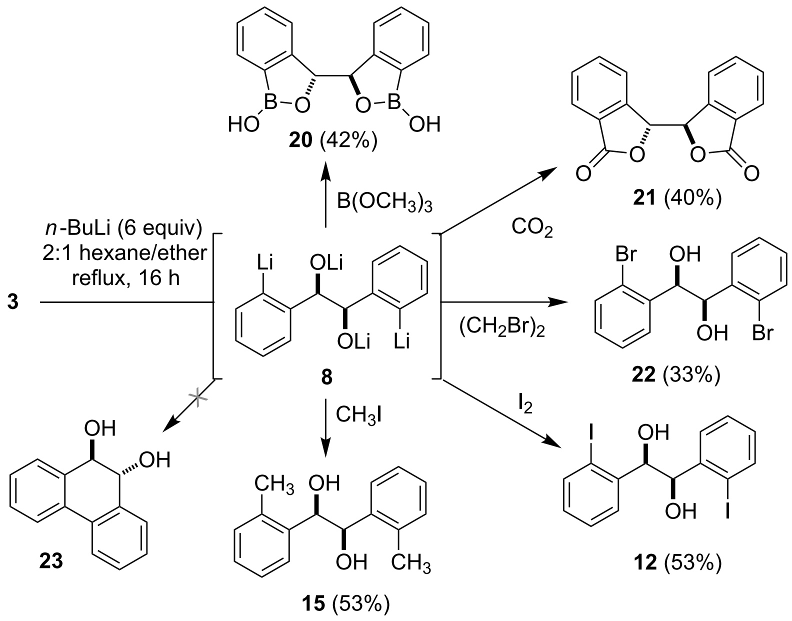


Figure 3: Percentage of methylhydrobenzoin (**14**) (■), and dimethylhydrobenzoin (**15**) (Δ) as determined by ^{1}H NMR spectroscopy. The remainder of the material is recovered (*R*,*R*)-hydrobenzoin (**3**).



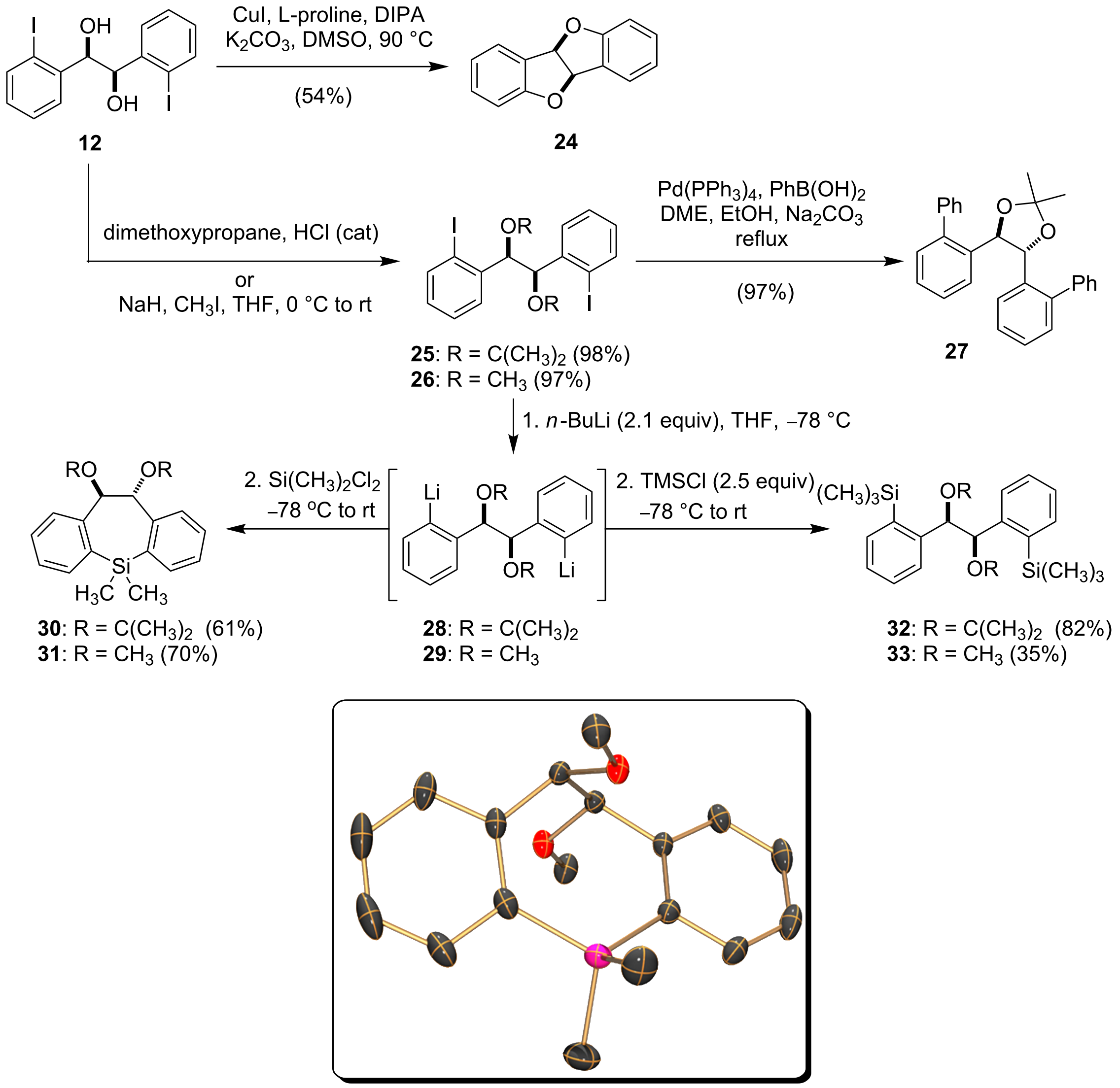
Scheme 2: Formation of the tetralithio intermediate **8** and the X-ray crystal structure of the bis(siloxane) **19**.



Scheme 3: Reaction of the tetralithio intermediate **8** with various electrophiles.

corresponding monofunctionalized hydrobenzoin (e.g., **14**, Figure 3) was also produced, but was readily separable from the desired product by flash chromatography. Unfortunately, reaction of the tetralithio intermediate **8** with carbonyl electrophiles (e.g., acetone, acetaldehyde, diethyl carbonate, valeraldehyde, cyclohexanal, crotonaldehyde, formaldehyde, DMF, benzaldehyde), trimethylsilyl chloride, or allyl/benzyl chloride/bromide failed to provide the desired products in reasonable yield. For example, treatment of the tetralithio intermediate **8** with benzyl chloride resulted in recovery of (*R*,*R*)-hydrobenzoin along with 1-chloro-1,2-diphenylethane, the latter of which arises through the deprotonation of benzyl chloride by **8** and reaction of the resulting benzyl anion with a second equivalent of benzyl chloride. Likewise, attempts to effect a reductive coupling of the tetralithio intermediate to afford the dihydrophenanthrenediol **23** [22] with the aid of various copper or iron halides [31], or palladium(II)chloride [32] were unsuccessful. In an effort to fine-tune the procedure by attenuating the reactivity of the tetralithio intermediate **8**, transmetalation with $ZnCl_2$ or $MgBr_2$ followed by treatment with various electrophiles was also investigated. Disappointingly, these efforts failed to offer any improvement in the coupling of **8** with DMF, benzaldehyde, or allyl bromide and consequently we focused our attention on reactions of the readily available diiodohydrobenzoin **12** and bis(benzoxaborol) **20**.

As highlighted in Scheme 4, attempts to directly engage diiodohydrobenzoin **12** in Cu-catalyzed C–N cross-coupling



Scheme 4: Reactions of the diiodohydrobenzoin **12** and X-ray crystal structure of the dihydrosilepin **31**.

reactions [33] led only to the formation of *cis*-4b,9b-dihydrobenzofuro[3,2-*b*]benzofuran (**24**) [34]. Consequently, the diol **12** was converted to the corresponding acetonide **25** or methyl ether **26** prior to cross-coupling. In this manner, the diphenylhydrobenzoin derivative **27** could be accessed in excellent overall yield [3,23]. Alternatively, lithium–halogen exchange carried out on diiodohydrobenzoins **25** or **26**, followed by reaction with various electrophiles affords access to a wider array of hydrobenzoin derivatives than those highlighted above in Scheme 3 [17]. For example, electrophiles such as TMSCl and dichlorodimethylsilane engage in high yielding reactions with the dianions **28** and **29** to provide the silyl-functionalized hydrobenzoin derivatives **30**–**33**.

The bis(benzoxaborol) **20** also proved to be a versatile intermediate for the synthesis of hydrobenzoin derivatives through Pd-catalyzed cross-coupling reactions (Scheme 5). This approach compliments those described above and avoids the need to protect the diol function prior to the cross-coupling step. Notably, purification of the bis(benzoxaborol) **20** proved unnecessary as the diphenylhydrobenzoin **34** was prepared in an overall yield of 32% from (*R*,*R*)-hydrobenzoin (**3**) without purification of **20**, compared to 21% when the intermediate bis(benzoxaborol) **20** was purified by column chromatography [23]. Finally, the efficiency of this process was demonstrated in a short formal synthesis of (*R*,*R*)-Vivol (**4**). Thus, a Pd-catalyzed cross-coupling of the known triflate **35** [35] with the bis(benzoxaborol) **20** afforded the dicyclooctenylhydrobenzoin **36**, which was reduced in quantitative yield to afford Vivol (**4**) by Hall [3]. Notably, this three-step procedure for the preparation of optically pure Vivol compares well with the reported synthesis and should be effective for the rapid production of new ligands for asymmetric synthesis.

Conclusion

In conclusion, an efficient and economical process was developed for the direct functionalization of hydrobenzoin that relies on a directed ortho,ortho'-dimetalation strategy. Importantly, a wide variety of chiral diols (e.g., Vivol (**4**)) are now readily accessible in optically pure form following this one-pot reaction. Although the range of electrophiles that engage in synthetically useful reactions with the tetralithio intermediate **8** is limited, the diiodohydrobenzoin **12** and bis(benzoxaborol) **20** are both prepared in good yield and are readily derivatized through cross-coupling reactions. We are currently exploring the utility of the bis(benzoxaborol) **20** and derivatives of this substance as chiral Lewis acids and will report our findings in due course.

Supporting Information

Supporting Information File 1

Experimental details and characterization data for all compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-154-S1.pdf]

Supporting Information File 2

X-ray crystallographic information files (CIFs) for crystals of **19** and **31**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-154-S2.cif]

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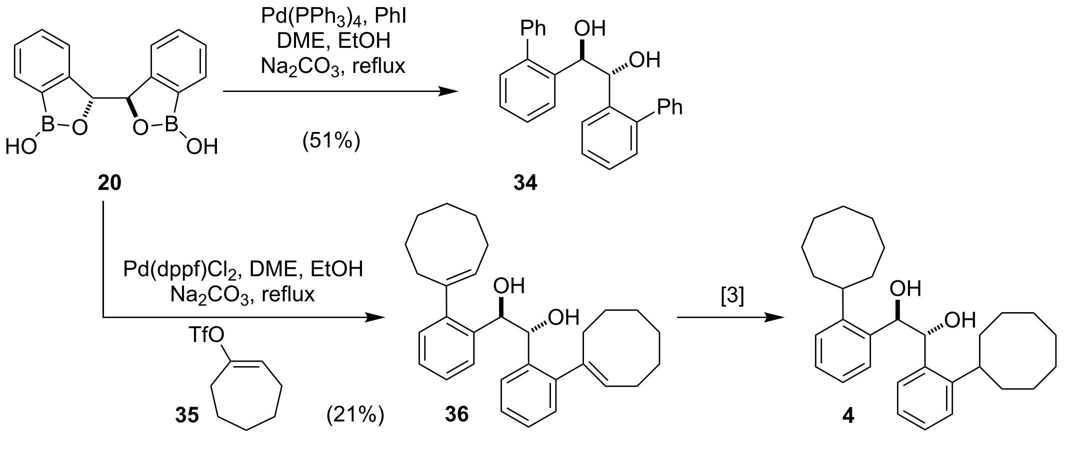

Scheme 5: Cross coupling reactions of the bis(benzoxaborol) **20** and a short formal synthesis of (*R*,*R*)-Vivol (**4**).

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Carbamate-directed benzylic lithiation for the diastereo- and enantioselective synthesis of diaryl ether atropisomers

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Letter

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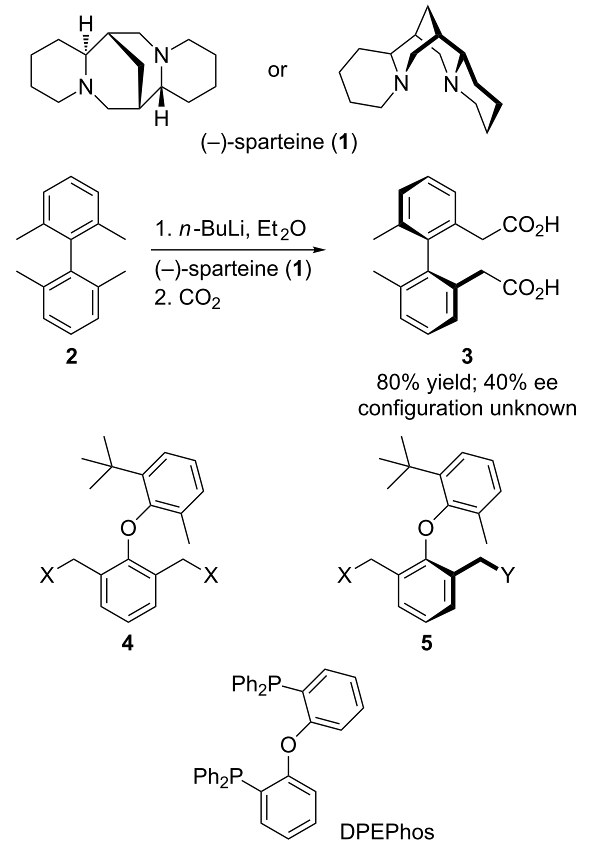
Abstract

Diaryl ethers carrying carbamoyloxymethyl groups may be desymmetrised enantio- and diastereoselectively by the use of the *sec*-BuLi–(−)-sparteine complex in diethyl ether. Enantioselective deprotonation of one of the two benzylic positions leads to atropisomeric products with ca. 80:20 e.r.; an electrophilic quench typically provides functionalised atropisomeric diastereoisomers in up to 97:3 d.r.

Introduction

One of the first uses of the chiral diamine (−)-sparteine (**1**) in its now familiar role of controlling asymmetric deprotonation/electrophilic quench reactions [1] was an enantioselective benzylic deprotonation of bis(2,6-dimethylbenzene) with the aim of generating an atropisomeric product in enantiomerically enriched form (Scheme 1) [2]. Enantioselective lithiation has since then commonly been used to generate axial or planar chirality [3], in many cases by desymmetrising deprotonation of a functionalised aromatic system. The relative acidity of benzylic protons makes enantioselective deprotonation in the style of Scheme 1, of one of a pair of enantiotopic aromatic methyl, alkoxymethyl or acyloxymethyl substitutents, a viable approach to the asymmetric synthesis of atropisomeric molecules.

We have developed a number of methods for the synthesis of “nonstandard” atropisomer structures containing rigid fragments joined by a hindered single bond, but which are different from the typically well-studied biaryl compounds [4,5]. These non-biaryl atropisomers have included aromatic amides [6-8], ureas [9], ethers [10-12], sulfides and sulfones [13], and many of the methods we developed for their asymmetric synthesis



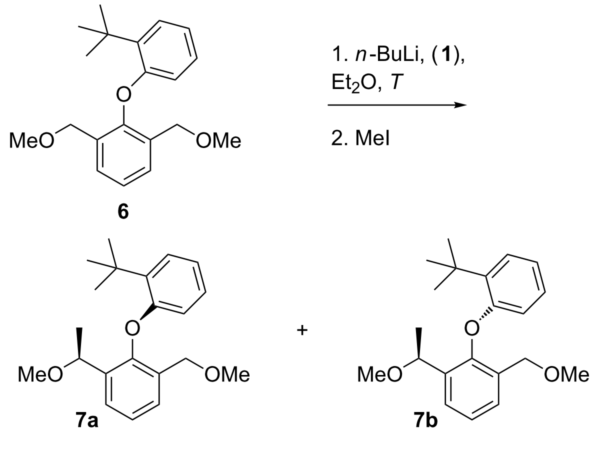
Scheme 1: Desymmetrising metallation for the enantioselective synthesis of atropisomers.

employed dynamic resolution techniques under kinetic or thermodynamic control [6,11,13-16]. The mechanistic possibilities associated with dynamic resolution were initially elaborated by Beak for organolithium compounds having varying degrees of configurational stability [17,18], and in our studies on ureas and amides we were able to identify correlated inversion processes linking configurational inversion at organolithium centres with conformational inversion of atropisomeric chirality by bond rotation [19]. Several of the classes of atropisomers we have studied contain functional groups which are excellent directors of lithiation [20], and indeed our original interest in lithiation stemmed from the need to build these atropisomeric structures rapidly and efficiently [21].

We recently reported on the enantioselective synthesis of diaryl ethers (a potential new class of chiral ligand having a structure related to the wide bite angle diphosphine DPEPhos) by biocatalytic oxidation or reduction, and which made use of desymmetrisation of a "pro-atropisomeric" substrate **4** to achieve the required enantiomeric enrichment in the product **5** [22]. In this paper we report parallel studies on the attempted asymmetric synthesis of atropisomeric diaryl ethers in diastereomerically and/or enantiomerically enriched form by the directed deprotonation and electrophilic quench of benzylic positions ortho to a sterically hindered diaryl ether linkage.

Results

An aryloxy group is a weak director of metallation [20,23], but in preliminary studies we were able to deprotonate and methylate the hindered diaryl ether **6** [10] by treatment with *n*-BuLi in ether at 0 °C with or without (−)-sparteine (Scheme 2). Methylation of the resulting organolithium returned the product **7** in up to 88% yield as a mixture of diastereoisomers (by NMR). Previous data on the conformational stability of related diaryl ether [10], coupled with our inability to separate these diastereoisomers, and the invariant ratio in which they were obtained, suggested that they are insufficiently hindered to exist as stable atropisomers and they interconvert on a relatively short timescale, of seconds to minutes, at room temperature.

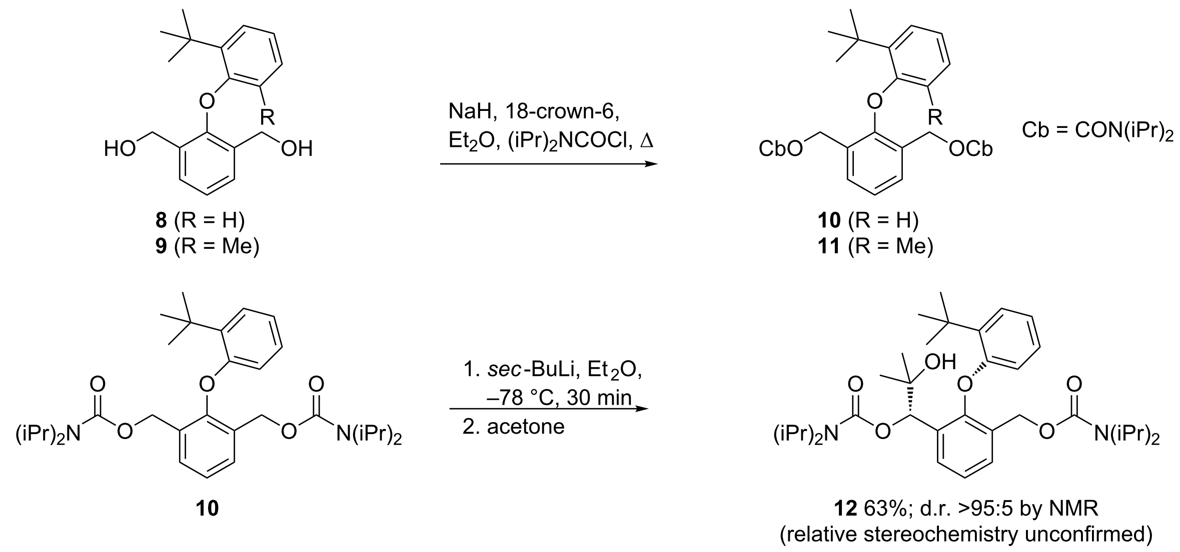


d.r. 66:34 by NMR
(relative stereochemistry unconfirmed)

with **1**: *T* = –78 °C: 49%; *T* = 0 °C: 80%
without **1**: *T* = –78 °C: 0%; *T* = 0 °C: 88%

Scheme 2: Benzylic lithiation of a diaryl ether.

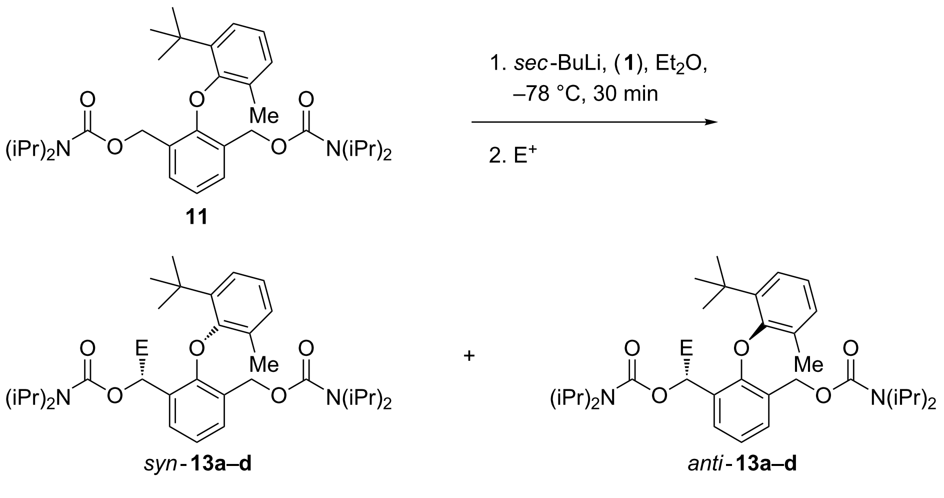
In order to enhance the ease of metallation of the substrates (**6** gives low yield at −78 °C unless sparteine is present), two diols **8** and **9**, available from previous work, were converted to the biscarbamates **10** and **11**. The metallation of *O*-benzylcarbamates has been studied extensively by Hoppe [1,24-26], and the deprotonation of **10** was achieved with *sec*-BuLi in ether and the addition of acetone, returning **12** as a single diastereoisomer (by NMR). Presumably in this case the diastereoisomers still interconvert, but the bulk of the new substituent means that one of the two diastereoisomers is significantly more stable than the other [27]. However we were unable to confirm the relative stereochemistry of the major diastereoisomer of the functionalised products (Scheme 3).



Scheme 3: Benzylic metallation of a diaryl ether α to a carbamate.

Moving to the 6'-methyl analogue **11** gave products that were expected to be atropisomeric [10], because they have four substituents ortho to the ether linkage, one of them tertiary. Deprotonation with *sec*-BuLi in Et_2O at −78 °C and quenching with acetone, cyclobutanone, TMSCl or acetic anhydride all gave good yields of functionalised products with d.r.'s which varied according to the electrophile but were generally high (Scheme 4 and Table 1, entries 1–4). Having established good reactivity in a potentially atropisomeric substrate, we next evaluated the ability of (−)-sparteine [1,3] to control the enantioselectivity of these reactions. Premixing the *sec*-BuLi with (−)-sparteine in Et_2O, before addition of the reaction substrate and then the electrophile, led to products being formed in high d.r. in each case and with e.r.'s between 73:27 and 81:19 (Table 1, entries 5–8).

The reaction behaviour was very revealing when the benzyllithiums generated in the presence or absence of (−)-sparteine were quenched with the electrophile Bu_3SnCl (Scheme 5 and Table 2). Unlike previous examples, the quench provided a product only very slowly; 16 h at −78 °C was required to reach a ca. 60% yield of the stannane **13e** (Table 2, entry 3). After this

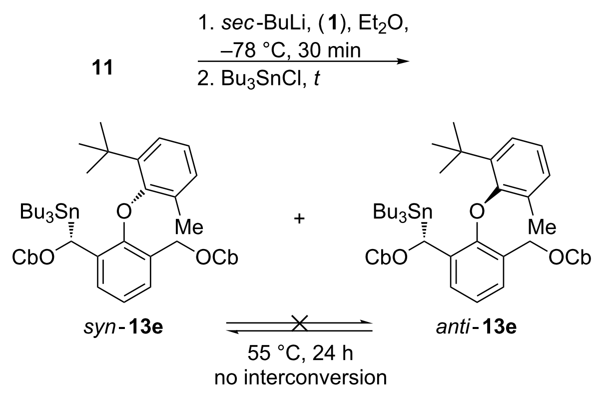


Scheme 4: Diastereo- and enantioselective synthesis of atropisomeric ethers by benzylic lithiation.

Table 1: Yields and selectivities in the metallation/quench of **11**.

entry	**1** present?	E^+ =	E =	product	yield	d.r.	e.r.
1	No	acetone	$C(OH)Me_2$	**13a**	75	95:5	–
2	No	cyclobutanone	$C(OH)(CH_2)_2$	**13b**	56	85:15	–
3	No	Me_3SiCl	$SiMe_3$	**13c**	70	95:5	–
4	No	Ac_2O	COMe	**13d**	69	85:15	–
5	Yes	acetone	$C(OH)Me_2$	**13a**	86	>97:3	75:25
6	Yes	cyclobutanone	$C(OH)(CH_2)_2$	**13b**	26	>97:3	73:27
7	Yes	Me_3SiCl	$SiMe_3$	**13c**	72	95:5	78:22
8	Yes	Ac_2O	COMe	**13d**	66	95:5	81:19

time the diastereoselectivity was good, but it was clear that this was a result of a slow improvement in the product ratio as the reaction proceeded (Table 2, entries 1–3). Arresting the electrophilic quench after 90 min produced only a 9% yield of a 2:1 ratio of diastereoisomers of **13e**, while intermediate reaction times gave ratios that slowly approached the ratio of 9:1 observed after 16 h. The diastereoisomeric ratios of the products remained unchanged even when the products were heated at 55 °C for 24 h, confirming that the *anti* and *syn* diastereoisomers of the stannanes are stable atropisomers.



Scheme 5: Atroposelective stannylation.

Table 2: Variation of yield and selectivity with quench time.

entry	**1** present?	*t* [h]	yield	d.r.	e.r.
1	No	1.5	9	65:35	–
2	No	6	42	80:20	–
3	No	16	58	90:10	–
4	Yes	16	62	95:5	75:25
5	Yes	26	59	95:5	73:27

This proven conformational stability of the products **13e** indicates that the change in product ratio as the reaction proceeds must be due to a slow change in the structure or diastereoisomeric composition of the lithiated intermediate as the reaction progresses. The results with Bu_3SnCl suggest that lithiation generates an approximately 20:1 mixture of configurationally stable diastereoisomeric benzyllithiums of which the minor is significantly more reactive than the major (see below). A form of kinetic resolution occurs in which the minor organolithium is rapidly converted to product, followed slowly by the major organolithium [28]. Hoppe observed a related effect in the alkylations of cinnamyllithiums [29].

Previous results from the laboratories of Hoppe indicated that lithiated *O*-benzylcarbamates are typically configurationally unstable in ether on the macroscopic timescale [1], although Hoffmann detected microscopic configurational stability [30]. To demonstrate that the organolithium intermediates here do have some configurational stability, we treated samples of **13e** of different diastereoisomeric and enantiomeric ratios with *n*-BuLi in ether at −78 °C to induce tin–lithium exchange, quenching the products with either acetone or Me_3SiCl (Scheme 6).

$$\mathbf{13e} \xrightarrow[\text{2. Me}_3\text{SiCl or acetone}]{\text{1. }n\text{-BuLi, 2 h}} \mathbf{13a} \quad \text{or} \quad \mathbf{13c}$$

Scheme 6: Stereospecific tin–lithium exchange/quench reactions.

The major product diastereoisomers were the same as those formed by direct deprotonation quench (Scheme 2). Importantly, in Table 3, entries 1 and 3 show that the diastereoisomeric ratio of the product was at least partly dependent on the d.r. of the starting stannane, necessarily indicating some degree of macroscopic configurational stability. The ratios were not identical, but yields were low, thus differential rates of the reaction of the two diastereoisomeric organolithiums may again be to blame. Enantiomerically enriched stannane returned enantiomerically enriched product, showing that racemisation (which necessarily involves either rotation about the Ar–O–Ar axis or deprotonation–reprotonation) is also slow.

Table 3: Stereospecificity in the tin–lithium exchange/quench reactions.

entry	**13e** d.r.	**13e** e.r.	E^+ =	product, d.r.	e.r.
1	90:10	–	Me_3SiCl	**13c**, 94:6	–
2	90:10	–	acetone	**13a**, >95:5	–
3	80:20	–	Me_3SiCl	**13c**, 88:12	–
4	>95:5	80:20	Me_3SiCl	**13c**, >95:5	80:20

Discussion

Due to the gummy nature of the products, it turned out to be impossible to establish unequivocally the relative or absolute stereochemistry of the products obtained from the lithiations. However, we can make several important conclusions from this work.

Firstly, racemisation of the intermediate organolithiums is demonstrably slow, because an enantioenriched stannane yields, after tin–lithium exchange and quench, products with conserved e.r. (Table 3, entry 4). The e.r. of the products formed by deprotonation with an alkyllithium-(−)-sparteine complex must therefore be determined during the deprotonation step, in which the alkyllithium-(−)-sparteine complex elects to deprotonate one of the two enantiotopic CH_2OCb groups of the starting material. Every e.r. produced during this study fell between 75:25 and 81:19, irrespective of the electrophile, so our conclusion is that this selectivity represents the enantioselectivity of the alkyllithium-(−)-sparteine deprotonation step.

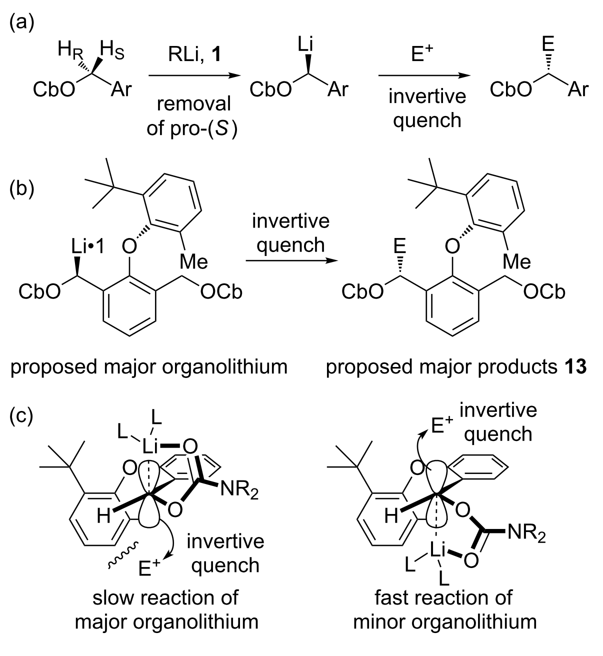
Secondly, since epimerisation of the organolithiums is also slow enough for different d.r.'s of a stananne to yield different d.r.'s of a product (Table 3, entries 1 and 3), we can be certain that the secondary benzyllithium centre is macroscopically stable on the timescale of these reactions. This is in contrast with previous reports of benzyllithiums derived from primary benzylcarbamates [1], though not for secondary benzylcarbamates [24], so we assume that steric bulk or electron donation from the ether group is responsible.

Thirdly, the change in ratio of the stannane products in Table 2 with time indicates that two diastereoisomeric organolithiums are formed in unequal quantities. Our best estimate is that the diastereoisomeric ratio of the organolithiums is of the order of 90:10 or 95:5, perhaps better in the presence of (−)-sparteine since d.r.'s were uniformly higher when (−)-sparteine was present (though this may also be due to an improvement in the stereospecificity of the quench).

Fourthly, diastereoselectivity, unlike enantioselectivity, varies significantly according to the electrophile employed, showing that the product d.r. is determined in the electrophilic quench step. Precedent studies suggest that electrophilic quench of benzylcarbamates is typically invertive [24]: All documented stannylations of benzyllithiums are invertive [23], and all documented tin–lithium exchanges (except one, where there is no adjacent heteroatom [31]) are retentive [23]. If these assumptions hold true here, then formation of the same diastereoisomer of the product silane **13a** or alcohol **13c**, by either deprotonation or by stannylation tin–lithium exchange (Table 3, entries 1 and 2), therefore indicates that both of these electrophiles also react with inversion. Lower d.r.'s may result from some electrophiles by competitive reaction with up to 15% retention (Table 1), and the effect of (−)-sparteine on the d.r.'s in Table 1 may be because its steric bulk helps to suppress this competing retentive pathway.

Lack of crystallinity has meant that we cannot unequivocally assign absolute or relative stereochemistry in this work. However, a few reasonable assumptions allow us to propose likely assignments, and these are the ones used in the structural diagrams in this paper:

1. (−)-Sparteine favours deprotonation of the pro-*S* proton of carbamates. Invertive quench would result in the formation of the products with stereogenic centres as illustrated in Scheme 7(a).



Scheme 7: Proposed stereochemical pathway.

2. The slower invertive reaction of the major organolithium diastereoisomer with Bu_3SnCl suggests that the product of this reaction is more hindered (Scheme 7(c)), and we therefore propose that the major diastereoisomers of the reactions are as shown in Scheme 7(b).

Conclusion

Overall, we have shown in this paper that the use of an alkyllithium-(−)-sparteine deprotonation can desymmetrise a proatropisomeric biscarbamoyloxy diarylether, with enantiomeric ratios of up to 81:19. Some mechanistic details of the stereochemical course of the lithiation–substitution reactions have been elucidated, and further work remains to exploit this transformation for the potential synthesis of new classes of chiral ligands [12].

Supporting Information

Supporting Information File 1

Experimental details and spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-156-S1.pdf]

Acknowledgements

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Directed aromatic functionalization in natural-product synthesis: Fredericamycin A, nothapodytine B, and topopyrones B and D

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Review

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Abstract

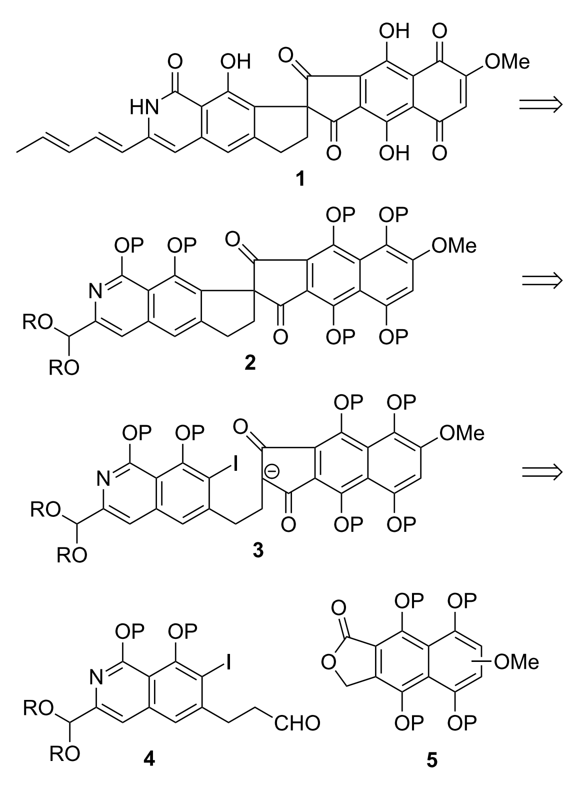
This is a review of our efforts toward the synthesis of a group of natural products that display noteworthy biological activity: Fredericamycin A, nothapodytine B, and topopyrones B and D. In each case, directed aromatic functionalization methodology greatly facilitated the assembly of the key molecular subunits.

Review

Our laboratory is primarily interested in the total synthesis of natural products, and does not conduct research on directed aromatic functionalization ("DAF") per se. On numerous occasions, however, DAF technology has been key to the success of specific synthetic endeavors in our group. Herein, we illustrate the application of such techniques to three representative problems that we have addressed over the years: The syntheses of fredericamycin A, nothapodytine B, and topopyrones B and D.

Fredericamycin A

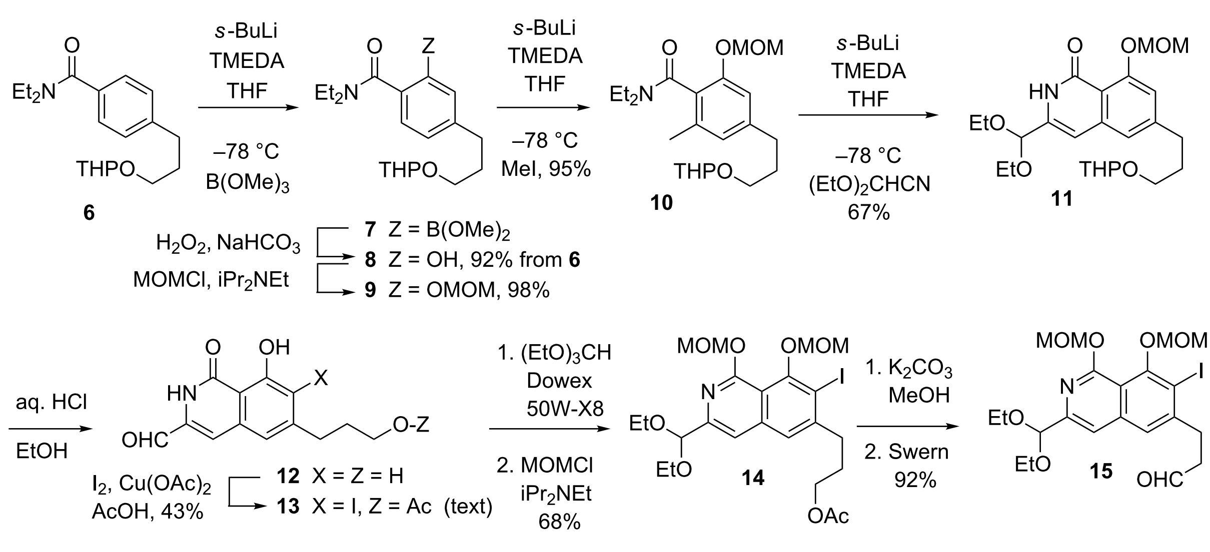
This initial portion of the present review recounts the first project that the senior author of this paper launched as an independent academic in 1984. A structurally novel natural product by the name of fredericamycin A (**1**, Scheme 1) had been discovered only two years prior and determined to be strongly cytotoxic [1-5]: A finding that spawned a flurry of activity in the synthetic arena. Indeed, seven total syntheses [6-16] and numerous approaches [17-30] have been described since. Fredericamycin seemed to be a superb vehicle to address an issue for which no solution existed at that time: The arylation of stabilized enolates. Indeed, the retrosynthetic analysis illustrated in Scheme 1 suggests that **1** could result from the cyclization of **3**, which in turn would ensue through the union of fragments **4** and **5**. These two subunits were prepared by DAF technology [31].



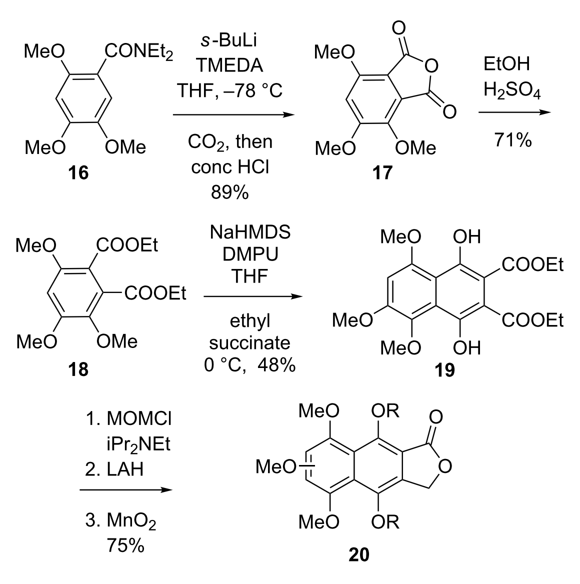
Scheme 1: Structure and retrosynthetic analysis of fredericamycin A.

The starting point for the assembly of an appropriate variant of **4** was diethylamide **6** (Scheme 2), which underwent smooth Beak–Snieckus-type *ortho*-deprotonation [32-35] with the *sec*-BuLi–TMEDA complex and consequent borylation in high yield. Oxidation of the ensuing **7** to phenol **8** and O-protection served as a prelude to a second *ortho*-deprotonation en route to methyl derivative **10**. A third round of *sec*-BuLi–TMEDA treatment induced highly selective deprotonation of the methyl group, and in keeping with the observations of Kelly [6,7], the intervening anion was intercepted by diethoxyacetonitrile [36] to furnish isoquinolone **11** directly. Relative to **4**, compound **11** lacks an iodo substituent, which was introduced by reaction of the free aldehyde **12** with I_2 and $Cu(OAc)_2$ in refluxing AcOH [37]. Only the unprotected **12** performed satisfactorily in this step, which, unfortunately, afforded an essentially 1:1 mixture of the desired phenolic *ortho*-iodide **13** and the corresponding *para*-isomer. These were readily separated after reprotection of the aldehyde and of the phenol, i.e., at the stage of **14**. Notice that in the course of the reaction the primary OH group in **12** was converted into an acetate ester (Fischer-type esterification). Compound **15**, a form of **4** suitable for the conduction of subsequent operations, was secured by deacetylation of **14** and Swern oxidation.

Fragment **5** was best produced in the guise of compound **20**, the construction of which also relied upon DAF methodology. Thus, *ortho*-deprotonation of diethylamide **16** (Scheme 3) and carboxylation afforded anhydride **17** directly after workup with 12 N aqueous HCl. Fischer esterification and condensation of the resultant **18** with diethyl succinate, according to Kelly [6,7], afforded **19**, which was then elaborated to a 1:1 mixture of regioisomers of naphthalide **20**. It will be seen shortly that the formation of regioisomers at this stage is inconsequential.

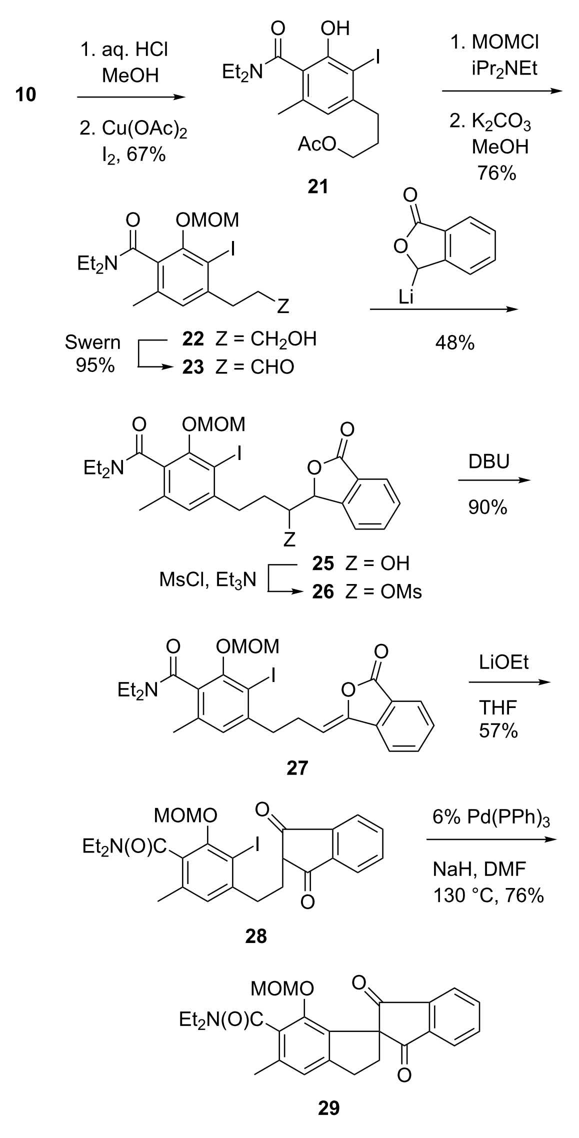


Scheme 2: Assembly of the isoquinolone segment of fredericamycin.



Scheme 3: Synthesis of a naphthalide precursor to the quinoid moiety of fredericamycin.

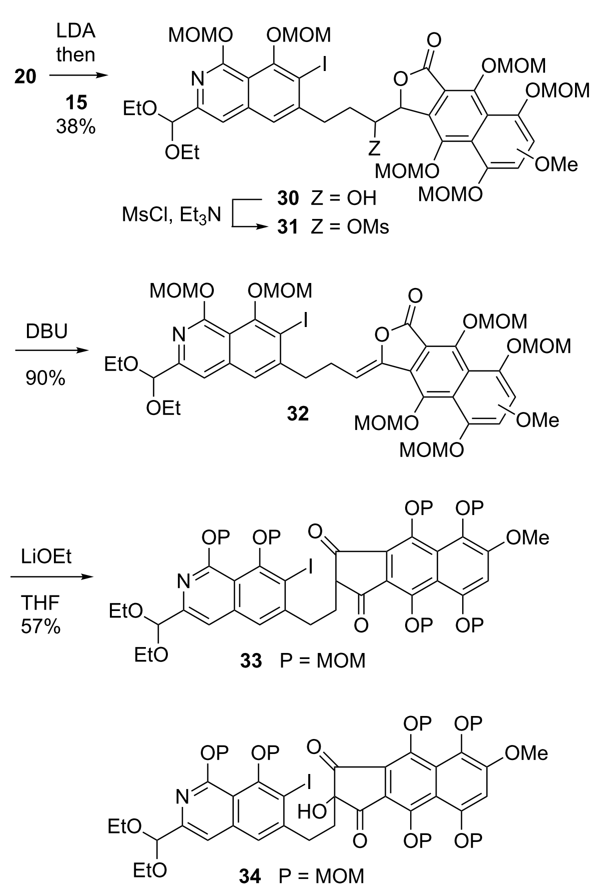
Parallel work had concentrated on defining a protocol for the merger of the two fragments, and especially for the conduct of the crucial, and the time highly novel, arylation step. The first issue, the more tractable of the two, was addressed by converting **10** into aldehyde **23** as a model of the more elaborate **15** (Scheme 4). Ironically, and contrary to the case of **12**, the iodination of this simpler system proceeded with superb ortho-selectivity to furnish **21** as the sole product. The aldehyde underwent tandem addition of the anion of simple phthalide (a model for **20**; prepared from the parent compound by deprotonation with LDA) and dehydration via mesylate **26** to provide **27**, which upon reaction with EtOLi (EtOH + BuLi) in THF rearranged to diketone **28**. Experiments involving **28**, as well as simpler model systems [38], revealed that the few techniques of enolate arylation then known were completely ineffective for the desired transformation. Remarkably, however, heating a DMF solution of the preformed sodium enolate of **28** (NaH) in the presence of $Pd(PPh_3)_4$ triggered cyclization to **29** in a very satisfactory 76% yield [39].



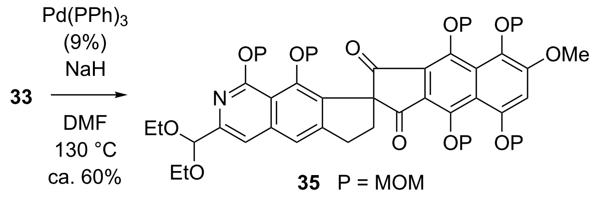
Scheme 4: Palladium-mediated cyclization of a fredericamycin model system.

On the basis of these results, the anion of naphthalide **20** was condensed with aldehyde **15** following the same protocol to yield compound **32** (Scheme 5). A distressing observation was made at this juncture: The base-promoted transposition of **32** to **33** was complicated by the unexpected propensity of the diketone to react with atmospheric oxygen to form the corresponding 2-hydroxy derivative **34**. This transformation was virtually instantaneous when the anion of **33** was exposed to the atmosphere, whereas **33** itself was completely hydroxylated in about 30 minutes at room temperature. Silica gel appeared to act as an effective catalyst for the process, further complicating purification, which ultimately had to be carried out in a glove box.

Not without some difficulty, a batch of material consisting largely of **33** was subjected to the palladium-mediated cyclization reaction. This led to the formation of compound **35** in about 60% yield (based on ^1H NMR; Scheme 6). A late intermediate in the Kelly synthesis of **1** [6,7] is structurally very similar to **35**. Consequently, the preparation of **35** corresponds to a formal synthesis of fredericamycin A [31]. In the years since, Pd-mediated arylation reactions of enolates have been extensively developed and improved, especially by Buchwald [40-43] and Hartwig [44-46].



Scheme 5: Synthesis of the precursor of fredericamycin and the facile air oxidation thereof.



Scheme 6: Formal synthesis of fredericamycin A.

Nothapodytine

Our group cultivates a long-standing interest in furan chemistry, especially in connection with a process that we describe as the “aza-Achmatowicz reaction” [47-52]: A transformation that has attracted the attention of a number of researchers worldwide [53-62]. In the course of such endeavors, we have often resorted to the facile C-2 deprotonation of furan as a means to generate appropriate derivatives. This is of course a special case of directed aromatic functionalization. A significant example of this chemistry was key to our synthesis of nothapodytine B, **36** (Figure 1) [63]. This substance is also known as mappicine ketone, in that it is an oxidized form of the alkaloid, mappicine [64], and indeed it can be converted into the latter by $NaBH_4$ reduction of the ethyl ketone. A brief historical aside: The term “mappicine ketone” was apparently introduced by Kametani [65], who synthesized **36** in the course of investigations directed toward mappicine, and this more than 20 years before **36** was itself determined to be a natural product. In any event, nothapodytine exhibits interesting antiviral properties [66,67] and it has been the target of a number of total syntheses [68-74] and synthetic studies [75-79].

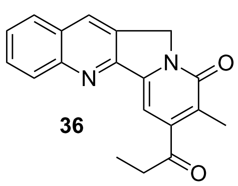
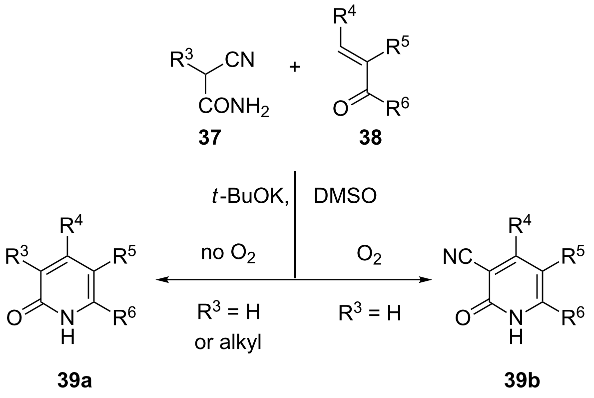


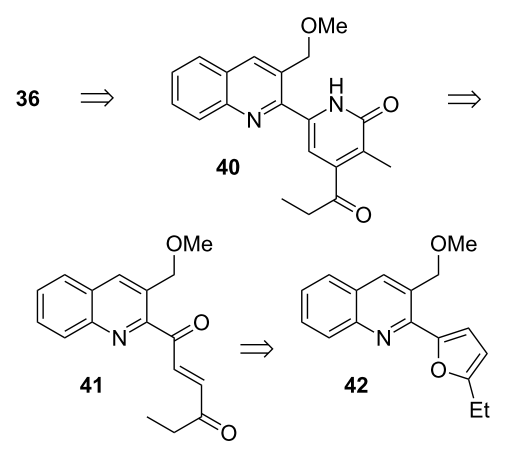
Figure 1: Structure of nothapodytine B.

The central problem we wished to address was the preparation of the 3-alkyl-2-pyridone moiety of **36** by an unusual [3 + 3] construction developed in our laboratory [80]. This chemistry (Scheme 7) promotes the condensation of a cyanoacetamide **37**, with an enone or enal **38**, in the presence of *t*-BuOK in DMSO. Under anoxic conditions, a series of events, culminating in the elimination of HCN from a presumed dianion intermediate, leads to the formation of pyridones **39a**, wherein R^3 may be H, alkyl, or aryl. Conduct of the reaction with plain cyanoacetamide (cf. **37**, R^3 = H) under an oxygen atmosphere produces cyanopyridones **39b** instead.



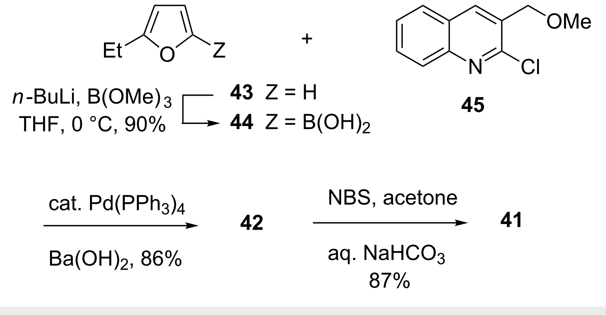
Scheme 7: A useful pyridone synthesis.

In keeping with a principle introduced during our work on camptothecin [81-83], the five-membered ring of **36** was imagined to result upon acid treatment of **40** (Scheme 8) [84], which in turn could be assembled by using the chemistry of Scheme 8 on substrate **41**, provided that the more electrophilic quinolyl ketone would direct an initial conjugate addition of the anion of a suitable cyanoacetamide to its own β-position. A particularly direct way to produce **41** seemed to be the oxidative cleavage of the furan ring in **42**, which thus became the first subgoal of our study. In that regard, we elected to prepare **42** by Suzuki coupling [85] between a furylboronic acid and a 2-chloroquinoline [86].



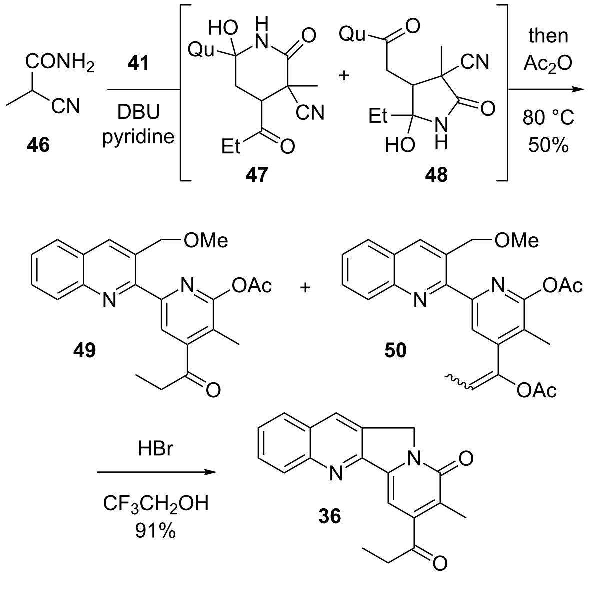
Scheme 8: Retrosynthetic logic for nothapodytine B.

The (relative) acidity of the C-2 position of furan is such that *n*-BuLi without added TMEDA suffices to induce lithiation. Accordingly, treatment of commercial 2-ethylfuran with *n*-BuLi in THF at 0 °C and cannulation of the resulting mixture into a solution of trimethyl borate in THF afforded boronic acid **44** (Scheme 9) in 90% yield after the customary aqueous workup [87]. This material underwent smooth Suzuki coupling with the known **45** [81-83], and the action of aqueous NBS [88] upon the resultant **42** delivered the requisite **41** in 87% yield.



Scheme 9: Preparation of a key nothapodytine fragment.

Happily, it transpired that the conjugate addition chemistry of **41** is indeed controlled exclusively by the quinolyl ketone. This enabled the conduct of our pyridone-forming sequence, which in the present case, however, had to be implemented in the slightly modified form seen in Scheme 10. Thus, Michael addition of 2-methyl cyanoacetamide converted **41** into a mixture of diastereomers of hemiamidals **47** and **48**. Attempts to force this mixture to advance to the desired pyridone under basic conditions yielded uniformly unsatisfactory results. This was due in part to undesired base-promoted reactions of the enolizable ketone segments, but also to the slow rate of interconversion of **47** and **48** (only the former can produce the desired pyridone). Experiment revealed that it was best to carry out the Michael step with DBU in pyridine, followed by addition of Ac_2O and warming to 80 °C for an extended period of time. Under these conditions, a mixture of 2-acetoxypyridines **49** and **50** was obtained. Both compounds were transformed into **36** [89] upon exposure to HBr in CF_3CH_2OH (Boger conditions [68,69]).



Scheme 10: Total synthesis of nothapodytine B.

Topopyrones B and D

Topopyrones A–D (Figure 2) were discovered during research aimed at identifying new topoisomerase inhibitors [90,91]. Initial evidence [90,91] suggested that these compounds may be selective inhibitors of topoisomerase-I (topo-I), a potentially significant finding. It should be noted that two topoisomerases are known, namely topo-I and topo-II. These nuclear enzymes relax superhelical tension in DNA during replication, transcription and repair. They operate by reversibly breaking one (topo-I) or both (topo-II) strands in double-stranded DNA and unwinding the severed strand(s), thereby relieving torsional energy. Inhibition of topoisomerases, which are overexpressed in cancerous cells, is fatal to the cell [92]. Subsequent studies revealed that topopyrones are in fact dual inhibitors of topo-I and topo-II [93]: A finding that diminished the biomedical relevance of the natural products. Regardless, the biological properties of topopyrones are sufficiently interesting that a number of groups embarked on a total synthesis [94-96].

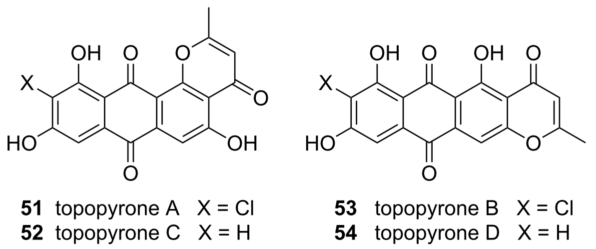
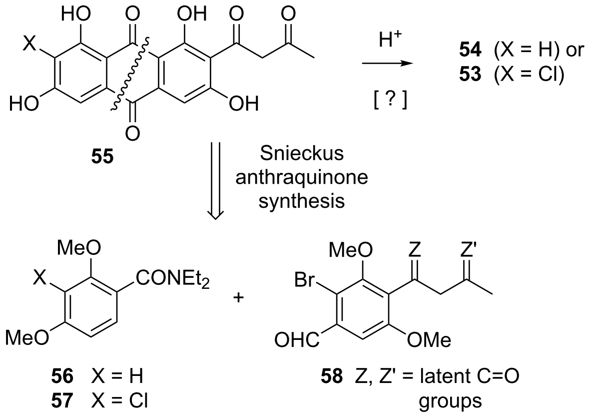


Figure 2: Structures of topopyrones.

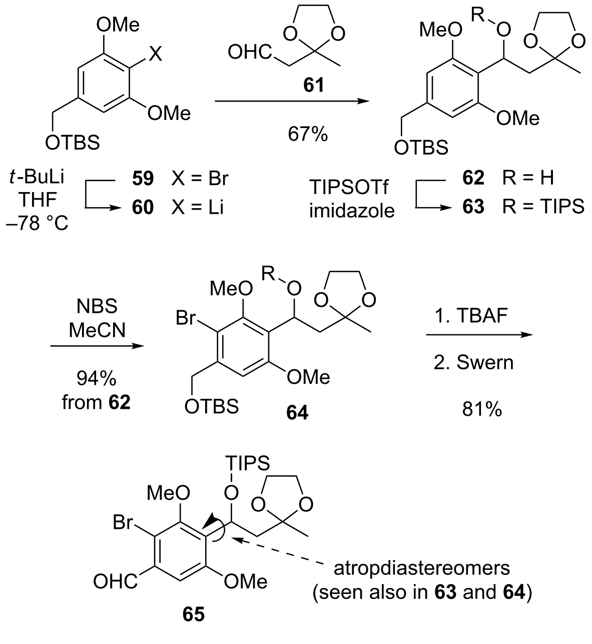
Our own involvement in this area was motivated by an interest in topoisomerase-I inhibitors, which are important antineoplastic resources [97], the archetype of which is camptothecin [81-83,98,99]. The objective of the present effort was to obtain the target molecules by any means, as rapidly as possible, and in a fashion that might enable the production of analogs for structure–activity relationship studies. By contrast, our work on fredericamycin and nothapodytine had chiefly reflected a desire to illustrate applications of the new methodology to the synthesis of interesting natural products.

The linearly fused topopyrones B and D are especially potent, and indeed, the activity of **53** against topo-I appears to be comparable to that of camptothecin [90,91,100,101]. Accordingly, our research centered on the linear series of compounds. A piece of information that was key to our retrosynthetic planning is that the action of alkali on **51** and **52** induces rearrangement to **53** and **54** [90,91], signifying that the linearly fused topopyrones are thermodynamically favored over their angular congeners. This implied that the cyclization of a precursor such as **55** under equilibrating conditions should selectively afford topopyrones B and D (Scheme 11). Drawing from the work of Snieckus [102,103], we further surmised that the assembly of **55** could be carried out in a single operation through the union of fragments **56** or **57** with aldehyde **58**: The carrier of a moiety that is common to all topopyrones.



Scheme 11: Retrosynthetic logic for the linear series of topopyrones.

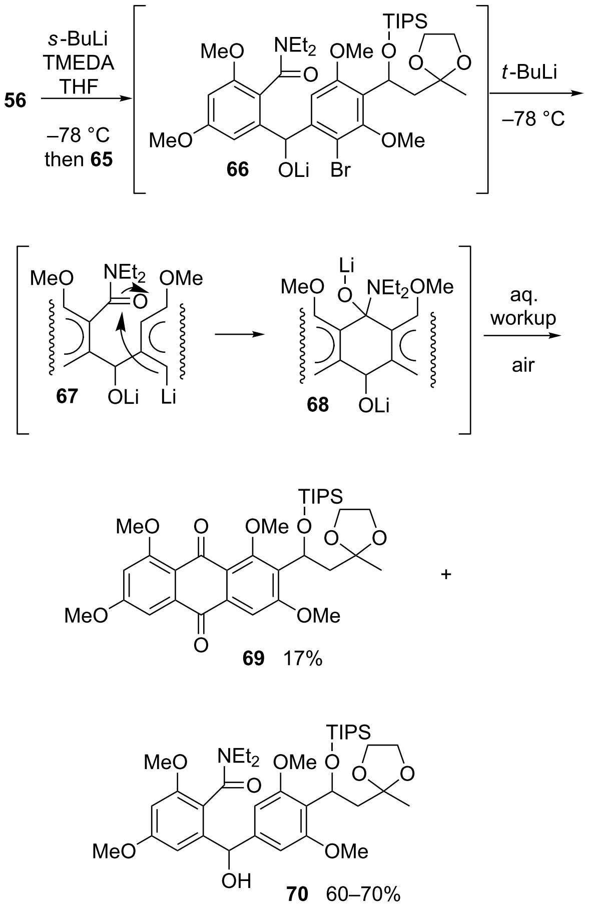
A serviceable form of **58** proved to be compound **65**, the preparation of which is outlined in Scheme 12. A key step in this sequence was the addition of the organolithium species **60**, obtained through halogen–metal exchange of **59** with *t*-BuLi, to aldehyde **61** [104], leading to alcohol **62** in 67% yield. Straightforward manipulations of **62** then furnished the requisite **65**.



Scheme 12: Construction of the molecular subunit common to all topopyrones.

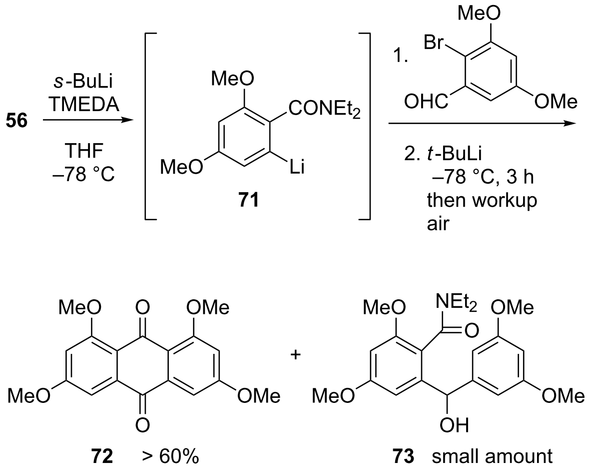
Interestingly, the ^{1}H and ^{13}C NMR spectra of all TIPS-protected compounds revealed that these substances exist as mixtures of atropdiastereomers. Furthermore, atropisomerism vanishes upon release of the TIPS unit (see below). An inspection of molecular models readily provides a qualitative illustration of this effect, in that the bulky TIPS group hampers rotation about the σ-bond connecting the benzylic carbon to the aryl segment (cf. arrows in **65**). An MM+ conformational study [105] of a simplified analog of **63** estimated an energy barrier for internal rotation equal to about 17 kcal/mol [106].

As seen in Scheme 13, DAF technology came into the picture at the stage of the union of aldehyde **65** with amide **56**. Thus, lithiation of benzamide **56** with *sec*-BuLi/TMEDA (1.05 equiv, 3 h, −78 °C) and addition of the resulting organolithium agent to **65** was presumed to form the alkoxide **66**. In situ treatment of **66** with *t*-BuLi induced bromine–lithium exchange and cyclization of organolithium species **67** to a product that was believed to be **68**. Aqueous workup arguably converted **68** into a dihydroanthraquinone, which upon exposure to the atmosphere was rapidly oxidized to the desired anthraquinone **69**. The yield of this material was a modest 17% after purification, the remaining balance of the initial mass of **65** being the debrominated material **70** (60–70%). The NMR spectra of both products indicated that they existed as slowly interconverting atropdiastereomers, too. Numerous experiments aimed at improving the yield of **69** led to no fruitful outcome, revealing instead that the ratio of the two products remained essentially constant (ca. 1:3.5–4) regardless of the length of time (from 3 to 12 h) over which the reaction mixture was allowed to evolve following the addition of *t*-BuLi to **66**.



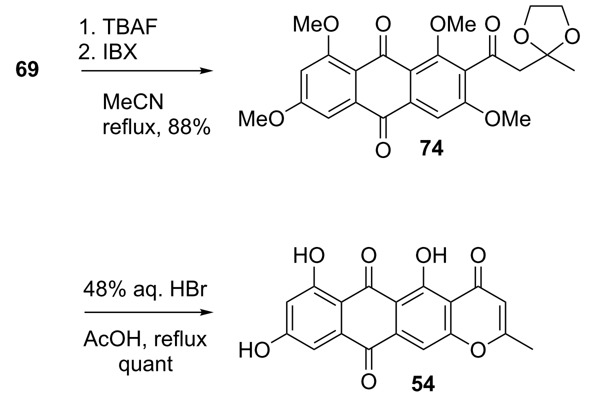
Scheme 13: Difficulties encountered during the merger of the topopyrone D moieties.

As a control experiment, we examined the preparation of the simpler anthraquinone **72** by the same method (Scheme 14). This exercise established that **72** formed considerably more efficiently than **69** (over 60% isolated yield), and that it was accompanied by only small amounts of the debrominated byproduct **73**. We thus concluded that the low yield of **68** must have been the consequence of the consumption of a portion of aryllithium species **67** through parasitic proton-transfer steps, probably involving one of its benzylic positions as the proton donor. While the yield of **69** could not be improved, its preparation in the fashion just described is highly convergent. Furthermore, an overall yield around 20% for a one-pot sequence that involves three major steps (addition of lithiated **56** to **65**, halogen–metal exchange, cyclization of aryllithium species **67**) corresponds to an average of 55–60% yield per step. In such a light, the modest yield seemed quite acceptable, and indeed, with **69** in hand, the synthesis of topopyrone D was completed quickly.



Scheme 14: Efficient synthesis of a simplified anthraquinone.

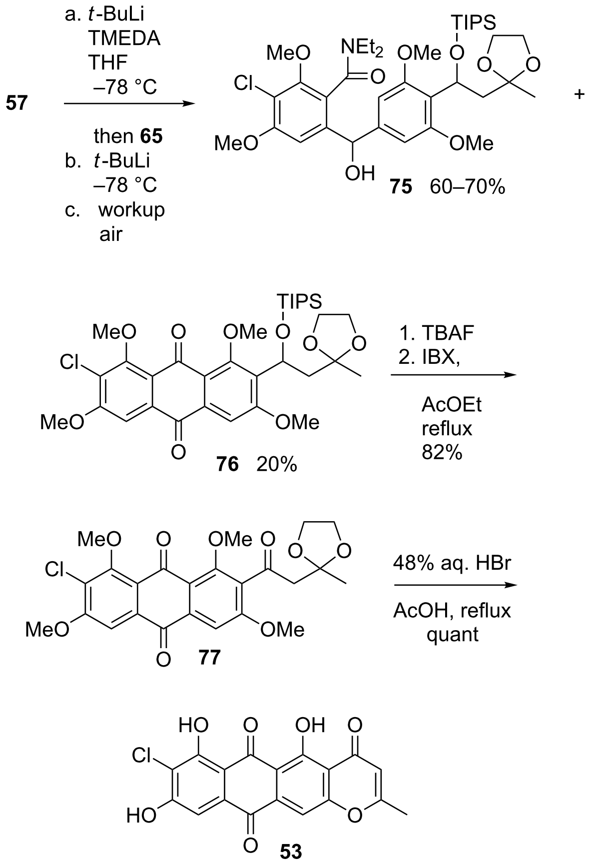
As shown in Scheme 15, desilylation of **69** (TBAF) furnished an alcohol that, contrary to the parent **69** or other TIPS-protected synthetic intermediates, exhibited no atropisomerism (single compound by ^{1}H and ^{13}C NMR). Oxidation (IBX) and treatment of the emerging ketone **74** with 48% aqueous HBr in AcOH under reflux afforded synthetic **54** in quantitative yield. No evidence for the formation of angular topopyrones could be garnered, reinforcing the notion that the linear series is the thermodynamically favored one. Substance **54** was fully characterized as such, as well as the considerably more soluble triacetyl derivative, as detailed in the isolation paper [90,91].



Scheme 15: Total synthesis of topopyrone D.

An unexpected problem materialized when the foregoing sequence was transposed to the case of topopyrone B, the synthesis of which required the execution of the same operations starting with benzamide **57**. Surprisingly, this material resisted deprotonation under Snieckus conditions. For instance, treatment with five equivalents (as opposed to the customary 1.05 equivalents) of *sec*-BuLi–TMEDA complex for a prolonged period of time resulted in no incorporation of deuterium upon quenching with CD_3OD. The reasons for this remain unknown to this date. Various chlorinated benzamides undergo *ortho*-deprotonation without difficulty [104], implying that the resistance of **57** cannot be attributed to the chloro substituent per se. Nor can the problem be ascribed to sequestration of the base through coordination/chelation [33] effects involving the chlorine atom. Such a hypothesis fails to account for the fact that **57** resisted deprotonation even in the presence of excess base. Moreover, 2,3,4-trimethoxybenzamide, a congener of **57** in which an OMe group replaces the Cl substituent, undergoes *ortho*-metallation without incident [107], even though the triad of adjacent OMe groups can surely sequester organo–Li species at least as effectively as the 2,4-dimethoxy-3-chloro arrangement present in **57**.

In any event, *ortho*-deprotonation was ultimately achieved by the reaction of **57** with the more basic *t*-BuLi–TMEDA complex (1 equiv, 3 h, –78 °C; complete deuterium incorporation upon CD_3OD quench). Accordingly, the organolithium species thus generated was processed as detailed earlier in Scheme 14, leading to a mixture of the desired anthraquinone **76**, obtained in 20% yield after chromatography, along with desbromo product **75**, again isolated in 60–70% yield (Scheme 16). The chemistry leading to **76** thus performed just as efficiently (inefficiently?) as before. The elaboration of **77** to the poorly soluble topopyrone B proceeded uneventfully, and in accordance with the isolation paper [90,91]; the ultimate **53** was most readily characterized as the trimethyl ether [108].



Scheme 16: Total synthesis of topopyrone B.

Conclusion

The work summarized in this review exemplifies, hopefully in a convincing fashion, the value of directed aromatic functionalization in the preparation of complex aromatic systems. Indeed, it is difficult today to imagine an efficient route to natural products such as fredericamycin, nothapoditine, and topopyrones that eschews DAF technology altogether. More importantly, the chemistry described herein is a testimony to the far-sightedness of the pioneers in the field of directed aromatic functionalization. These giants have provided the chemical community with immensely powerful tools that have truly revolutionized the business of producing elaborate aromatic compounds, both in the academic laboratory and in the industrial plant, and that continue to produce countless benefits to society in the form of new medicines and new materials.

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Asymmetric synthesis of quaternary aryl amino acid derivatives via a three-component aryne coupling reaction

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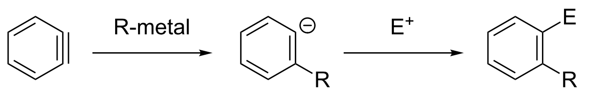
Guest Editor: V. Snieckus

Abstract

A method was developed for the synthesis of α-alkyl, α-aryl-bislactim ethers in good to excellent yields and high diastereoselectivities, consisting of a facile one-pot procedure in which the aryl group is introduced by means of a nucleophilic addition to benzyne and the alkyl group by alkylation of a resultant benzylic anion. Hydrolysis of the sterically less hindered adducts gave the corresponding quaternary amino acids with no racemization, whereas hydrolytic ring opening gave the corresponding valine dipeptides from bulkier bislactims.

Introduction

Arynes are exceptionally versatile reactive intermediates in organic synthesis. Not only are they able to participate in cycloaddition reactions, they also readily undergo addition reactions with nucleophiles, and the resultant aryl anions may be protonated or undergo alternative transformations [1-6]. We are particularly interested in the use of arynes in multicomponent coupling reactions, in which the resultant aryl carbanion following nucleophilic attack is allowed to react with a further electrophile, providing *ortho*-disubstituted, functionalized aromatic products in a one-pot procedure [7-9]. In particular, we have focused on the addition of carbon-based nucleophiles in such systems (Scheme 1) and have applied this methodology to the syntheses of natural products ent-clavilactone B and dehydroaltenuene B [10,11].



Scheme 1: 3-Component coupling reactions of arynes. E^+ = electrophile.

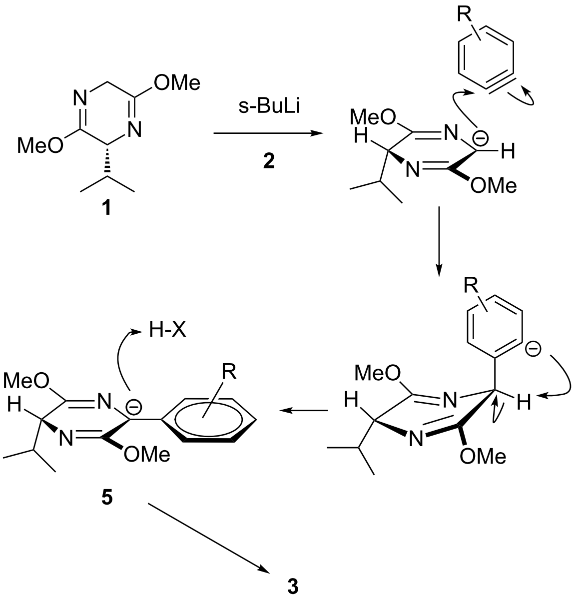
Recently, we reported the diastereoselective addition of Schöllkopf's bislactim ether **1** [12] to substituted arynes **2**, which, following hydrolysis of the *syn*-adducts **3**, provided α-aryl amino acids **4** with moderate to high enantioselectivities (Scheme 2) [13].

The arynes were produced by a directed *ortho*-metallation [14] and an elimination sequence, and after attack of **1** the ensuing carbanion **5** was not aryl as expected but instead benzylic, due to an inter- or intramolecular proton transfer. Kinetic protonation of this anion on the face opposite to the isopropyl group accounted for the observed diastereoselectivity of the reaction (Scheme 3).

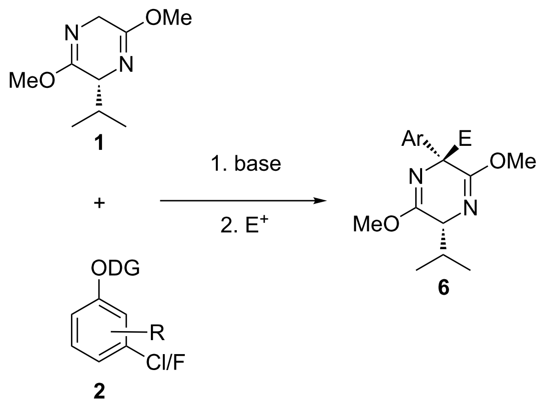
To extend this methodology to a multicomponent system, we considered that quenching the key aza-enolate intermediate with an electrophile, rather than a proton source, should provide quaternary Schöllkopf adducts **6** (Scheme 4).

The potential utility of chiral α-quaternary α-aryl amino acids in medicinal chemistry is diverse. Incorporation of such units into peptidomimetics, not only affects lipophilicity, but also the secondary structure and hence the conformational rigidity, which can increase the resistance to enzymatic degradation [15-19]. Such units are also found in biologically interesting natural products, such as the antibacterial fumimycin [20].

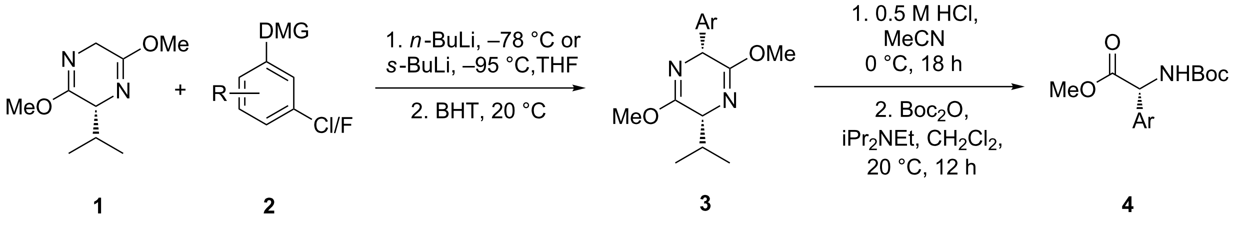
Herein, we describe our endeavours towards the synthesis of such valuable compounds by utilizing the multicomponent aryne reaction.



Scheme 3: Proposed mechanism of α-arylation.



Scheme 4: Proposed extension of the methodology to synthesize quaternary adducts.

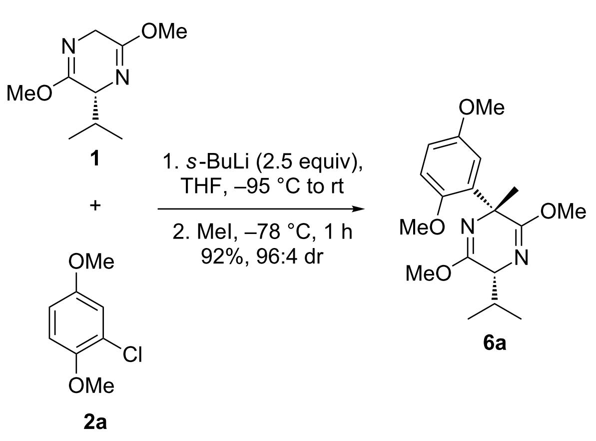


Scheme 2: Aryne mediated α-arylation of amino acids. DMG = directed metallation group. BHT = 2,6-di-*tert*-butyl-4-methylphenol.

Results and Discussion

Formation of quaternary Schöllkopf adducts

The same procedure was carried out as for the α-arylation reactions: The benzyne precursor **2a** and Schöllkopf's bislactim ether **1** were allowed to react with 2.5 equivalents of *sec*-butyllithium at –95 °C to carry out the required *ortho*-lithiation for benzyne formation from **2a** and the deprotonation of bislactim **1**. During warming to room temperature, fragmentation to dimethoxybenzyne occurred and nucleophilic attack of the Schöllkopf auxiliary took place. Addition of four equivalents of iodomethane at this temperature and stirring for 1 h gave the desired quaternary species **6a** in 88% yield with a dr of 85:15. Lowering the quench temperature to –78 °C increased both the yield and the dr to 92% and 96:4, respectively (Scheme 5).



Scheme 5: Formation of α-methyl, α-aryl Schöllkopf adduct.

The major diastereoisomer was confirmed to have the isopropyl and aryl moieties *syn*, by ^{1}H NMR NOESY analysis; a clear NOESY correlation was observed between the methyl group and the proton at C-3 (Figure 1).

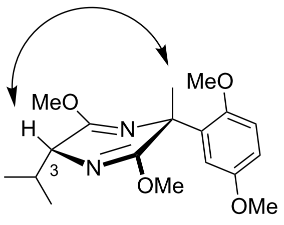


Figure 1: NOESY correlation observed for **6a**.

The scope of the reaction was then examined to determine which electrophiles could be introduced at C-6 (Table 1).

Alkylations employing benzyl bromide, allyl bromide and propargyl bromide (Table 1, entries 2, 3 and 5) proceeded smoothly, furnishing the desired products **6b**, **6c** and **6e** in excellent yields and high diastereoselectivity. Interestingly, adduct **6b** displays a large upfield shift (around 2 ppm) at the C-3 proton compared to other analogues. This indicates that the product has adopted an "aryl-inside" conformation in which the C-3 proton is situated in the shielding cone of the aromatic ring [21]. A single-crystal X-ray crystallographic analysis confirmed the presence of this conformation, at least in the crystal lattice (Figure 2).

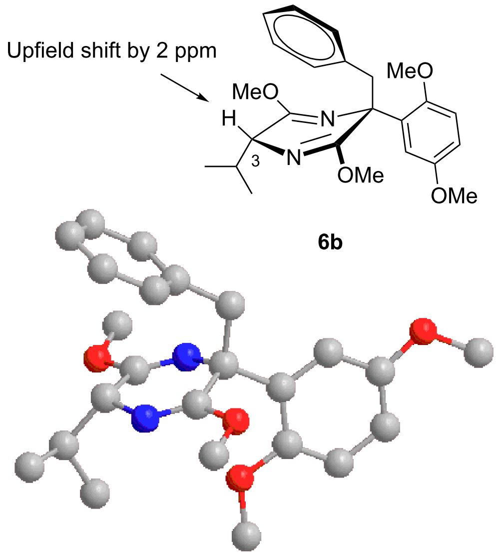
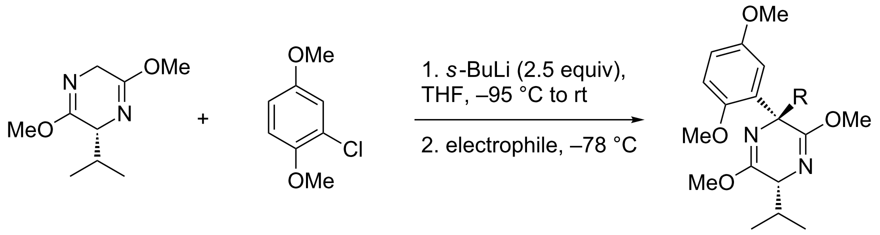


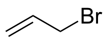
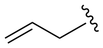
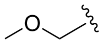
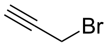
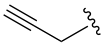
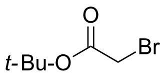
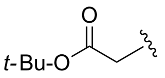
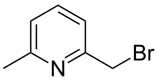
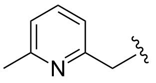
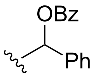
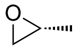
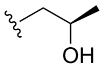
Figure 2: X-ray crystal structure of **6b**.

Further alkylations with methyl chloromethyl ether, *tert*-butyl bromoacetate and 2-(bromomethyl)-6-methylpyridine (Table 1, entries 4, 6 and 8) provided adducts **6d**, **6f** and **6h** respectively, also with high diastereoselectivity, but in more modest yields. Acylation with acetyl chloride (Table 1, entry 7) afforded ketone **6g** in 59% yield, with a lower dr of 89:11, most likely due to the less sterically hindered nature of this electrophile. Replacing acetyl chloride with its corresponding Weinreb amide gave none of the required product. An aldol type reaction with benzaldehyde (Table 1, entry 9) afforded alcohol **6i** in good yield, with complete diastereoselectivity at C-6, but no selectivity at the alcohol stereocenter (1:1). Examination of the two possible Zimmerman–Traxler type transition states for such reactions (Figure 3), as proposed by Schöllkopf [22], reveals that **TS$^{\neq}$ A**, with the phenyl group axial, is consistent with there being an unfavourable 1,3-diaxial interaction with the methoxy group. However, there is an equally unfavourable interaction in **TS$^{\neq}$ B** where the phenyl group occupies the equatorial position, as there is now a 1,2-gauche interaction with the bulky

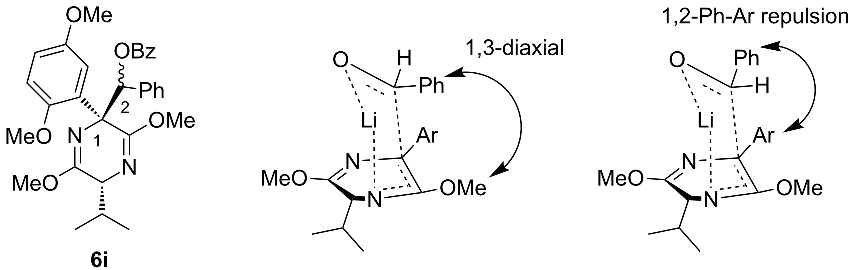
Table 1: Formation of quaternary Schöllkopf adducts employing a range of electrophiles.



1 **2a** **6a–j**

Entry[a]	Electrophile	R	Time (h)[b]	Product	Yield (%)[c]	dr[d]
1	MeI	Me	1	**6a**	92	96:4
2	BnBr	Bn	6	**6b**	88	>98:2
3			1	**6c**	85	>98:2
4	MOMCl		1	**6d**	53	95:5
5			1	**6e**	80	>98:2
6			3	**6f**	51	>98:2
7	AcCl	COMe	6	**6g**	59	89:11
8			5	**6h**	71	>98:2
9	PhCHO		12	**6i**[e]	69	>98:2[f]
10	 $BF_3{\cdot}OEt_2$		1	**6j**	50	>98:2

[a] Reactions were carried out on a 1 mmol scale in THF (0.2 M) with 1.5 equiv of halide **2a** and 2.75 equiv *s*-BuLi at –95 °C, followed by warming to room temperature over 18 h, recooling to –78 °C, and the addition of 4 equiv of electrophile. [b] Reactions were monitored by GC–MS. [c] Isolated yield. [d] Determined by ^1H NMR integration. [e] **6i** was isolated as its benzoyl ester, due to retro-aldol reactions occurring when the free alcohol was subjected to flash-column chromatography. [f] The adduct **6i** was obtained as a mixture of epimeric benzylic alcohols (1:1).



6i

1: dr >98:2
2: dr 50:50

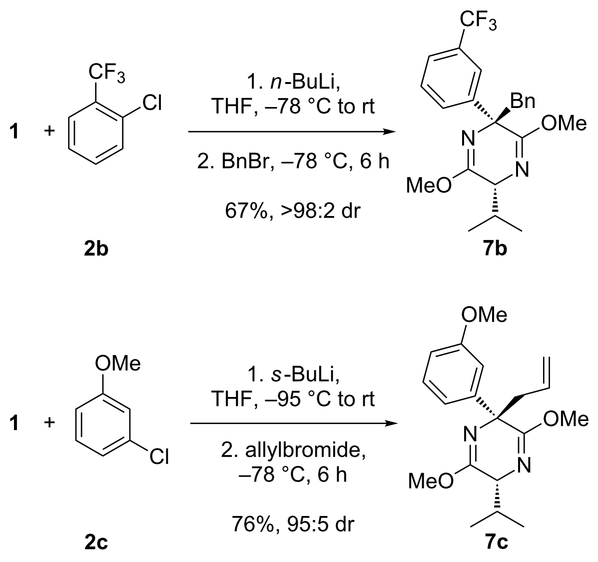
TS≠ A **TS≠ B**

Figure 3: Transition state analysis to explain the lack of diastereoselectivity at C-2.

di-methoxyaryl group adjacent to it. We consider that neither of these transition states is lower in energy, which would be consistent with the lack of diastereoselectivity.

Finally, the addition of (*R*)-propylene oxide as the electrophile in the presence of boron trifluoride etherate (Table 1, entry 10) gave alcohol **6j**. When (*S*)-propylene oxide was used instead there was no reaction, and indeed Schöllkopf noted significant levels of kinetic resolution when such reactions were performed with racemic oxiranes [23].

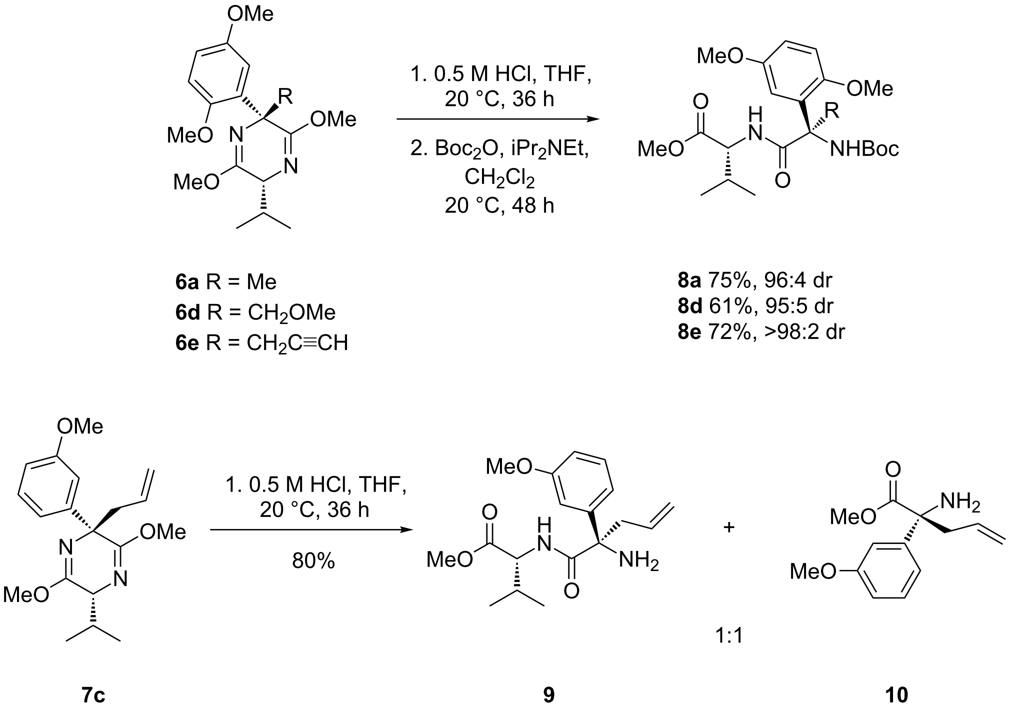
In our previous publication, we demonstrated the scope of the methodology over a range of *ortho*-lithiation benzyne precursors. To establish that any one of these precursors could be used to form quaternary adducts, we subjected the benzylation conditions to precursor **2b** and the allylation conditions to precursor **2c**, affording adducts **7b** and **7c**, respectively, again in good yields and dr's and with complete regioselectivity for these asymmetric benzynes (Scheme 6).



Scheme 6: Formation of quaternary adducts.

Hydrolysis of quaternary adducts

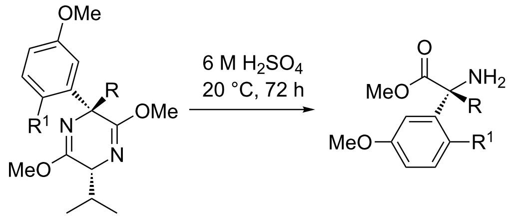
The next task to be undertaken was the hydrolysis of the sterically restricted quaternary bislactim ethers. A selection of the relatively less bulky products, **6a**, **6d** and **6e**, was subjected to standard, mild hydrolysis conditions, employing 0.5 M HCl in THF at room temperature [12], affording the desired quaternary methyl esters as their corresponding dipeptides, **8a**, **8d** and **8e**, in good yields (Scheme 7). The less shielded imidate group underwent complete hydrolysis, but the imidate functional group α to the quaternary center experienced incomplete cleavage to the peptide bond, a trend which is common in the literature for quaternary adducts [21,24-26]. Subjecting



Scheme 7: Hydrolysis of quaternary adducts.

analogue **7c**, with just one methoxy group on the aromatic ring, to the same conditions yielded the dipeptide **9** and the desired methyl ester **10** in a 1:1 ratio (Scheme 7).

Screening of various acidic hydrolysis reaction conditions in these systems led to the observation that when either **6a** or **7c** was stirred in neat 6 M sulfuric acid for three days, the required constituent amino acid **11** or **10** was isolated in reasonable yields (Scheme 8). Chiral HPLC analysis confirmed the expected high enantioselectivity of these esters.



6a R = Me, R^1 = OMe
7c R = $CH_2CH{=}CH_2$, R^1 = H

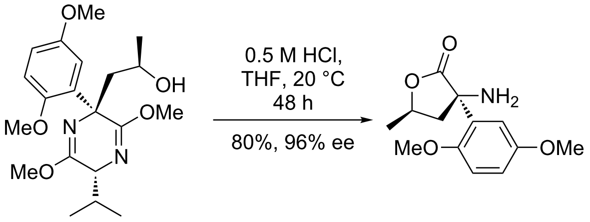
11 R = Me, R^1 = OMe, 56%, 90% ee
10 R = $CH_2CH{=}CH_2$, R^1 = H, 58%, 90% ee

Scheme 8: Hydrolysis to amino acids.

These results are promising, as they demonstrate that if the aryl group is derived from a less sterically hindered benzyne precursor, hydrolysis is more facile, as was observed by Lee [27] for unsubstituted aryl, quaternary bislactim ethers. Using high concentrations of acids with more-nucleophilic conjugate bases resulted in the predominate formation of diketopiperazines, and low concentrations of all of the acids tested gave the dipeptide as the major product for all analogues with two methoxy groups (**6a**–**6i**).

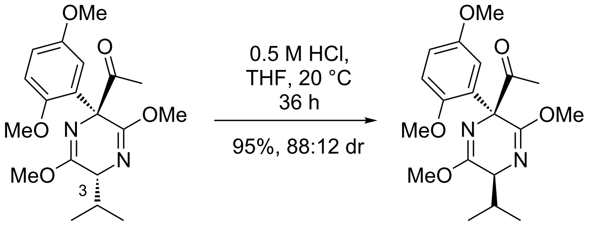
The only example where the use of low concentrations of acid coupled with a dimethoxy aryl group resulted in the principal formation of the desired ester was in the case of alcohol **6j**. Mild acidic hydrolysis with 0.5 M HCl gave lactone **12** in 80% yield and 96% ee (Scheme 9). The ability of the alcohol to undergo lactonization under the reaction conditions clearly aided the hydrolysis of this more sterically hindered imidate.

We assumed that ketone **6g** would also undergo hydrolysis due to its nonbulky nature. However, upon exposure to 0.5 M HCl, epimerization of the isopropyl group at C-3 occurs in near quantitative yield, giving adduct **13** (Scheme 10). The electron-withdrawing effect of the carbonyl moiety must increase the acidity of the C-3 proton to such an extent that the acidic media simply epimerizes at this center to afford the more thermodynamically stable *anti*-adduct.



6j **12**

Scheme 9: Hydrolysis of analogue **6j**.



6g **13**

Scheme 10: Epimerization at C-3 of **6g**.

Conclusion

The extension of the aryne α-arylation methodology allowed for the synthesis of quaternary aryl bislactim ethers in good to excellent yields and high diastereoselectivity by means of a three-component coupling reaction in which the reaction of an electrophile with the intermediate benzylic anion gave a range of C–alkyl and hydroxyalkyl derivatives. Hydrolysis of these quaternary adducts gave the constituent amino acid methyl esters in high enantioselectivity for less substituted compounds. Adducts with two methyl ethers on the aryl unit underwent hydrolysis to the corresponding valine dipeptides.

Supporting Information

Supporting Information File 1

Detailed experimental procedures and analytical data for compounds **6a**–**j**, **7b**–**c**, **8a**, **8d**, **8e** and **9**–**13**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-185-S1.pdf]

Supporting Information File 2

NMR spectral data for compounds **6a**–**j** and **7b**–**c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-185-S2.pdf]

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   See this reference and [8,9] for examples of 3-component coupling reactions of arynes.
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Recent advances in direct C–H arylation: Methodology, selectivity and mechanism in oxazole series

Cécile Verrier, Pierrik Lassalas, Laure Théveau, Guy Quéguiner,
François Trécourt, Francis Marsais and Christophe Hoarau*§

Review

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Keywords:
ate complex; catalytic direct arylation; mechanism; oxazole;
selectivity; transition-metal catalysis

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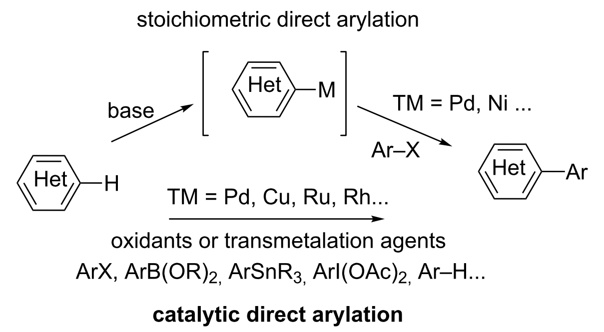
Abstract

Catalytic direct (hetero)arylation of (hetero)arenes is an attractive alternative to traditional Kumada, Stille, Negishi and Suzuki–Miyaura cross-coupling reactions, notably as it avoids the prior preparation and isolation of (hetero)arylmetals. Developments of this methodology in the oxazole series are reviewed in this article. Methodologies, selectivity, mechanism and future aspects are presented.

Introduction

Deprotonative metalation of aromatics is widely used as a powerful method for regioselective functionalization. Ortholithiation by means of alkyllithium and lithium amides bases has been extensively developed as lithiated species display a high reactivity towards many electrophiles, leading to various substitutions (e.g., halogenation, carboxylation, acylation, hydroxymethylation, aminomethylation, sulfuration, oxygenation). However, aryllithiums can rarely be directly involved in transition-metal-catalyzed cross-coupling reactions and are usually transformed into organometallic fragments suitable for efficient Negishi, Stille, Suzuki–Miyaura, and Hiyama cross-coupling reactions [1,2]. Over the past decade, alternatives for more expeditive, practical and chemoselective arylating technics have arisen, thanks mainly to the great development of novel, stoichiometric and catalytic, direct arylation methodologies (Scheme 1).



Scheme 1: Stoichiometric and catalytic direct (hetero)arylation of arenes.

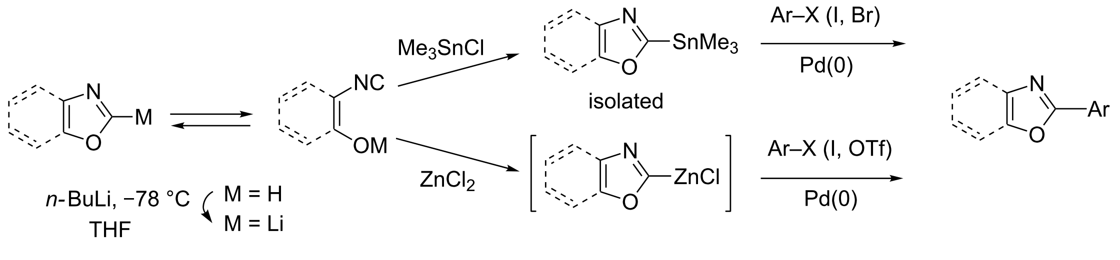
Thus novel classes of metallating agents resulting from various combinations of organometallic compounds with alkali, including various ate complexes, have been designed, such as zincates ($R_2Zn(TMP)Li\cdot TMEDA$) [3,4] ($(TMP)_2Zn\cdot 2MgCl_2\cdot 2LiCl$) [5], magnesates ($(TMP)_3MgLi$, $Bu_2(TMP)MgLi$, $Bu(TMP)_2MgLi$, $(TMP)_4MgLi_2$) [3,6], aluminates ($iBu_3Al(TMP)Li$, $Al(TMP)_3\cdot 3LiCl$) [3,7], manganate ($(Me_3SiCH_2)_2Mn(TMP)Li\cdot TMEDA$) [3,8], cuprates ($MeCu(TMP)(CN)Li_2$, $(TMP)_2CuLi$) [9,10] and cadmium amides ($(TMP)_3CdLi$) [11,12], for regio- and/or chemoselective deprotonative metalation of aromatics, producing arylmetal intermediates under smooth reaction conditions that are directly suitable for electrophilic reactions as well as transition-metal-catalyzed cross-coupling reactions. By contrast, the methodology for transition-metal-catalyzed direct arylation [13-18] is based upon the use of various catalytic metalation processes, such as electrophilic metalation, oxidative addition, halogen- or base-assisted metalation–deprotonation, and carbometalation [19-22] combined with diverse functionalizing agents, such as alkenes and alkynes [23], oxidants [24], nucleophiles, organometallics and arenes [25,26] (Scheme 1). In this review we focus on recent developments in catalytic, direct (hetero)arylation of (benz)oxazoles for the preparation of (hetero)aryl(benz)oxazoles, which are common structural units of numerous natural products and are also employed in pharmaceuticals and materials [27].

Review

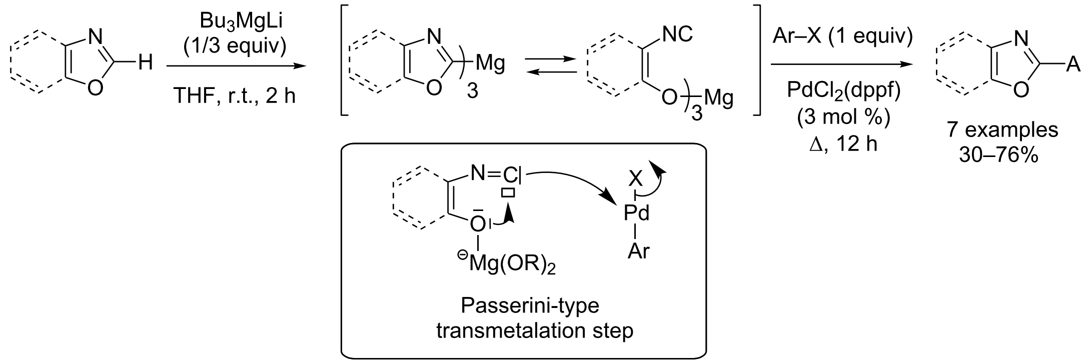
Stoichiometric direct (hetero)arylation of (benz)oxazoles

Dondoni first explored the reactivity of the 2-lithio-oxazoles resulting from the ready deprotonation, with *n*-BuLi at low temperature, of the most acidic C2-proton (pK_a = 20–22 was suggested), which is complicated by the coexistence of a ring-open isonitrile tautomer. In particular, the treatment by trimethylstannylchloride favours the formation of the 2-stannyl-oxazole, which is isolated as the major product and then successfully engaged in Stille cross-coupling reactions with various (hetero)aryliodides and bromides [28-30]. The subsequent transmetalation reaction following lithiation with zinc dichloride also favours the ring-close oxazole, a trend that is evidenced by ^{1}H NMR spectroscopy and attributed to the strong covalent carbon–zinc bond along with the zinc's low oxophilicity, and this thus allows subsequent palladium-catalyzed Negishi cross-coupling [31-33]. This first, highly efficient, stoichiometric direct arylation of oxazole was further improved for scale-up (Scheme 2) [34].

The C2-magnesation of oxazole was first performed with lithium tributylmagnesate at room temperature, and rapid evolution of the C2-magnesated oxazole to a ring-open isonitrile tautomer was evidenced by ^{1}H NMR spectroscopy analysis [35]. Nevertheless, subsequent cross-coupling reactions under palladium catalysis were successfully achieved. Similarly to the Passerini reaction, it was hypothesized that the crucial transmetalation step proceeds throught a nucleophilic displacement of the halogen from the σ-arylpalladium complex by the isonitrile function, leading to the ring-close aryloxazol-2-yl palladium complex delivering products after a final reductive elimination step (Scheme 3).



Scheme 2: Stille and Negishi cross-coupling methodologies in oxazole series [28,30,31,33,34].

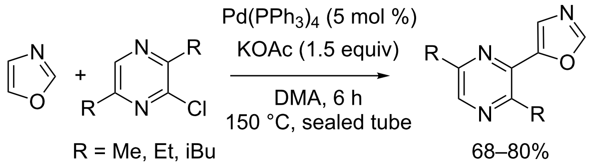


Scheme 3: Stoichiometric direct (hetero)arylation of (benz)oxazole with magnesate bases [35].

Catalytic direct (hetero)arylation of (benz)oxazoles

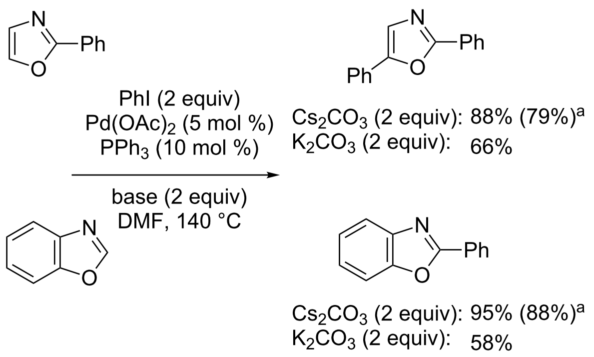
Palladium- and/or copper-catalyzed direct (hetero)arylation with halides: Synthetic methodology

The first examples of direct C–H heteroarylation of various azoles were reported by Ohta, including the direct C5-selective pyrazinylation of oxazole with chloropyrazines in the presence of $Pd(PPh_3)_4$ as catalyst and potassium acetate base (Scheme 4) [36,37].

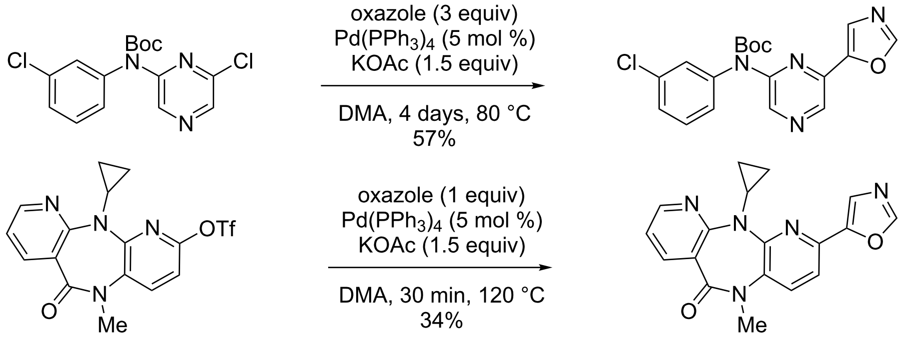


Scheme 4: Ohta's pioneering catalytic direct C5-selective pyrazinylation of oxazole [36,37].

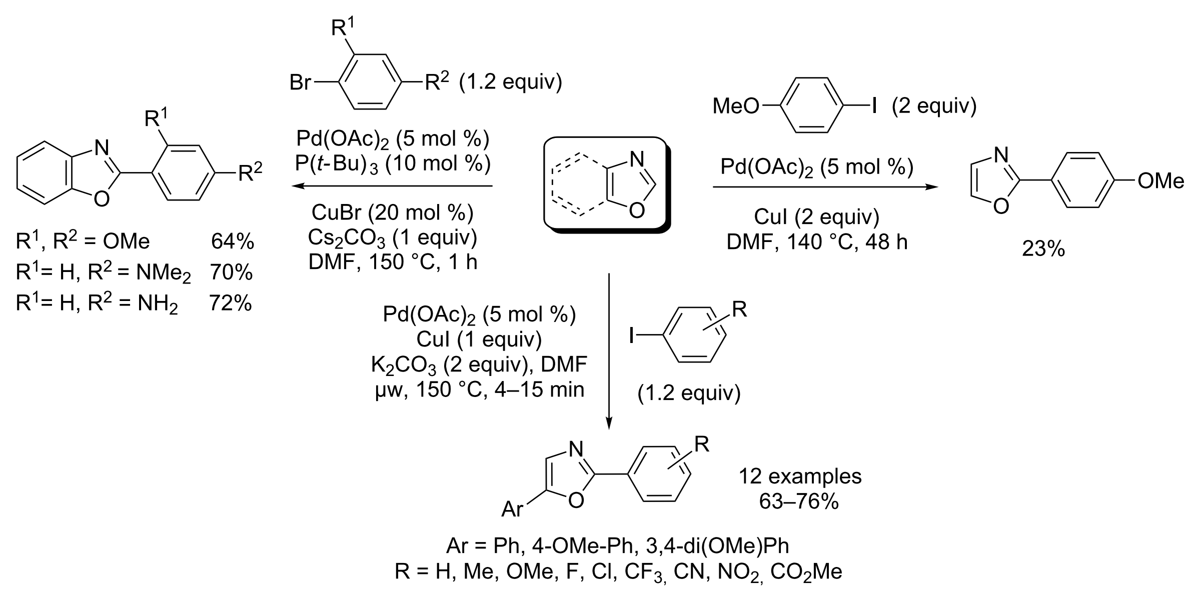
This protocol was successfully applied to the preparation of two potential inhibitors of vascular endothelial growth factor receptor-2 (Scheme 5) [38,39]. In 1998, Miura reported the first study of Pd(0)-catalyzed direct arylation of imidazoles, oxazoles and thiazoles with iodo- and bromobenzene [40]. It was notably shown that the use of the strong caesium carbonate base led to better results, which was attributed to a better solubility of the base along with a lower solubility of the generated CsI compared to KI salts, preventing an iodide-inhibition effect (Scheme 6). Moreover, copper iodide used as a cocatalyst was able to improve the reactivity at the C2 position significantly. Tamagnan further reported the first example of Pd(0)/Cu(I)-catalyzed direct arylation of benzoxazole (Scheme 7) [41].



Scheme 6: Miura's pioneering catalytic direct arylations of (benz)oxazoles [40]. [a]Isolated yield.



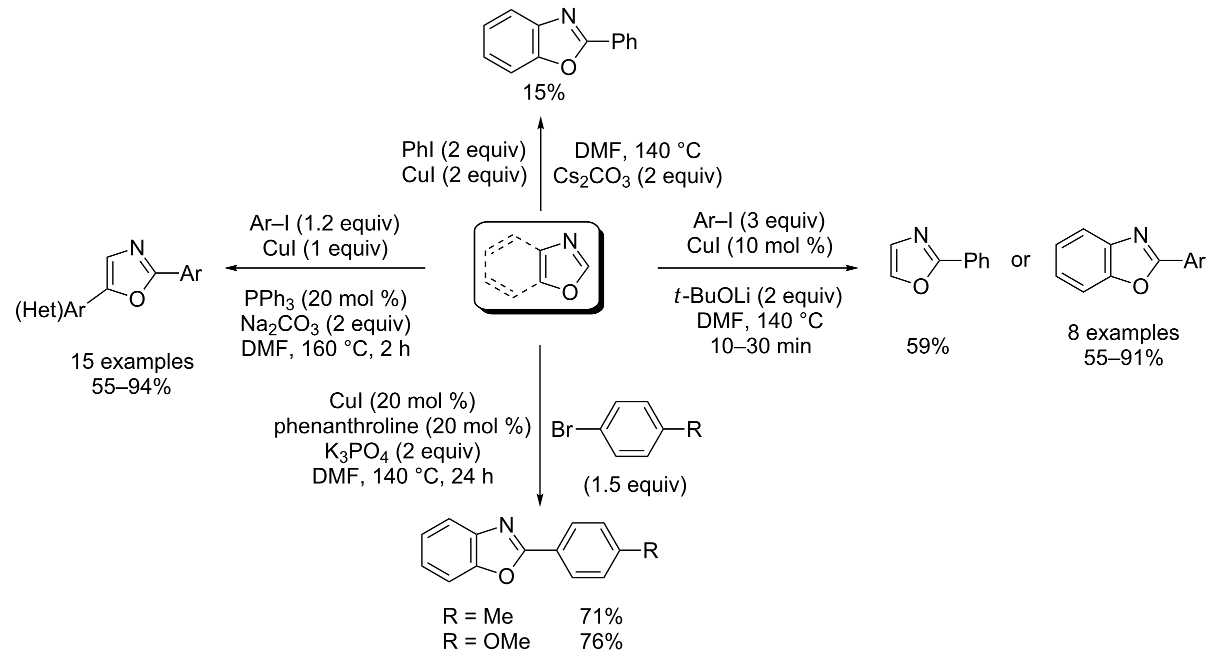
Scheme 5: Preparation of pharmaceutical compounds by following the pioneering Ohta protocol [38,39].



Scheme 7: Pd(0)- and Cu(I)-catalyzed direct C2-selective arylation of (benz)oxazoles [41-44].

Interestingly, Bellina and Rossi reported the Pd(0)/Cu(I)-catalyzed direct arylation of indoles, imidazoles, oxazoles and thiazoles with aryliodides under base-free and ligandless conditions in DMF as solvent [42,43]. However under the developed conditions, the direct coupling of oxazole proved to be inefficient (Scheme 7). More recently, Piguel disclosed an original, ligandless, microwave-assisted, Pd(0)/Cu(I)-catalyzed protocol, which was highly effective in the direct arylation of oxazoles with various arylbromides (Scheme 7) [44].

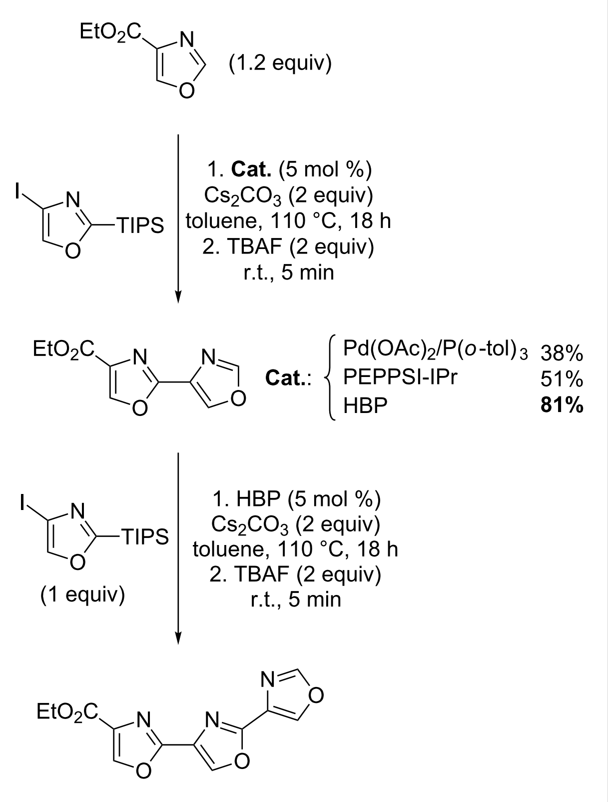
In his initial study, Miura observed a substantial amount of C2-arylation of azoles, including benzoxazole, using Cu(I) alone as catalyst (Scheme 8) [40]. In 2007, this methodology was judiciously extended by Daugulis who reported a first



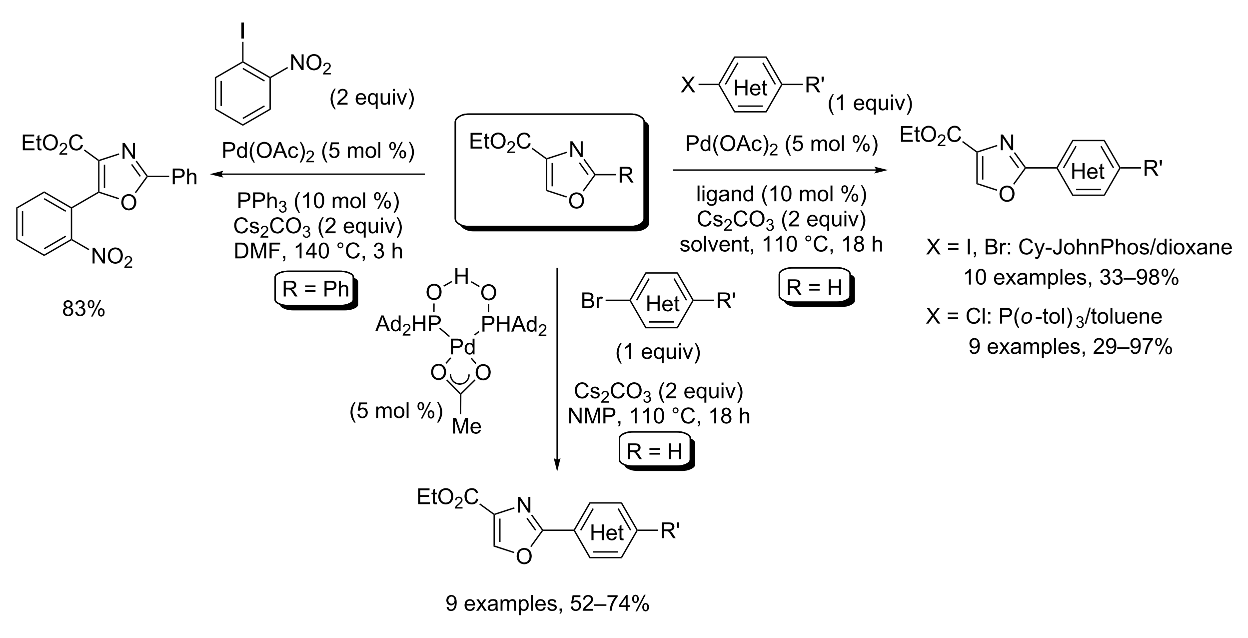
Scheme 8: Cu(I)-catalyzed direct C2-selective arylations of (benz)oxazoles [40,45-47].

general methodology for the Cu(I)-catalyzed direct arylation of heterocycles by using aryl iodides electrophiles and based upon the use of lithium *tert*-butoxide as a strong base [45]. In particular, monoarylation of oxazole occurred selectively at the C2 position in 59% yield (Scheme 8). Miura subsequently disclosed the Cu(I)-catalyzed direct arylation of 5-arylated oxazoles with aryl iodides by employing triphenylphosphine ligand and sodium carbonate base (Scheme 8) [46]. Recently, You et al. reported convenient conditions for Cu(I)-catalyzed direct arylation of heterocycles, including electron-rich azoles with aryl bromides, by using potassium phosphate as a base and phenanthroline as a ligand (Scheme 8) [47].

Over the past few decades, it has also been demonstrated that copper catalysis is not required in order to attain good yield and selectivity in Pd(0)-catalyzed direct C–H coupling of azoles, with the main advantage being the possibility to use of a number of Pd salt–ligand combinations to ensure an oxidative addition step and selectivity. Thus, following Miura's catalysis protocol, Hodgetts used the initial ligand to achieve direct C5-arylation of ethyl 2-phenyl-oxazole-4-carboxylate (Scheme 9) [48]. Hoarau selected Cy-JohnPhos and P(*o*-tol)$_3$ electron-rich ligands for the direct, C2-selective arylation of ethyl oxazole-4-carboxylate with iodides, bromides and chlorides (Scheme 9) [49,50]. Greaney and Ackermann further revealed the high performance of the Herrmann–Beller precatalyst (HBP) as well as the (1-Ad)$_2$P(O)H/Pd(OAc)$_2$ combination for the direct coupling of ethyl oxazole-4-carboxylate, with iodides and bromides, respectively (Scheme 9) [51,52]. Greaney's methodology was remarkably applied to the preparation of bis- and trisoxazoles units that occur in natural products (Scheme 10).

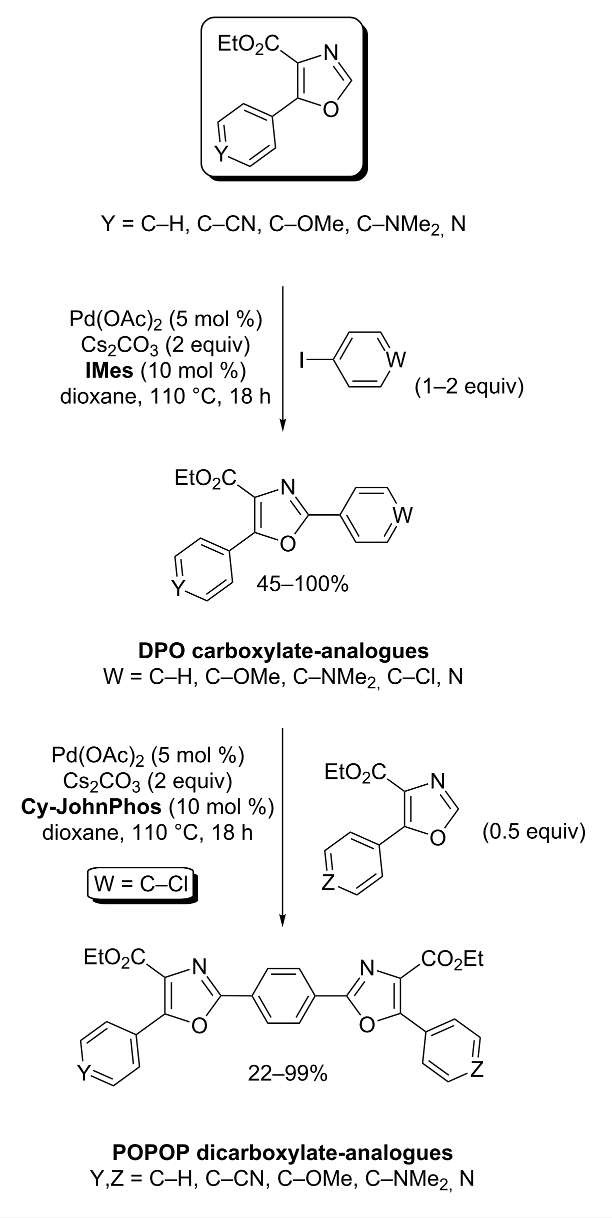


Scheme 10: Iterative synthesis of bis- and trioxazoles [51].



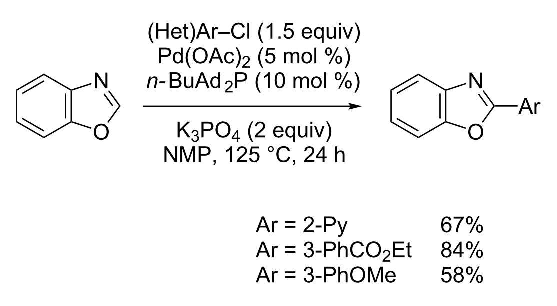
Scheme 9: Copper-free Pd(0)-catalyzed direct C5- and C2-selective arylation of oxazole-4-carboxylate esters [48-50,52].

As an example of application in materials, Hoarau recently reported a novel, sequential, palladium-catalyzed, direct arylation of ethyl oxazole-4-carboxylate, giving a rapid access to DPO and POPOP (di)carboxylate analogues (Scheme 11). Two novel sensors were identified with a two- and three-fold Stokes shift as compared to their DPO (diphenyloxazole) and POPOP (phenyloxazolephenyloxazolephenyl) references, and with high quantum yields (Scheme 11) [53].



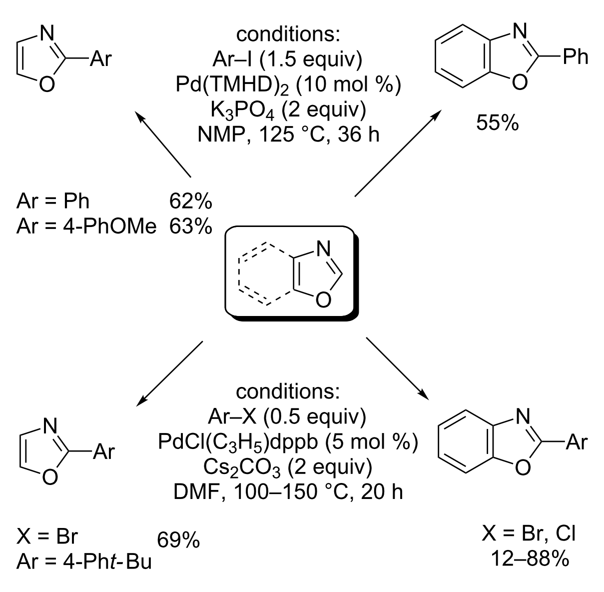
Scheme 11: Preparation of DPO- and POPOP-analogues [53].

Daugulis used the bulky butyldi-1-adamantylphosphine associated with the potassium phosphate base to achieve Pd(0)-catalyzed direct arylation of various electron-rich heterocycles, including benzoxazole with aryl chlorides (Scheme 12) [54].



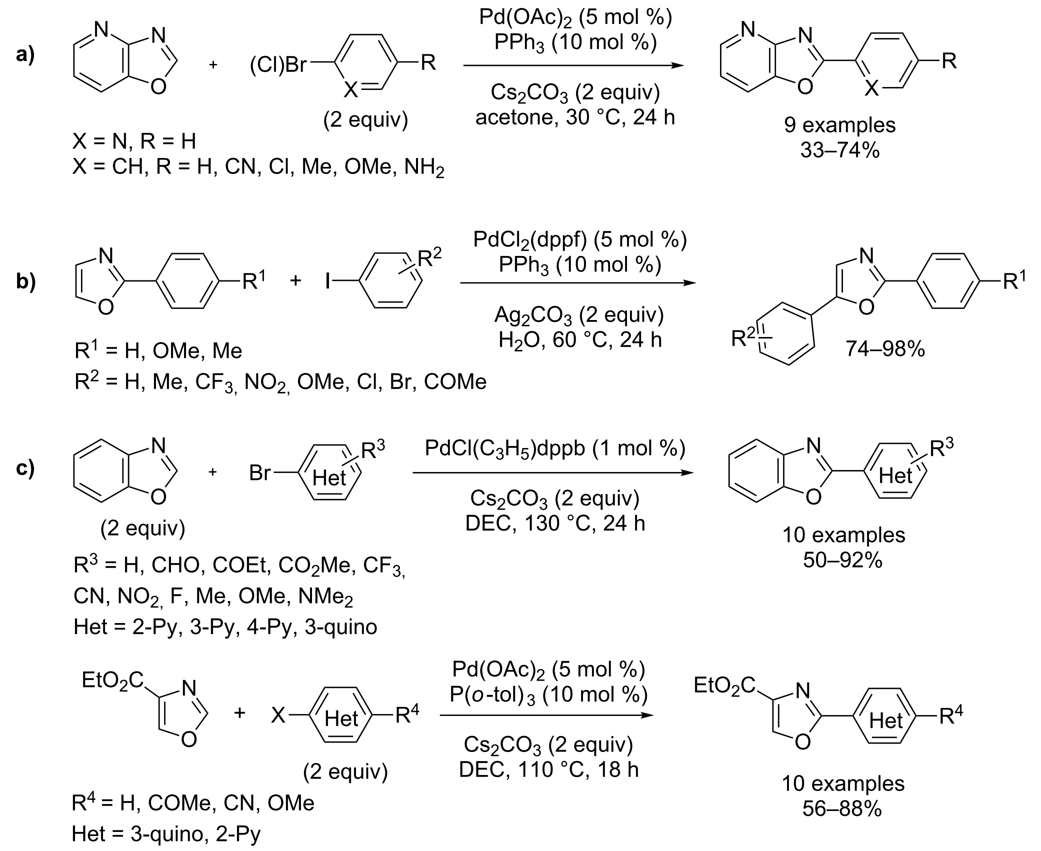
Scheme 12: Pd(0)-catalyzed direct arylation of benzoxazole with aryl chlorides [54].

Bhanage proposed the use of 2,2,6,6-tetramethyl-3,5-heptanedione ligand (TMHD) to achieve regioselective, Pd(0)-catalyzed, direct arylation of *N*-methylindole, thiazoles and oxazoles, using phosphate or carbonate bases (Scheme 13) [55]. The same year, Doucet demonstrated the high efficiency of $PdCl(dppb)(C_3H_5)$ precatalyst in Pd(0)-catalyzed direct arylation of thiazoles and oxazoles with arylbromides (Scheme 13) [56]. Notably under these two protocols, oxazole was monoarylated selectively at the C2 position in 62% and 69% yields, respectively.



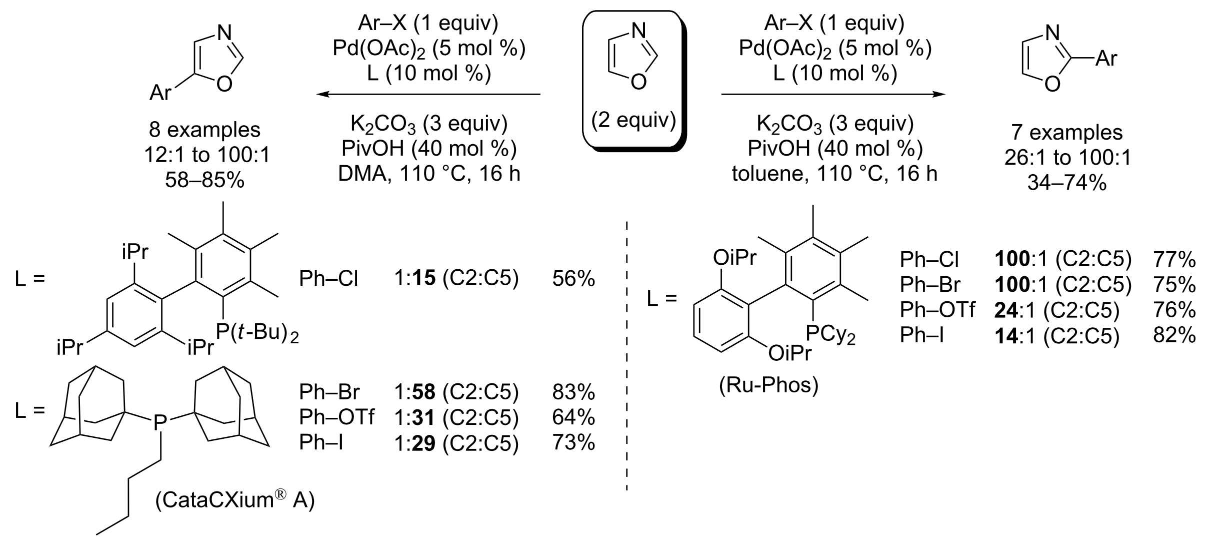
Scheme 13: Pd(0)-catalyzed direct C2-selective arylation of (benz)oxazoles with bromides and chlorides using bidentate ligands [55,56].

More user-friendly conditions for palladium catalysis were also developed for the direct arylation of azoles by Zhuralev [57,58], Greaney [59,60], and Hoarau–Doucet [61,62] using, respectively, acetone solvent at low temperature, water as dispersing agent and diethylcarbonate (DEC) (Scheme 14).



Scheme 14: Palladium-catalyzed direct arylation of oxazoles under green conditions; (a) Zhuralev direct arylation of 2-azabenzoxazole at low temperature [57,58]; (b) Greaney direct arylation of oxazole in water [59,60]; (c) Hoarau–Doucet direct arylation of (benz)oxazole in diethylcarbonate [61,62].

In 2010, Strotman and Chobanian reported the first highly challenging C2- and C5-selective Pd(0)-catalyzed direct arylation of oxazole with arylbromides, chlorides and triflates (Scheme 15) [63]. Interestingly, under the same catalytic conditions, the C2 (versus C5) position was preferred in nonpolar toluene solvent (versus polar DMF solvent) with RuPhos ligand (versus

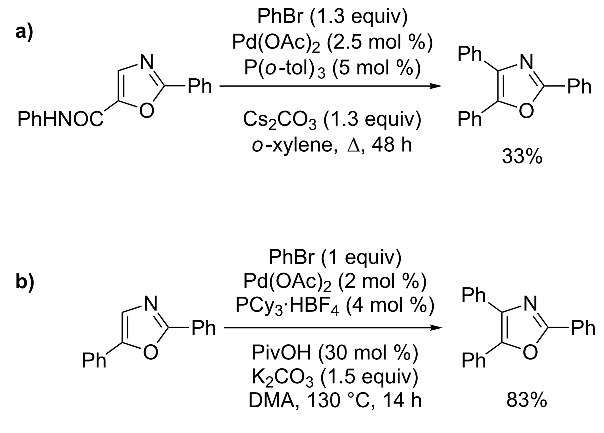


Scheme 15: Pd(0)-catalyzed C2- and C5-selective (hetero)arylation of oxazole [63].

CataCXium® A or 3,4,5,6-tetramethyl-*tert*-butyl-XPhos ligands).

This year, Hoarau proposed the C2- and C5-regioselective Pd(0)-catalyzed direct (hetero)arylation of ethyl oxazole-4-carboxylate with arylbromides and chlorides in dioxane solvent by using K_2CO_3 as base. The C2 position was attained by using specifically $P(t\text{-Bu})_3$/PivOH or JohnPhos/PivOH pairs, whilst PCy_3/PivOH pair or PCy_3, JohnPhos or dppf ligands used alone allowed reversing of the selectivity in favour of the C5 position (Scheme 16) [64].

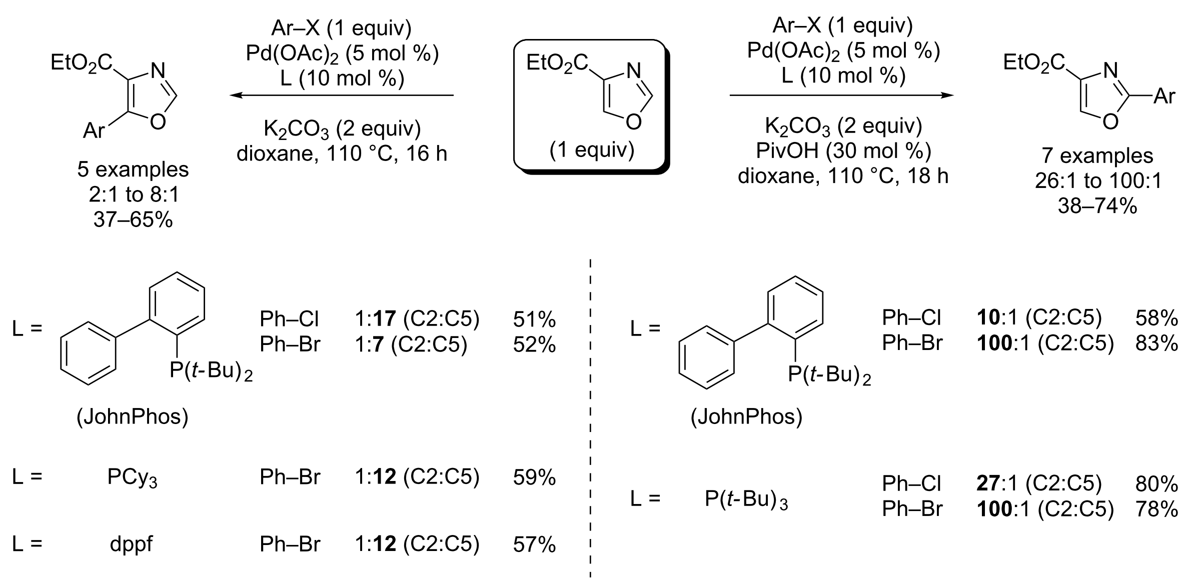
Miura first highlighted the reactivity of the C4 position of the oxazole ring in a direct substitutive-coupling methodology by reacting *N*-phenyl-2-phenyloxazole-5-carboxamide with phenylbromide (Scheme 17) [65]. Nevertheless, the introduction of a phenyl group also occurred subsequently at the C5 position, exclusively producing the 2,4,5-triphenyloxazole. Fagnou then reported the direct C4-phenylation of 2,5-diphenyloxazole with phenylbromide by using a general catalysis that had proved to be useful in catalytic direct arylation of azoles (Scheme 17) [66].



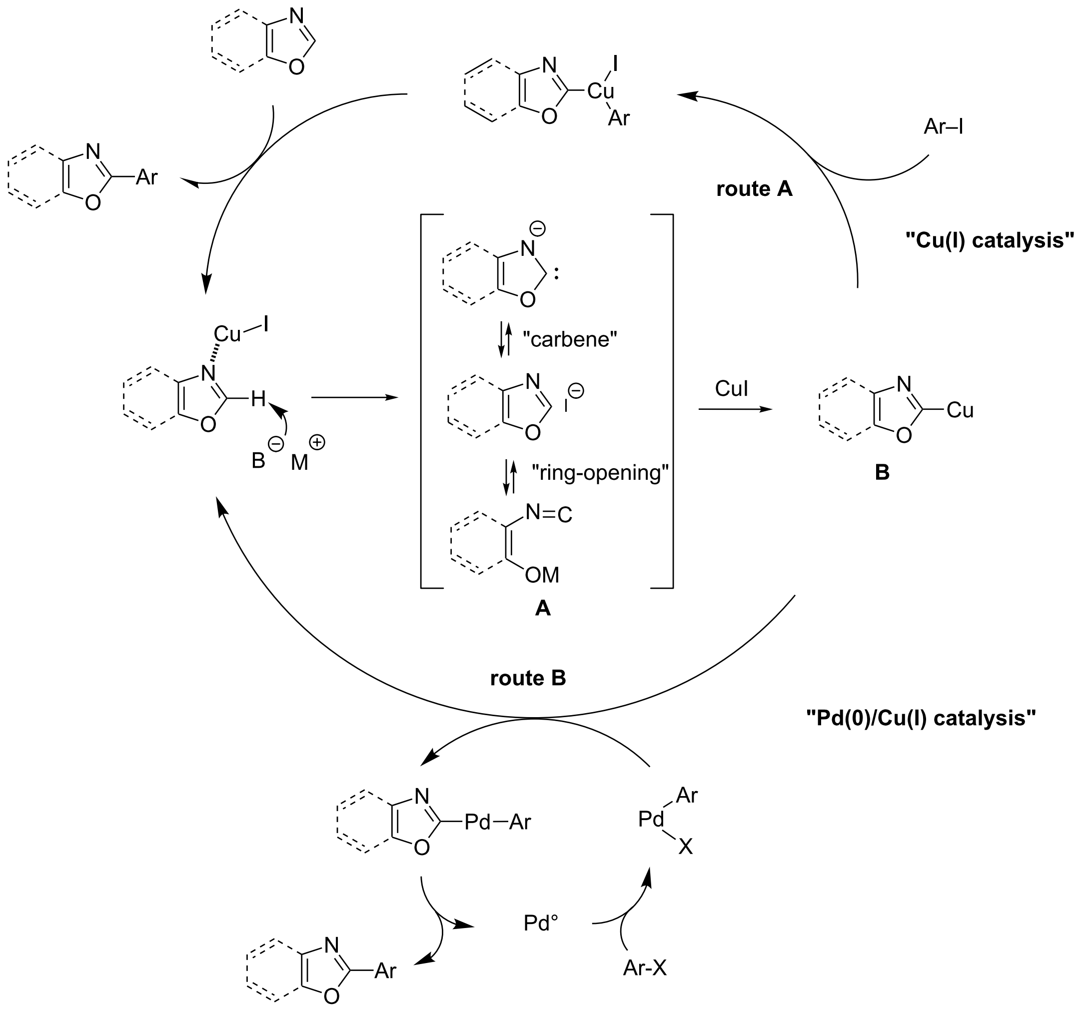
Scheme 17: Pd(0)-catalyzed direct C4-phenylation of oxazoles; (a) Miura's procedure [65]; (b) Fagnou's procedure [66].

Palladium- and copper-catalyzed direct (hetero)arylation with halides: Progress in mechanisms

Regarding the C5>C4>C2-reactivity scale of electron-rich azoles under electrophilic reaction, Miura proposed an SEAr-type mechanism for selective C5-arylation of imidazoles, thiazoles and oxazoles. [40] However, the C2-selectivity observed in the presence of Cu(I) salts as cocatalyst, or used alone, was suspected to arise from a proton–metal exchange of the most acidic position leading to an organocopper intermediate suitable for a nucleophilic substitution reaction. Daugulis reported a first rationalized route for the direct arylation of azoles, including oxazoles, by using a strong base under Cu(I) catalysis and based upon the previous formation of the oxazol-2-ylcuprate intermediate suitable in a subsequent oxidative step with aryliodide (Scheme 18, route A) [45]. However, Bellina and Rossi underlined the fact that the initial C2-oxazolylcopper formation stays currently unclear. Thus, they suggested a copper-induced reinforcing-acidity effect to facilitate the C2-deprotonation step, which could then be ensured by a very



Scheme 16: Pd(0)-catalyzed C2- and C5-selective (hetero)arylation of ethyl oxazole-4-carboxylate [64].

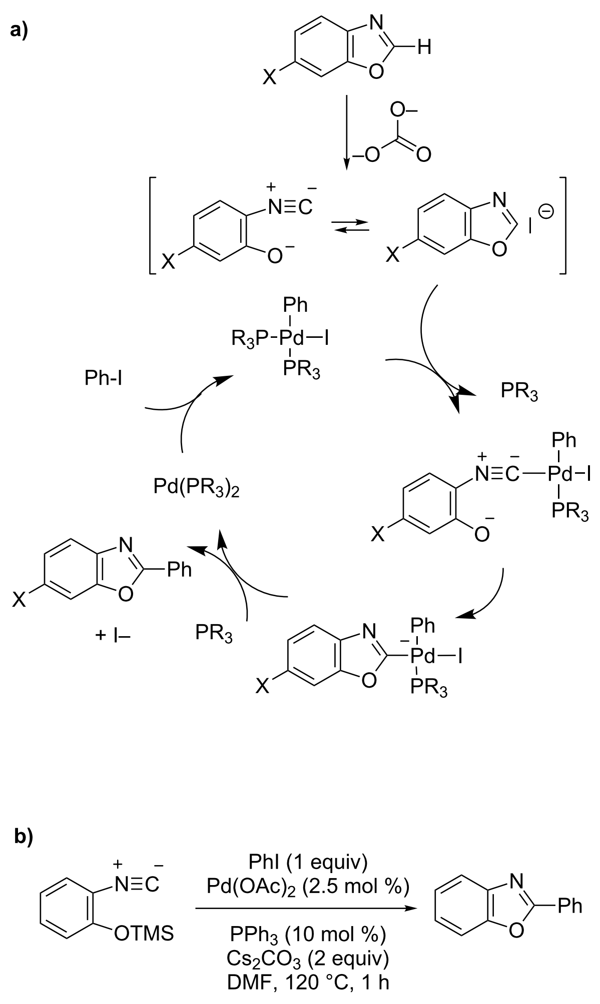


Scheme 18: Catalytic cycles for Cu(I)-catalyzed (routeA) and Pd(0)/Cu(I)-catalyzed (route B) direct arylation of oxazoles with halides proposed by Bellina and Rossi [67].

weak base-like caesium fluoride or even by DMF solvent (Scheme 18) [67]. The resulting C2-carbanion may be in equilibrium with a stabilized carbene intermediate and finally reacts with copper iodide to give the organocopper intermediate. Bellina and Rossi also noted that this last transmetalation step may be complicated by a second, well-known equilibrium of the 2-metallated oxazole with its ring-open tautomer [67]. Using Pd(0)/Cu(I) catalysis, the C2-cuprated oxazole may act as a transmetallating agent through a standard cross-coupling reaction (Scheme 18, route B) [67].

Under Pd(0)- and Cu(I)-free catalysis, Zhuralev identified a cross-coupling-type mechanism for direct arylation of benzoxazole and the aza-analogues using a strong base [57,58]. Thus, the arylpalladium complex is engaged in a Passerini-type reaction with the 2-metallated benzoxazole ring-open tautomer, leading directly to the ring-close benzoxazol-2-yl(aryl)palladium complex, and finally to the 2-arylated benzoxazole after a reductive elimination step (Scheme 19a). Deuterium-incorporation experiments and DFT calculations highly support this pathway as well as the successful palladium-catalyzed arylation of the *O*-silylated 2-isonitrilephenolate (Scheme 19b). Last year, Strotman and Chobanian retained this cross-coupling-type mechanism for their recently developed protocol for the Pd(0)-catalyzed, highly C2-selective, direct (hetero)arylation of oxazole [63].

By contrast, Hoarau recently discarded the cross-coupling-type mechanism in favour of the direct (hetero)arylation of the more acidic oxazole-4-carboxylate employing strong Cs_2CO_3, K_3PO_4 or DBU bases, through deuterium-incorporation experiments in dioxane and toluene solvents, which led in both cases to the production of C2 and C5 deuterated ethyl oxazole-4-carboxylate [64]. Thus, an electrophilic substitution-type mechanism is



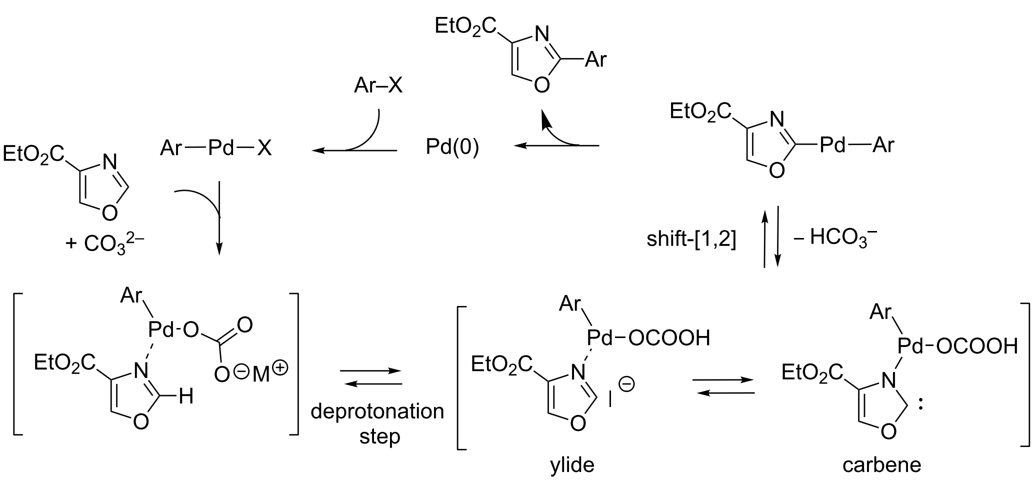
Scheme 19: Base-assisted, Pd(0)-catalyzed, C2-selective, direct arylation of benzoxazole proposed by Zhuralev [58]; (a) Proposed cross-coupling-type mechanism; (b) Ring-close direct C2-arylation.

preferred which is more in accordance with previous observations and a specific directed nitrogen-chelating effect (Scheme 20).

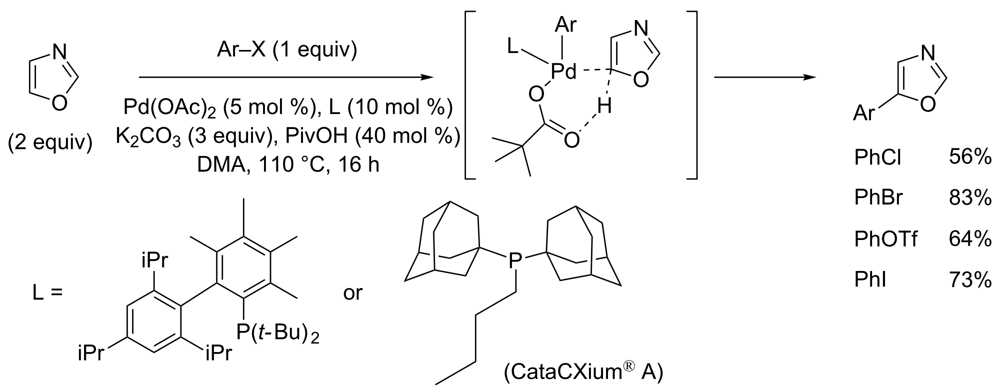
Thus, C2-selectivity may arise from a prior interaction of the palladium catalyst with nitrogen. The coordination of oxazole to arylpalladium(II) complex may lower the pK_a of oxazole more significantly and promote the deprotonation, and, as well, it may prevent the formation of the ring-open tautomer, according to Vedej's observations of the high stability of the 2-lithiated oxazole previously coordinated with triethylborate [68].

In parallel to the emergence of a strong-base-assisted, nonconcerted, metalation–deprotonation mechanism evoked for the C2-selective direct substitutive coupling of electron-rich azoles under strong base conditions, the last five years has witnessed the particular ascension of the Pd(0)-catalyzed carbonate or pivalate-assisted concerted metalation–deprotonation (CMD) mechanism [19,69], which has now proved to be effective for a broad range of aromatics and heteroaromatics, including electron-rich as well as electron-deficient heterocycles [20,21,70]. Although Fagnou demonstrated the good reactivity of several azoles under CMD conditions [70], Strotman and Chobanian were the first to favour a CMD mechanism for their methodology for the highly C5-selective direct arylation of oxazole based upon the use of potassium carbonate and pivalate bases (Scheme 21) [63]. As the main argument, a strong pivalate-assisted effect was observed.

This year, after demonstrating that the C5 (versus C2) position is slightly favoured under a carbonate-assisted internal CMD mechanism in the oxazole-4-carboxylate series, through DFT calculations of the Gibbs free energy of the CMD transition

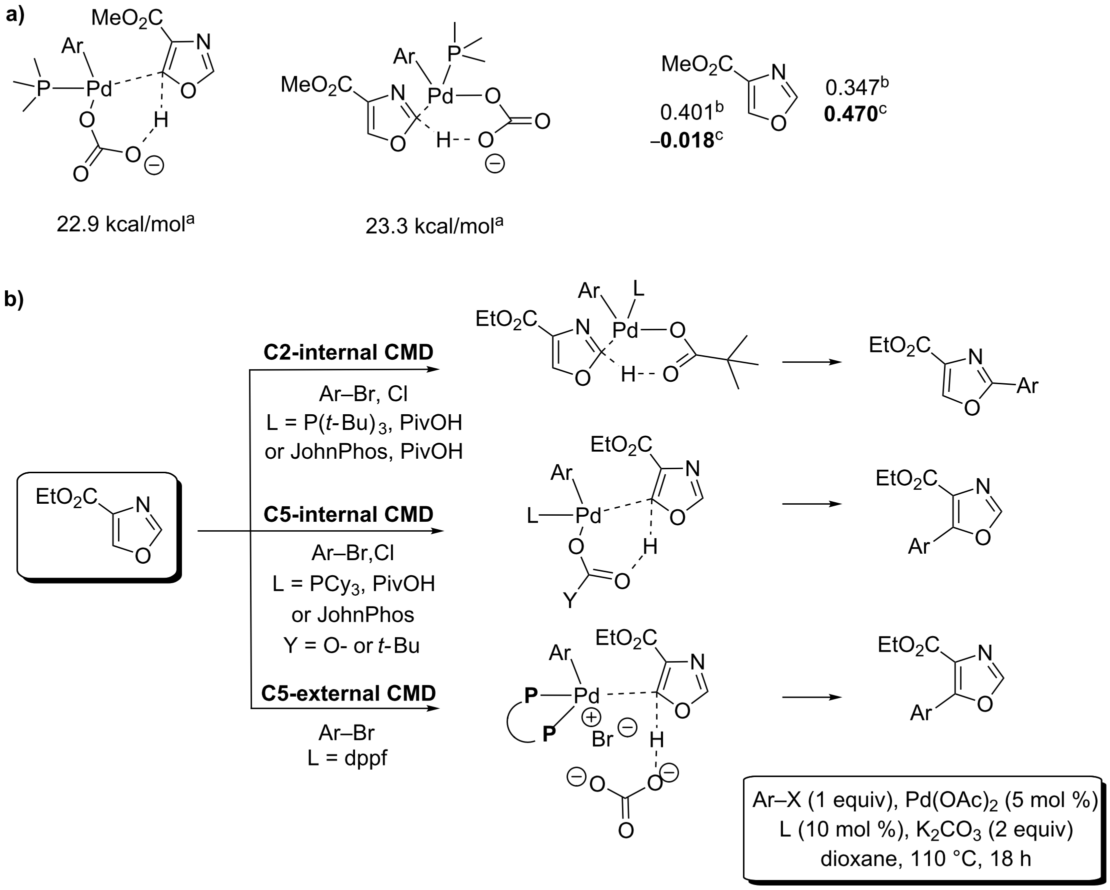


Scheme 20: Electrophilic substitution-type mechanism proposed by Hoarau [64].



Scheme 21: CMD-proceeding C5-selective direct arylation of oxazole proposed by Strotman and Chobabian [63].

state calculated at the C2 and C5 positions (Scheme 22a), Hoarau developed novel methodologies for the C2- and C5-selective direct arylation proceeding by CMD and using aryl bromides and chlorides (Scheme 22b) [64]. In particular, the charge-control interaction was identified as the main discriminating parameter since the HOMO levels are identical at both C2 and C5 positions (Scheme 22a). Thus, C2 selectivity was only attained by using the highly steric P(t-Bu)$_3$/PivOH pair,



Scheme 22: DFT calculations on methyl oxazole-4-carboxylate and consequently developed methodologies for the Pd(0)-catalyzed C2- and C5-selective direct arylations proceeding by CMD [64]; (a) DFT calculations on oxazole-4-carboxylate; (b) Developed novel CMD direct arylation methodologies. [a]TS CMD Free Gibbs energy; [b]HOMO coefficient; [c]partial charge (ESP).

whereas the less electron-donating tri(alkyl)arylphosphines as well as bidentate ligands were prompted to form an aryl-palladium complex possessing a highly electrophilic character, leading to C5-arylation.

Catalytic direct arylation of (benz)oxazoles with (pseudo)halides, carboxyarenes and organometallics

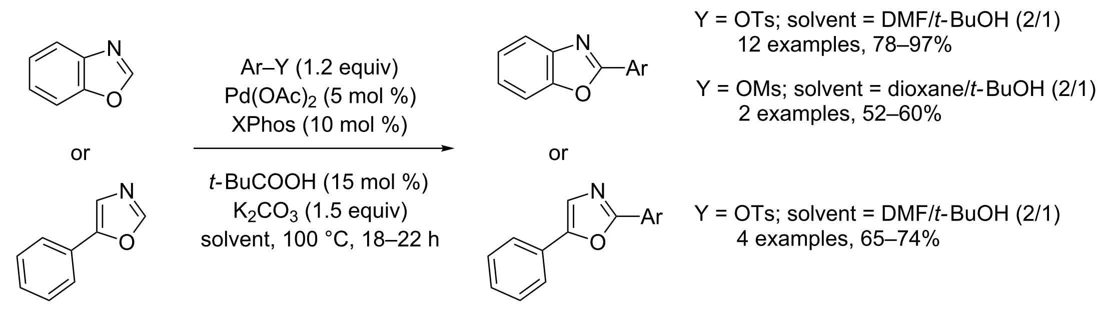
Ackermann was the first to find convenient conditions for the base-assisted, Pd(0)-catalyzed direct substitutive coupling of heteroarene applicable to tosylate and mesylate electrophiles, which are prepared from inexpensive and easily available phenol derivatives (Scheme 23) [71].

More user-friendly sulfamates also proved to be convenient arylating agents in Pd(0)-catalyzed direct substitutive arylation of various oxazole series (Scheme 24) [72].

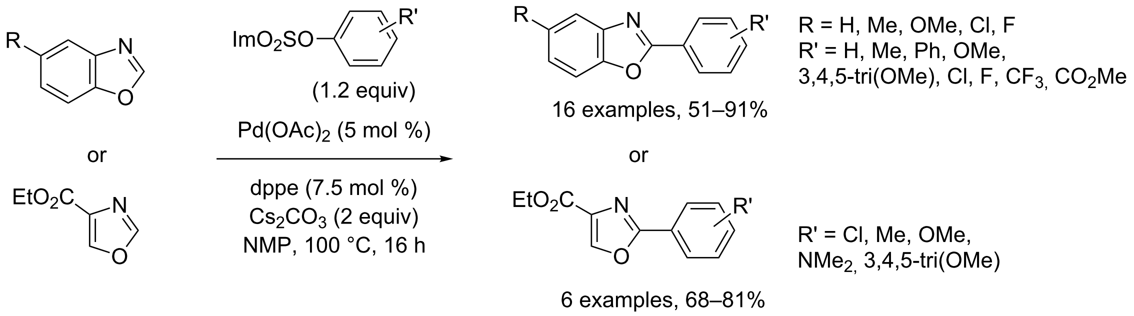
The first remarkable examples of catalytic, decarboxylative direct arylation of azoles were recently reported by the groups of Greaney and Tan [73,74]. Greaney selected the oxazole-4-carboxylate esters and 4-carboxyoxa(thia)zoles as substrates to prepare the naturally occurring 2,4-linked bis(azole). Interestingly, poly(azole) structures are also prepared by repeating the decarboxylative direct C–H cross-coupling sequence with the residual ester group (Scheme 25a) [73]. Mechanistically, a Cu(II)-catalyzed decarboxylation reaction produces the C4-cuprated azole, which intercepts the arylpalladium acetate complex produced by prior palladation of the substrate at the C2-position, to form the diazolylpalladium complex as the key intermediate leading finally to the bisazole system (Scheme 25b). Thus interestingly, the Cu(II) catalyst is used as a decarboxylating agent as well as for the reoxidation of Pd(0)-generated at the end of the catalytic cycle.

Tan therefore used a copper-free, Pd(II)-based catalyst for direct decarboxylative cross-coupling of azole with various benzoic acids (Scheme 26a). In particular, benzoxazole was successfully coupled with 2,6-dimethoxybenzoic acid in 45% yield. Thus, without the assistance of a strong base, a carbopalladation was proposed as a key activation step of the benzoxazole by the arylpalladium complex, produced by a well-established silver-catalyzed decarboxylative palladation reaction. As its second role, the Ag(II) salt serves as a reoxidizing agent (Scheme 26b) [74].

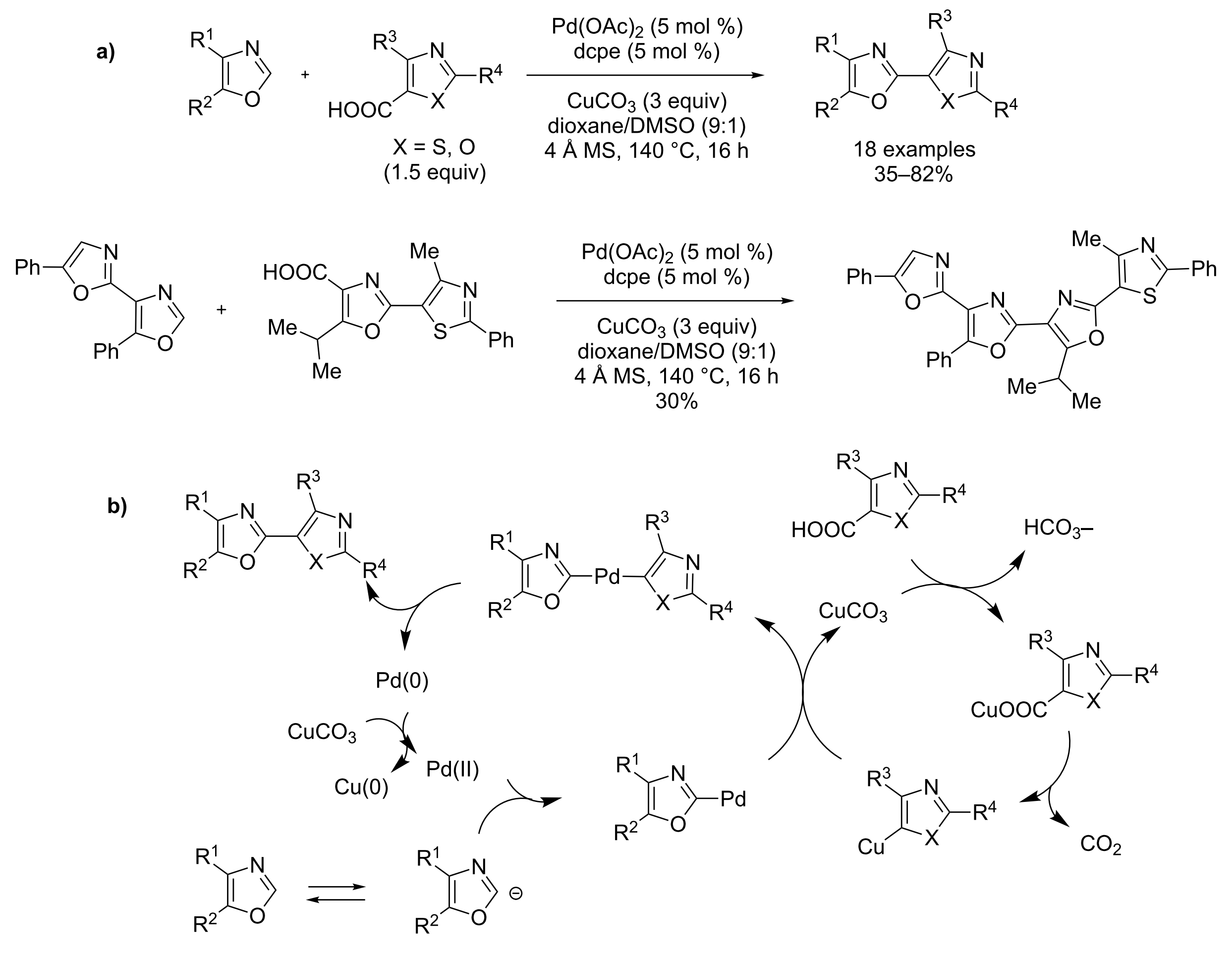
Recently, arylsilanes and arylboronic acids were also proposed as novel arylating agents in the strong-base-assisted, Pd(II)- and Ni(II)-catalyzed direct coupling of azole, by Liu, Hirano and Miura (Scheme 27a and Scheme 28a) [75-77].



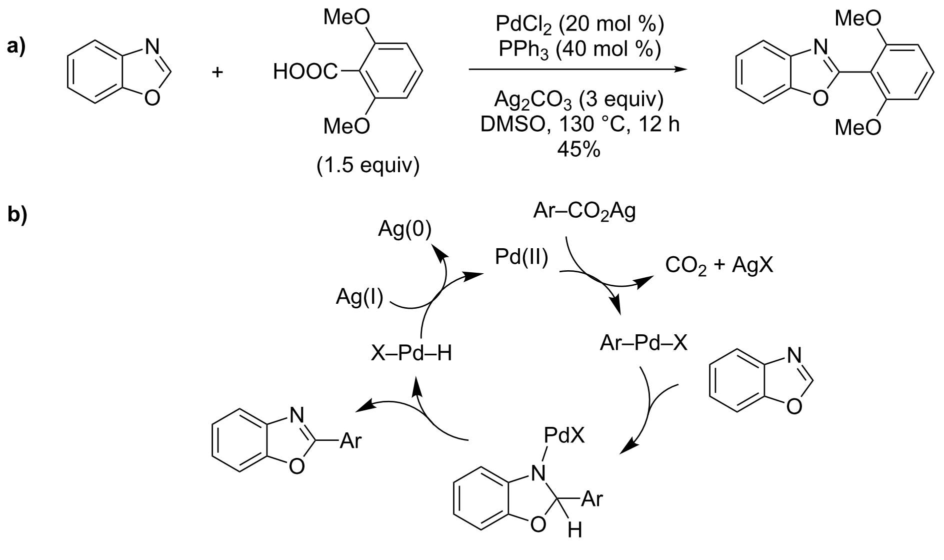
Scheme 23: Pd(0)-catalyzed direct arylation of (benz)oxazoles with tosylates and mesylates [71].



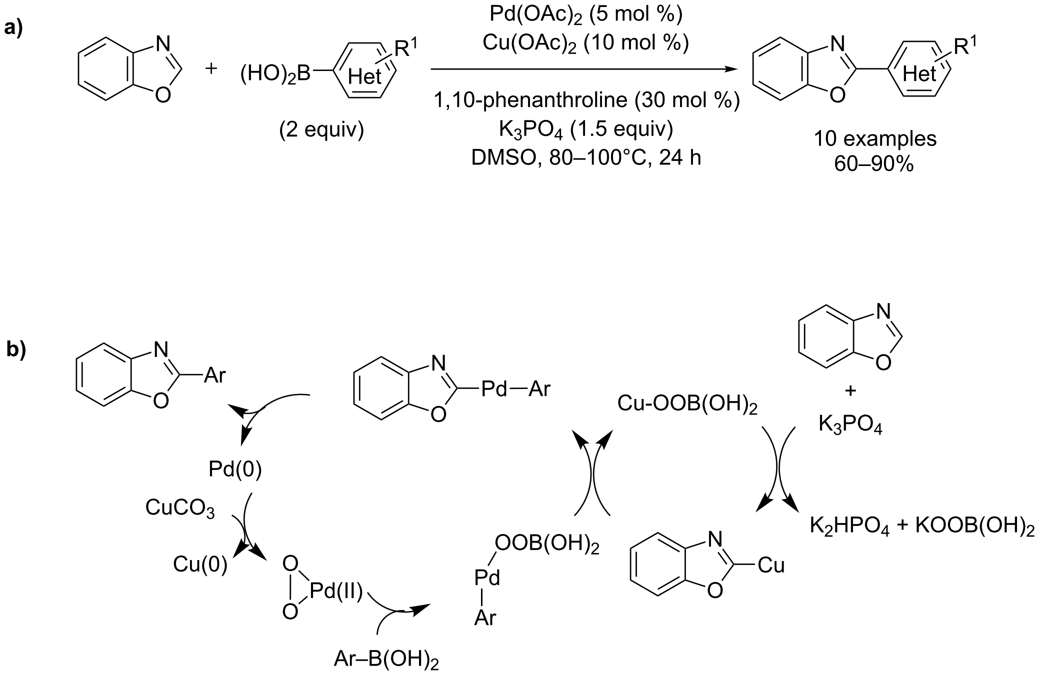
Scheme 24: Pd(0)-catalyzed direct arylation of oxazoles with sulfamates [72].



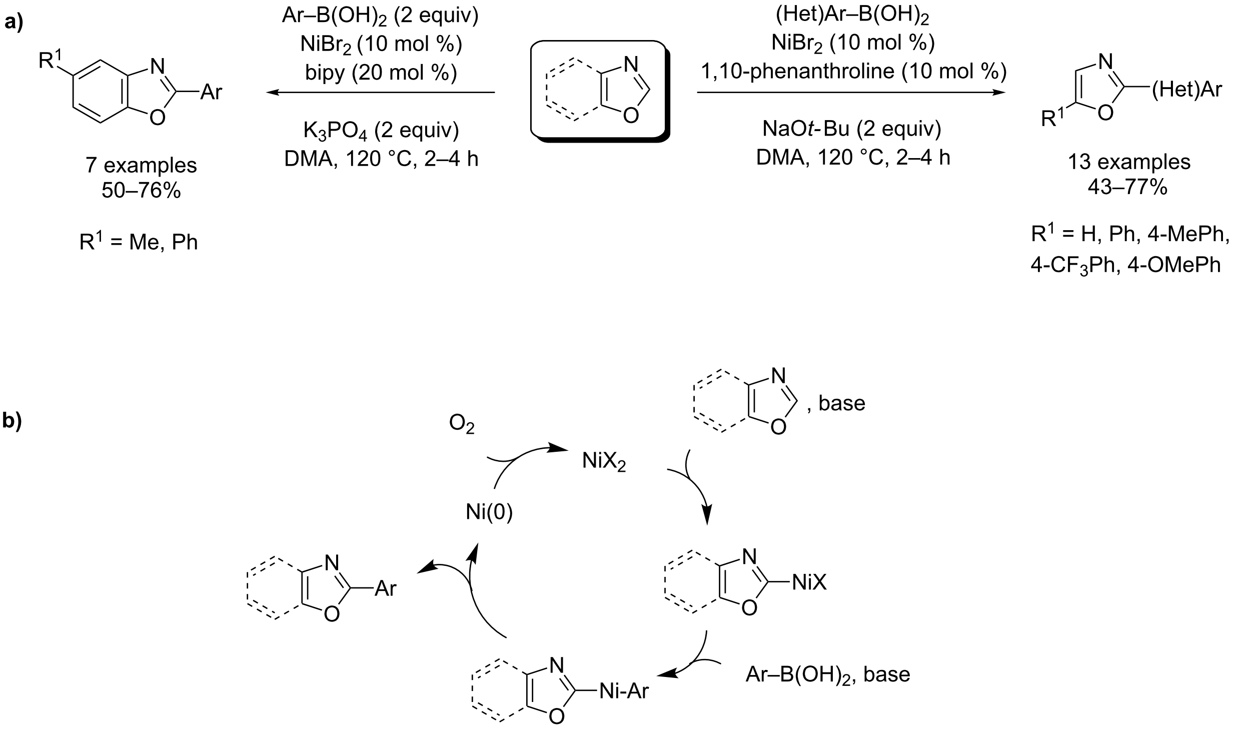
Scheme 25: Pd(II)- and Cu(II)-catalyzed decarboxylative direct C–H coupling of oxazoles with 4- and 5-carboxyoxazoles [73]; (a) procedure; (b) proposed mechanism.



Scheme 26: Pd(II)- and Ag(II)-catalyzed decarboxylative direct arylation of (benzo)oxazoles [74]; (a) procedure; (b) proposed mechanism.



Scheme 27: Pd(II)- and Cu(II)-catalyzed direct arylation of benzoxazole with arylboronic acids [76]; (a) procedure; (b) proposed mechanism.



Scheme 28: Ni(II)-catalyzed direct arylation of benzoxazoles with arylboronic acids under O_2 [76]; (a) procedure; (b) proposed mechanism.

Mechanistically, the Cu(II)-assisted palladation of the C2 position of benzoxazole is followed by a transmetalation step with arylboronic acids providing the arylazolylpalladium complex, which delivers the product (Scheme 27b and Scheme 28b).

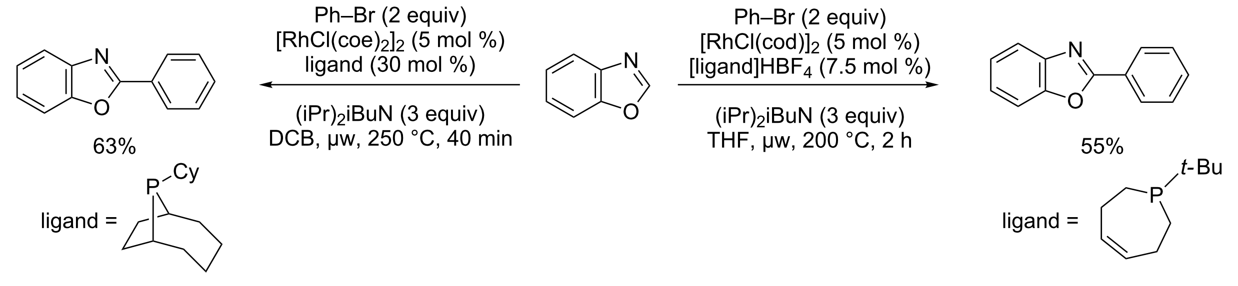
Rhodium- and nickel-catalyzed direct arylation of oxazoles with halides

The methodology for the Rh(I)-catalyzed direct substitutive coupling of azoles with halides was developed by the Bergman and Ellman group. In particular, the direct arylation of benzoxazole was performed under microwave activation with phenyl bromide (Scheme 29) [78,79].

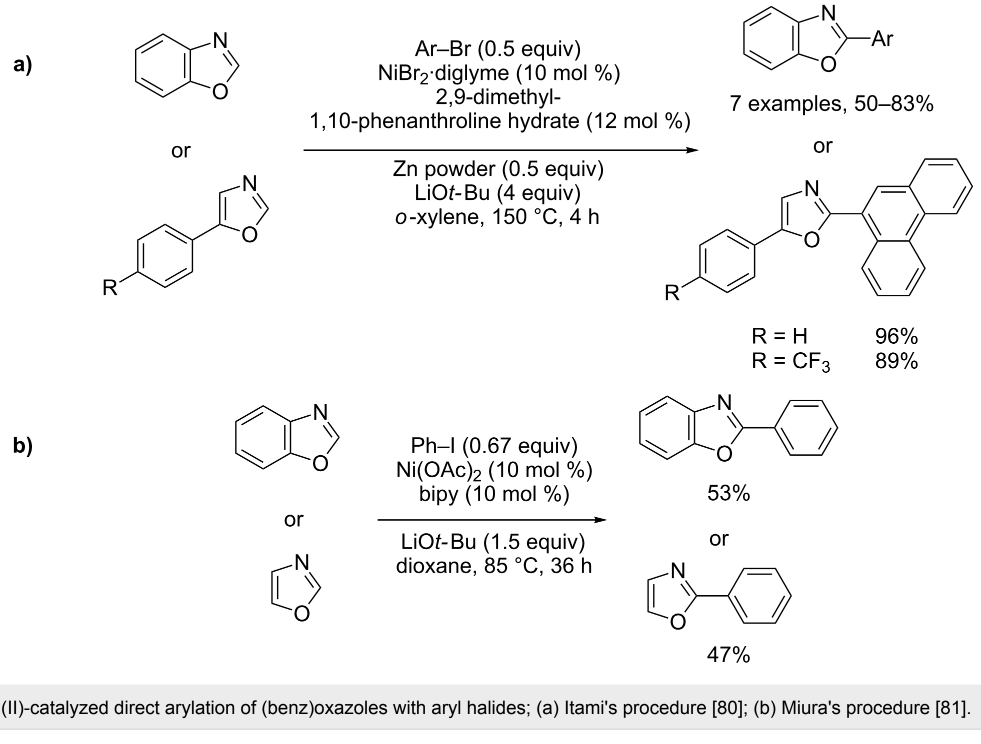
In 2009, Miura and Itami separately proposed the first convenient procedures for the direct substitutive coupling of azoles under Ni(II) catalysis with arylbromides (Scheme 30) [80,81].

Transition metal-catalyzed dehydrogenative cross-coupling

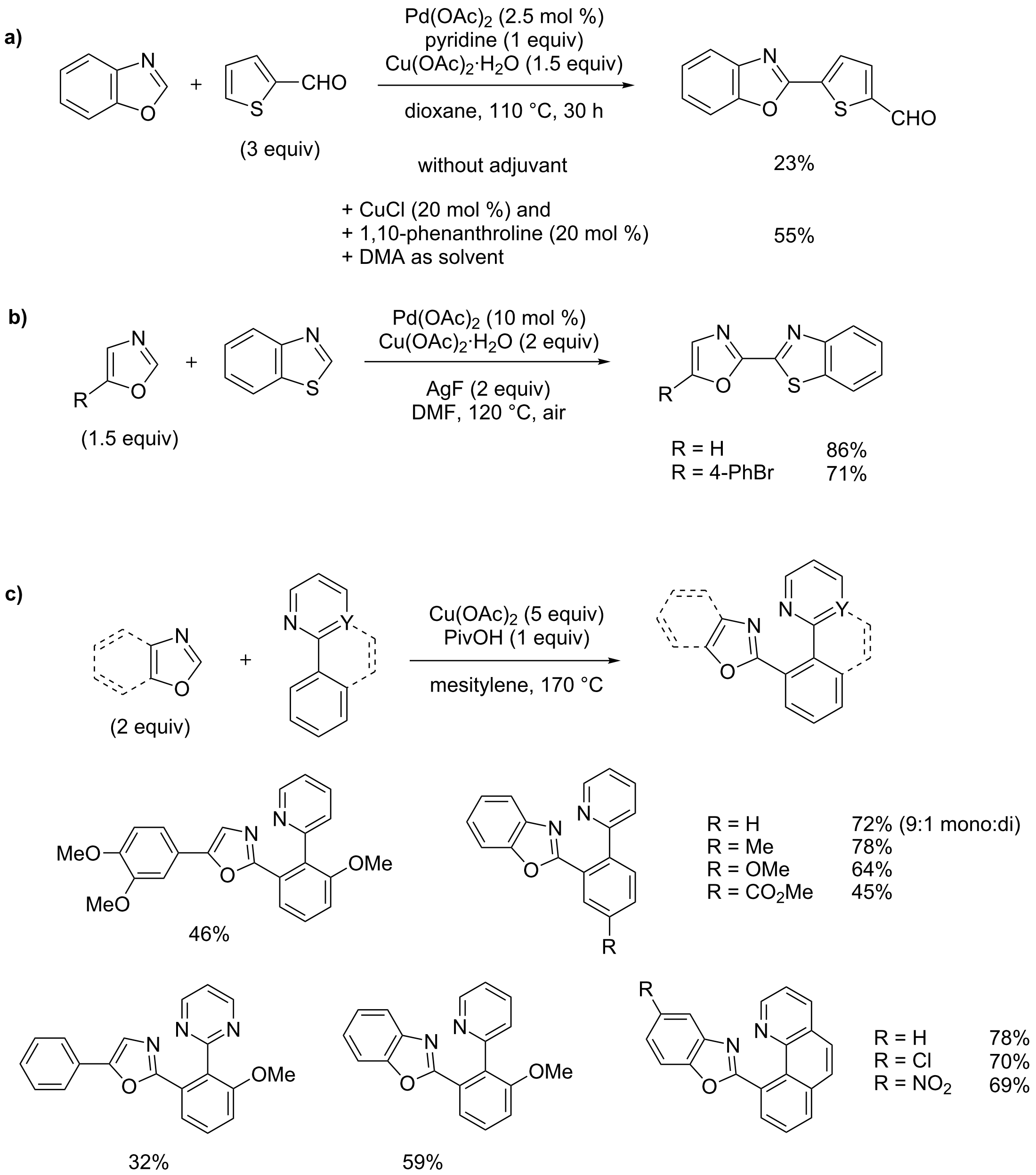
Last year, Hu and You reported the first extended study of Pd(II)- and Cu(II)- catalyzed oxidative C–H/C–H cross-coupling of electron-rich heteroarenes, including benzoxazole coupled with 2-formylthiophene by using Cu(I) cocatalyst and 1,10-phenanthroline in DMA solvent (Scheme 31a) [82]. This year, Oliaf studied more specifically the palladium- and copper-catalyzed oxidative C–H/C–H cross-coupling of various electron-rich 1,3-diazoles and reported notably the direct coupling of benzothiazole with two oxazoles, interestingly without a ligand but by using silverfluoride as cocatalyst (Scheme 31b) [83]. Miura recently reported the first remarkable palladium-free, Cu(II)-mediated direct oxidative C–H/C–H cross-coupling of arenes, using oxazoles and 2-arylazines as coupling partners (Scheme 31c) [84].



Scheme 29: Rhodium-catalyzed direct arylation of benzoxazole [78,79].



Scheme 30: Ni(II)-catalyzed direct arylation of (benz)oxazoles with aryl halides; (a) Itami's procedure [80]; (b) Miura's procedure [81].



Scheme 31: Dehydrogenative cross-coupling of (benz)oxazoles; (a) Pd(II)- and Cu(II)-catalyzed cross-coupling of benzoxazole with thiophene [82]; (b) Pd(II)- and Cu(II)-catalyzed cross-coupling of oxazoles with benzothiophene [83]; (c) Cu(II)-catalyzed direct cross-coupling of (benz)oxazole with arenes [84].

Conclusion

The direct arylation of (hetero)arenes through the cleavage of C–H bonds has been proved to be a viable alternative to standard cross-coupling reactions. (Benz)oxazoles have drawn particular attention and have often been separately studied as a highly challenging and valuable heterocycle series. Since the pioneering works of Ohta and Miura in the 1990s, the direct C–H substitutive coupling of (benz)oxazoles has been intensively studied under Pd(0)- and/or Cu(I)- and, more recently, Rh(I)- and Ni(0)- catalysis by using aryl (pseudo)halides, including less-expensive aryl chlorides, tosylates, mesylates and phosphonates. Research efforts in this field are now focused on mechanism considerations since the broad diversity of catalytic metalation pathways represents undoubtedly an attractive tool for regioselectivity and the development of novel methodologies. Up until very recently, novel catalytic direct arylations of oxazoles have been developed. Arylboronic and carboxy(hetero)arene acids have thus been proposed as coupling partners under base- and copper-assisted Ni(II)- or Pd(II)-catalysis. Additionally, the first examples of highly attractive Cu(II)- or Pd(II)-catalyzed dehydrogenative couplings of (benz)oxazoles with (hetero)arenes have been developed.

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License and Terms

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On the control of secondary carbanion structure utilising ligand effects during directed metallation

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Full Research Paper

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Abstract

N,*N*-Diisopropyl-2-propylbenzamide **6**-H undergoes lateral deprotonation by *t*-BuLi in the presence of the Lewis base PMDTA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine) to give a benzyllithium **6**-Li$_l$·PMDTA that incorporates a trigonal planar secondary carbanion. In the solid state, the amide directing group and the PMDTA additive work together to abstract the metal ion from the deprotonated α-C of the propyl group (4.107(4) Å). A short distance of 1.376(3) Å is observed between the deprotonated carbon centre and a planar aromatic system that shows a pattern of bond lengths which contrasts with that reported for related tertiary carbanion systems. Analogous benzylic deprotonation is seen if **6**-H is treated with *t*-BuLi in the presence of diglyme to give **6**-Li$_l$·DGME. X-ray crystallography now shows that the metal ion more closely approaches the tertiary carbanion (2.418(6) Å) but that the planarity of the deprotonated carbon centre and the bonding pattern in the organic anion seen in the PMDTA complex are retained. DFT analysis corroborates both the short distance between aromatic ring and carbanion centre and the unperturbed nature of aromaticity in **6**-Li$_l$·L (L = Lewis base). The observation of two structure-types for the carbanion in solution is explained theoretically and by NMR spectroscopy in terms of *cis* and *trans* isomerism imparted by partial double bond character in the arene–(α-C) bond.

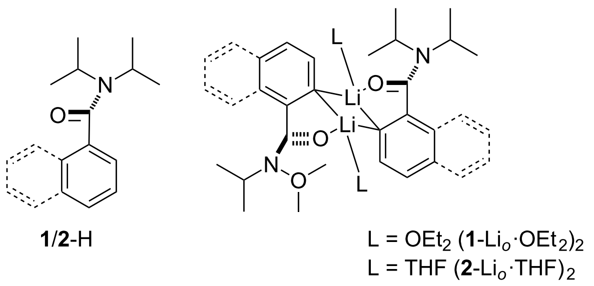
Introduction

Directed deprotonative lithiation – where the directing group generally combines inductive electron withdrawal with the presence of an electron-rich metal-coordinating atom [1] – has established itself as an enormously powerful tool for the elaboration of aromatic and heteroaromatic compounds [2-9] and continues to find new applications today [10,11]. Various highly selective aryl C–H deprotonative metallations have been reported because of the directing group's ability to inductively raise hydrogen atom acidity and because the incoming organometallic reagent closely approaches the reactive position (“*ortho* lithiation” when deprotonation occurs adjacent to the directing group [2,3], “directed remote metallation” when reaction is non-adjacent [12-15]).

However, the presence of substituents at the *ortho* position of the aromatic ring introduces the possibility of deprotonating the substituent at the benzylic (or α-) position (“lateral lithiation”) through the directing group coordinating the incoming organometallic substrate whilst conjugatively withdrawing electrons from the benzylic group [2]. In the case of lateral reaction, stabilisation of the resulting anion is expected to favour benzylic deprotonation when reactions are potentially competitive [16,17]. However, in practice, the exact nature of the lateral group may complicate matters. For example, the presence of a heteroatom at the β-position of the lateral group may either promote or retard lateral deprotonation on electronic grounds [1,2]. Moreover, steric effects have also been found to play an important role. Hence, whereas the formation of primary [18] and secondary [19] carbanions through lateral deprotonation has been known for many years, it is only very recently that the analogous formation of tertiary carbanions has been reported [20].

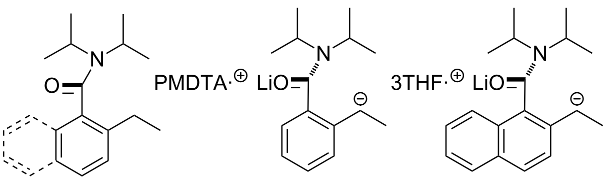
Amongst the most important, versatile and widely used agents for directing the deprotonative lithiation of aromatic substrates are amide type (or “N+O”) groups [3]. In the case of such systems, solid-state structural evidence for carbanion structure has only emerged in the last decade or so. These data focused on reactions directed by tertiary amides; with the *ortho* metallation of *N*,*N*-diisopropylbenzamide **1**-H and its naphthamide analogue **2**-H [21] giving species that have been characterised as solid-state dimers. These metallo-intermediates are each based on a (CLi)$_2$ core wherein each metal ion is further stabilised by one solvent molecule (OEt$_2$ or THF, Scheme 1) and an amide O-centre through modulation of the amide–arene twist angle (documented as being near perpendicular in the corresponding arylamide substrates [22]).

More recently, the focus has shifted towards the study of the competition between the *ortho* and lateral deprotonation of 2-alkylated benzamide substrates. Hence, 2-ethylated analogues of **1**-H and **2**-H (**3**-H and **4**-H, respectively; Scheme 2) have been treated with *t*-BuLi in the presence of either PMDTA (*N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine) (for **3**-H) [23] or THF (for **4**-H) [24] to yield **3**/**4**-Li$_l$·*n*L (*n* = 1, L = PMDTA; *n* = 3, L = THF). Notably, whereas the deptonation of **4**-H in the presence of THF yielded the lateral lithiate as a tris(THF) solvate, the tridentate electron donor PMDTA was required to replicate this chemistry with **3**-H. Attempts to utilise THF in this last system resulted, instead, in the isolation and characterisation of *ortho* metallated **3**-Li$_o$·THF, the solid-state structure of which revealed a dimeric structure analogous to those seen for **1**-Li$_o$·THF and **2**-Li$_o$·THF [21]. It was subsequently established that the conversion of this (kinetic) lithiate into the thermodynamic (lateral) species could be observed in solution spectroscopically (Scheme 3) [23].

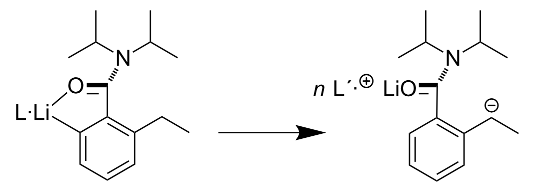

1/**2**-H

L = OEt$_2$ (**1**-Li$_o$·OEt$_2$)$_2$
L = THF (**2**-Li$_o$·THF)$_2$

Scheme 1: Molecular structures of **1**/**2**-H and their corresponding *ortho*-lithiates [21].

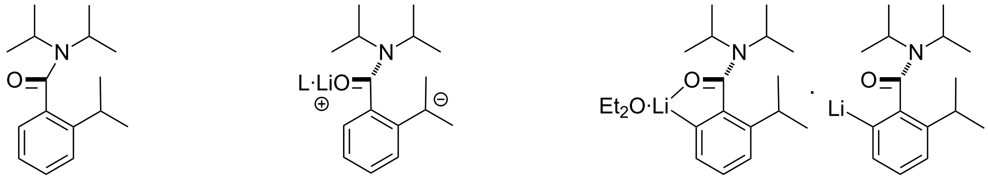

3/**4**-H **3**-Li$_l$·PMDTA **4**-Li$_l$·3THF

Scheme 2: Molecular structures of **3**/**4**-H and their corresponding lateral lithiates [23,24].


3-Li$_o$·L **3**-Li$_l$·*n*L'

Scheme 3: Conversion of kinetic *ortho*-lithiate into the thermodynamic lateral lithiate under the influence of strong (L = THF, *n* = 1, L′ = PMDTA) or excess (e.g., L = L′ = THF, *n* > 1) Lewis base [23].

The need to utilise multidentate donors in place of monodentate solvents such as OEt$_2$ or THF to incur the lateral deprotonation of 2-alkylated arylamides in which the 6-position is not blocked (contrast this scenario with the conversion of **4**-H into **4**-Li$_l$·3THF) recently led us to examine the hitherto unachievable formation of tertiary carbanions by directed lateral lithiation [16,17]. Accordingly, 2-isopropyl-*N*,*N*-diisopropylbenz-



5-H

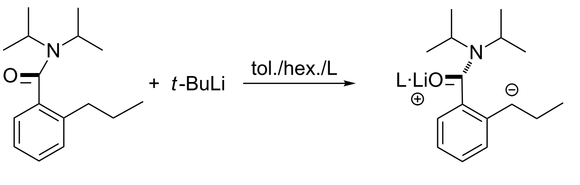
L = PMDTA, DGME **5**-Li$_l$·L

(**5**-Li$_o$)$_2$·OEt$_2$

Scheme 4: Molecular structure of **5**-H and its lateral and *ortho*-lithiates [20].

amide (**5**-H) has been used to source **5**-Li$_l$·L (L = PMDTA, DGME; DGME = diglyme) and also, under kinetic control, the remarkable hemi-solvated *ortho*-lithiate (Scheme 4). This development allowed thermodynamic lithiate **5**-Li$_l$·PMDTA to be successfully used to generate a variety of benzamides bearing quaternary C-centres at the aromatic 2-position [20].

In this work, we revisit the formation of secondary carbanions, reporting variously solvated lateral lithiates of *N*,*N*-diisopropyl-2-propylbenzamide **6**-H. We had previously prepared this compound as part of a study of the conformational stability and lability of tertiary aromatic amides bearing a single *ortho* substituent [25]. At ambient temperature, amides with this substitution pattern are conformationally mobile about their aryl–CO bond [26] on a timescale of seconds or less, and hence, inseparable into atropisomers [27]. However, at the temperatures commonly used to effect lithiation reactions, they should exist as chiral, racemic atropisomers. The stepwise lateral ethylation/*ortho* methylation of **3**-H and lateral methylation/*ortho* methylation of **6**-H [17] prior to warming returned conformationally rigid but oppositely configured amides with diastereomeric ratios >9:1; establishing that reaction was kinetically controlled [28]. Present structural studies of lateral lithiates of **6**-H reveal extensive charge delocalisation from a trigonal planar carbanion centre; the displacement of the metal from which is strongly solvent dependent (Scheme 5). Moreover, the improved quality of the crystallographic data for **6**-Li$_l$·L relative to that achievable for **3**-Li$_l$·PMDTA reveals significant structural parameters that are not available from the previously characterised secondary carbanion [23].



6-H

L = PMDTA, DGME **6**-Li$_l$·L

Scheme 5: Lateral metallation of **6**-H using *t*-BuLi in the presence of Lewis base L.

Results and Discussion

Solid-state structural studies

Based on our knowledge of the ability of Lewis base solvent or additives to influence the chemoselectivity of lithiation, **6**-H was treated at −78 °C with *t*-BuLi in a hydrocarbon medium to which 1 equiv of PMDTA had been added. The resulting dark purple solution was transferred directly to a freezer (−30 °C) whereupon storage afforded a product that X-ray crystallography revealed to be benzylically deprotonated **6**-Li$_l$·PMDTA; in which the metal is encapsulated by the amide oxygen atom and the three donor sites of PMDTA (Scheme 5, Figure 1 and Supporting Information File 1). Importantly, the use of a Pr substituent (cf. 2-Et in **3**-H) obviates the crystallographic disorder that limited the analysis of the structure of **3**-Li$_l$·PMDTA by preventing the anisotropic refinement of both the aromatic ring and the deprotonated alkyl chain [23]. In fact, the direct observation of H8 by Fourier difference synthesis [29,30] and the anisotropic refinement of this atom allows an exact understanding of the geometry at the carbanion centre: In

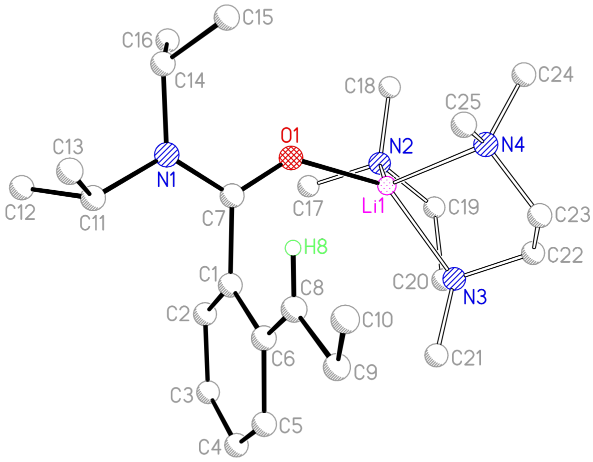
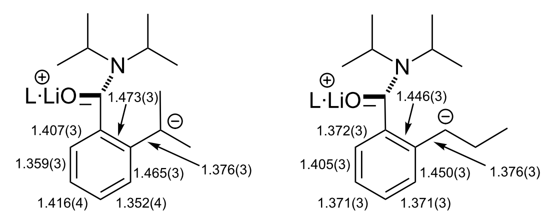


Figure 1: Molecular structure of **6**-Li$_l$·PMDTA; H-atoms (excl. H8) omitted for clarity. Selected bond lengths (Å) and angles (°): O1–Li1 1.845(3), N2–Li1 2.116(4), N3–Li1 2.097(3), N4–Li1 2.123(4), C8···Li1 4.107(4), C8–H8 0.957(19), C8–C9 1.497(3), C9–C10 1.510(3), C8–C6 1.376(3), C6–C5 1.450(3), C5–C4 1.371(3), C4–C3 1.371(3), C3–C2 1.405(3), C2–C1 1.372(3), C1–C6 1.446(3), C6–C1–C7–O1 88.4(2), C7–C1–C6–C8 6.1(3).

6-Li$_l$·PMDTA amide coordination and solvation by PMDTA have worked together to displace the Li$^+$ ion from deprotonated C8, resulting in an essentially flat secondary carbanion (C6–C8–C9 125.0(2)°, C6–C8–H8 120.9(11)°, C9–C8–H8 114.0(11)°).

Akin to the recently reported structure of **5**-Li$_l$·PMDTA, a short arene–(α-C) bond is noted in **6**-Li$_l$·PMDTA (1.376(3) Å). However, whereas the amide–arene orientation in a laterally lithiated tertiary aromatic amide has previously approximated to 80° in the presence of a secondary benzylic carbanion (viz. C(CLi)–C–C–O 79.2(4)° in **3**-Li$_l$·PMDTA [23], 82.5(5)° in **4**-Li$_l$·3THF [24]) and has been significantly reduced (to 42.8(3) and 39.7(2) in **5**-Li$_l$·L (L = PMDTA, DGME) [20]) in the presence of a tertiary benzylic carbanion, that in **6**-Li$_l$·PMDTA is higher (C6–C1–C7–O1 88.4(2)°), plainly precluding any azaenolate contribution to anion stability (C7–C1 1.493(3) Å). Moreover, though the analysis of charge delocalisation has recently been undertaken for benzylic tertiary carbanions, revealing a pentadienyl bonding pattern with alternating short and long bonds noted between the deprotonated (α-C) and the aromatic carbon centre *para* to it, the situation for secondary carbanionic **6**-Li$_l$·PMDTA is different. This could not be ascertained for previously reported **3**-Li$_l$·PMDTA [23], where crystallographic disorder meant that both the arene–(α-C) interaction and bonds within the aromatic ring were constrained. In the present case, both aromatic and lateral group carbon atoms could be refined freely, allowing us to compare bond lengths in *tert*-carbanion **5**-Li$_l$·PMDTA and *sec*-carbanion **6**-Li$_l$·PMDTA in Scheme 6. It is clear that bond–length alternation seen in **5**-Li$_l$·PMDTA (where the carbanion is best viewed as exhibiting pentadienyl character) is not replicated in **6**-Li$_l$·PMDTA. Instead, combined with the planarity of the ring system observed here, bond lengths in **6**-Li$_l$·PMDTA suggest the retention of aromaticity. Consistent with this, a torsion of only 6.1(3)° between directing and deprotonated groups (C(=O)–C–C–C(Li)) in **6**-Li$_l$·PMDTA contrasts with one of 32.6° in **5**-Li$_l$·PMDTA. The behaviour of the present system therefore contrasts with that reported previously for benzylically deprotonated analogues. Thus, benzyl anions [31-43] including amino- [44-46], phosphino- [47-49], thio-/sulfamido-/sulfimido- [50-53] and silylbenzyl anions [54-62], have all demonstrated long aryl–(α-C) distances (1.419–1.538 Å) with retention of aromaticity. In contrast, **5**-Li$_l$·PMDTA and laterally lithiated *N*-trimethylsilyl *o*-methylphenyldiphenylphosphinimine [63] demonstrated a short aryl-(α-C) distance (of 1.376(6) Å in both cases [20,63]) in tandem with a pentadienyl bonding pattern and significant perturbation of the aryl system. Uniquely, the secondary carbanion in **6**-Li$_l$·PMDTA shows both a short aryl–(α-C) distance *and* the significant retention of aromaticity.



Scheme 6: Comparison of aromatic and aryl–(α-C) bond distances in **5**-Li$_l$·L [20] and **6**-Li$_l$·L (L = PMDTA).

Similar charge delocalisation effects to those seen in **6**-Li$_l$·PMDTA are present in **6**-Li$_l$·DGME (Scheme 5, Figure 2 and Supporting Information File 2). Hence, the metal is wrapped by the amide and DGME oxygen atoms. Consistent with the view that oxygen is an inferior donor as compared with nitrogen (in PMDTA) and that DGME is a less sterically congesting donor additive than PMDTA, the solid-state structure of **6**-Li$_l$·DGME allows a significantly shorter (α-C)···Li distance of 2.418(6) Å. As was seen, however, for tertiary carbanion systems, the close approach of these two atoms need not incur any significant reorganisation of the geometry at C8, with both C8 and C9 lying essentially in the aromatic ring plane and the C6–C8–C9 bond angle of 124.9(3)° suggesting an essentially trigonal planar sp^2-hybridised carbanion. Akin to the short aryl–(α-C) distance in **6**-Li$_l$·PMDTA, that in the diglyme analogue is 1.377(5) Å. However, a point of significant contrast between the structures of **6**-Li$_l$·DGME and its PMDTA analogue is the C6–C1–C7–O1 torsional angle. Whereas this

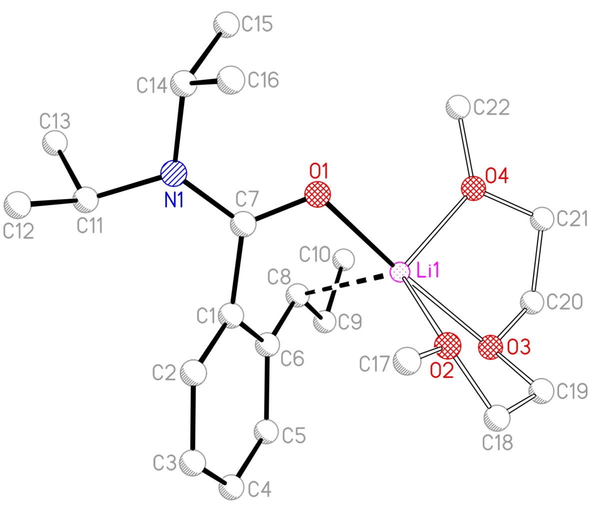


Figure 2: Molecular structure of **6**-Li$_l$·DGME; H-atoms omitted. Selected bond lengths (Å) and angles (°): O1–Li1 2.001(6), O2–Li1 2.058(6), O3–Li1 2.170(6), O4–Li1 2.036(6), C8···Li1 2.418(6), C8–C9 1.478(5), C9–C10 1.511(6), C8–C6 1.377(5), C6–C5 1.445(5), C5–C4 1.365(5), C4–C3 1.387(6), C3–C2 1.389(5), C2–C1 1.382(5), C1–C6 1.448(5), C6–C1–C7–O1 54.2(4), C7–C1–C6–C8 12.2(5).

was 88.4(2)° in the latter complex and >80° in each of the previously reported secondary carbanion systems **4**-Li$_l$·3THF [24] and **3**-Li$_l$·PMDTA [23], the (α-C)···Li interaction in **6**-Li$_l$·DGME reduces the torsional angle to only 54.2(4)°. In spite of this, at 1.485(5) Å the arene-directing group interaction is still long – arguing against any azaenolate contribution to anion stability.

NMR spectroscopic studies

NMR spectroscopic investigation of **6**-Li$_l$·PMDTA in [D$_8$]toluene solution reveals that dissolution affords multiple solution species. Limited reformation of the starting material **6**-H is observed (species #3, see Experimental section). This phenomenon has been seen in previous solution studies of the lateral metallates of aromatic tertiary amides [23] and is assumed to reflect the sensitivity of **6**-Li$_l$·PMDTA to traces of moisture in the deuterated solvent. However, in contrast to previous work, two forms of lateral metallate (#1 and #2, see Experimental section) are clearly seen. Based on previous work on the **4**-Li$_l$ system [64], we consider these two species to represent the *cis* and *trans* isomers of **6**-Li$_l$ that arise from slow rotation about the partially double arene–(α-C) bond in the PMDTA-solvated lithiate. The isomers exist in temperature independent major and minor forms, with the *trans* isomer assumed to dominate on steric grounds and the ratio between species approximating to 10:1:1 (#1:#2:#3). This can be clearly seen in the signals associated with the lateral alkyl chain, with a triplet and double doublet seen for the deprotonated methylene at δ 3.10 (#1) and 3.22 (#2) ppm, respectively, with **6**-H revealing a concomitant multiplet at δ 2.71–2.60 ppm. Consistent with the observation of essentially trigonal planar geometry at C8 in the solid-state structure of **6**-Li$_l$·PMDTA (Figure 1), both solution isomers reveal significantly deshielded deprotonated carbon centres. Hence, observed shifts of δ 67.1 (#1) and 71.9 (#2) ppm contrast with that of δ 35.3 ppm for the corresponding tetrahedral α-C in **6**-H. Although depletion of aromaticity was noted in the recently reported solid-state structure of tertiary carbanion **5**-Li$_l$·PMDTA, the character of the aromatic system in solution was less clear cut. While high-field aromatic signals (in the range of δ 6.94–5.78 ppm) were seen, computational studies suggested the close approach of the carbanionic centre and the metal, implying a more localised anionic charge in solution [20]. In the present case, the solid-state structure of **6**-Li$_l$·PMDTA reveals the clear retention of aromatic character and, in this context, it is noteworthy that ^{1}H NMR spectroscopic resonances of δ 6.90–5.58 (in major isomer #1) and 6.73–5.77 (in minor isomer #2) ppm compare closely with those seen for **5**-Li$_l$·PMDTA.

Just as ^{1}H NMR spectroscopy yields evidence for two lithiate structures in solution – in a ratio approximating to 10:1 – ^{1}H,^{7}Li-HOESY [65] reveals correlations between the major Li peak (δ 0.51 ppm) and ^{1}H signals which, at δ 3.10 (strong correlation), 2.08 (moderate) and 6.36 ppm (weak), represent the benzylic hydrogen atom, the central Me group of PMDTA and the *ortho* hydrogen atom, respectively (see Supporting Information File 3). An analysis of the corresponding through-space displacements in the solid-state structure of **6**-Li$_l$·PMDTA reveals H(benzylic)···Li and H(*ortho*)···Li (3.894(18) and 3.974(17) Å, respectively, viz. C8, C2) in the range expected to permit the observation of nOes [66]. This and theoretical results ([20] and see below) serve to reinforce the view that the dominant solution form of **6**-Li$_l$·PMDTA closely resembles the structure observed in the solid state insofar as the disposition of the partial double arene–(α-C) bond is *trans*. While the solid-state structure of **6**-Li$_l$·PMDTA also suggests the possibility of through-space interactions between the metal and NCH*Me* groups (viz. C15, C16), the well established dynamic behaviour of these latter groups [67] provides a rationale for the lack of associated nOes here. Similarly, the central PMDTA Me group (viz. C21) resides such that the associated hydrogen atoms are located 3–4 Å from the metal to which they reveal a HOESY correlation. However, while the terminal Me groups (viz. C17, C18, C24, C25) of the Lewis base also lie <4 Å from the metal, the lack of an associated correlation is consistent with greater dynamic activity. Lastly, the proposed model is consistent with the observation that the minor Li signal (δ 0.15 ppm) correlates only with the central PMDTA Me resonance at δ 2.08 ppm. *Cis*-**6**-Li$_l$·PMDTA might be expected to reveal a correlation between Li$^+$ and the β-hydrogen atoms of the deprotonated propyl group. However, both the low population of this species and the significant dynamic activity exhibited by the β-hydrogen atoms in solution – as evidenced by ^{1}H NMR spcectroscopy – significantly diminish the likelihood of observing such a correlation (see Supporting Information File 3).

The study of **6**-Li$_l$·DGME in [D$_8$]toluene by NMR spectroscopy reveals data comparable to that seen for the PMDTA system. In spite of the deployment of a Na mirror to dry the deuterated solvent, significant reformation of **6**-H is observed (species #3, see Experimental section) suggesting that the **6**-Li$_l$·DGME is highly solvent- and temperature-sensitive. The presence of hydrolyzed **6**-H is clear from the observation of the aliphatic region of the spectrum. Thus, the signals associated with the lateral alkyl chain in **6**-H reveal a multiplet (δ 2.69–2.58 ppm) for the α-CH$_2$, two multiplets (δ 1.79, 1.62 ppm) for the β-CH$_2$ and a triplet (δ 0.97 ppm) for Me. However, COSY reveals a laterally deprotonated species (#1) that expresses signals at δ 3.05 (α-CH), 2.35 (β-CH$_2$) and 1.36 ppm (Me). Comparable with what was seen for **6**-Li$_l$·PMDTA, the essentially trigonal planar geometry at C8 in the solid-state structure of **6**-Li$_l$·DGME appears to be reflected in solution, with a ^{13}C NMR shift of δ 64.6 ppm (α-CH, #1, cf. δ 67.1 ppm for the major isomer of **6**-Li$_l$·PMDTA) contrasting with that of δ 35.3 ppm (α-CH$_2$, #3). Lastly, the co-existence of two temperature-independent isomers of lateral lithiate (major #1, minor #2) can still be seen for the DGME system (see Experimental section). However, owing to the complexity of the spectra, the minor metallated form only expresses clear signals in the aromatic region of the ^{1}H NMR spectrum. An analysis of this reveals that the ratio between the three species approximates to 1:0.15:3 (#1:#2:#3). Hence, COSY correlations reveal signals at δ 7.13–7.00 ppm for **6**-H, at δ 6.88 (1H), 6.46 (1H), 6.38 (1H), 5.63 (1H) ppm for the dominant lithiate, and at δ 6.74 (0.15H), 6.63 (0.3H), 5.69 (0.15H) ppm for the minor lithiate.

Computational studies

The structures of **6**-Li$_l$·L (L = PMDTA, DGME) were optimised using density functional theory (DFT) calculations. For the use of either Lewis base, two isomeric forms of **6**-Li$_l$ were modelled. These were the *cis* and *trans* isomers expected to arise from slow rotation about the partially double arene–(α-C) bond (see above). For each Lewis base, calculation of the *trans* isomer identified two minimum energy structures with very different Li–C(carbanion) distances. In the case of **6**-Li$_l$·PMDTA these distances were 2.355 and 4.143 Å (Figure 3a and Figure 3b, respectively). The structure having the longer distance is found to be more stable by 2.6 kcal·mol^{-1}, this distance being close to the experimental value (4.107(4) Å). It is also possible to compare the measured C–C bond lengths in the aromatic ring and the exogenous C–C lengths with those

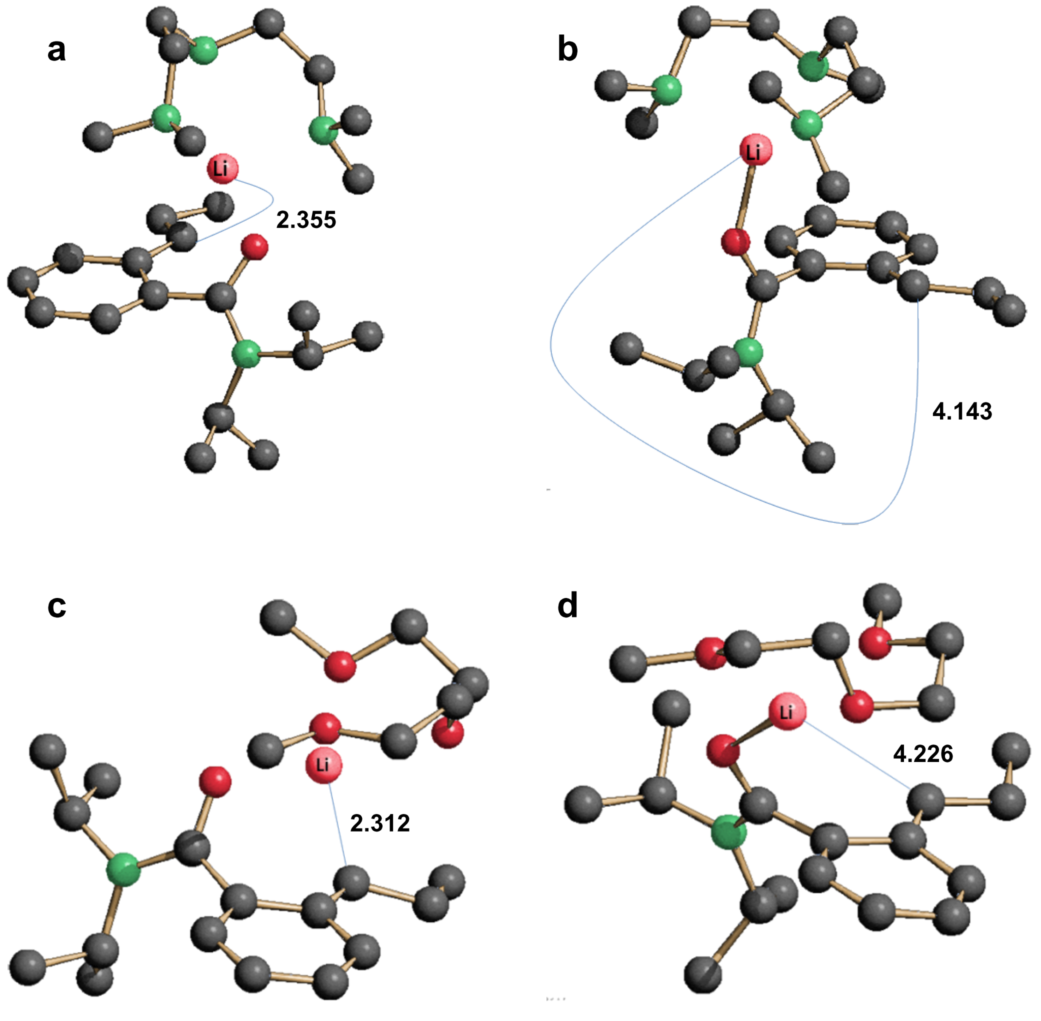


Figure 3: Computed minimum energy conformers (B3LYP density functional/6-311++G(2d,2p) basis set; H-atoms omitted for clarity) of *trans*-**6**-Li$_l$·PMDTA with and without a Li–(α-C) interaction (a and b) and *trans*-**6**-Li$_l$·DGME with and without a Li–(α-C) interaction (c and d).

predicted for the two structures by using the mean unsigned error (MUE) between the calculated and experimentally observed values. We found that the MUEs are 0.010 and 0.017 Å for the PMDTA-complexed structures with the long and short metal–carbon distances, respectively. Thus, in terms of the structure of the unsaturated ring, calculation of *trans*-**6**-Li$_l$·PMDTA favours the type of structure observed experimentally in the solid state.

A similar computational analysis to that undertaken for *trans*-**6**-Li$_l$·PMDTA also located two structures for *trans*-**6**-Li$_l$·DGME. However, in this case, the structure having the shorter Li–C(carbanion) distance (2.312 Å, Figure 3c) was computed to be more stable (by 2.4 kcal·mol^{-1}) than that expressing a longer distance (4.226 Å, Figure 3d). This theoretical result is in line with the corresponding distance measured in the solid-state structure (2.418(6) Å). Likewise, a comparison between the measured and predicted C–C distances involving the aromatic ring gave a similar result with MUE values of 0.009 and 0.010 Å found for the structures having short and long Li–C lengths, respectively.

Having computed the most stable *trans* forms of both the PMDTA and DGME complexes of **6**-Li$_l$, the corresponding *cis* isomers were modelled. These were found to be higher in energy; consistent with the view (see above) that they represent the less populous species in solution. Hence, *cis*-**6**-Li$_l$·PMDTA and *cis*-**6**-Li$_l$·DGME (see Supporting Information File 3) were 5.4 kcal·mol^{-1} and 2.2 kcal·mol^{-1} higher in energy than the minimum energy structures computed for each of *trans*-**6**-Li$_l$·PMDTA and *trans*-**6**-Li$_l$·DGME, respectively.

Conclusion

N,*N*-Diisopropyl-2-propylbenzamide **6**-H has undergone selective directed lateral metallation in the presence of both PMDTA and DGME (= L) to give the benzyllithium **6**-Li$_l$·L. Unlike previous examples of secondary carbanion formation under the influence of an aromatic tertiary amide directing group, the solid-state structure of **6**-Li$_l$·PMDTA is sufficiently well resolved to reveal (i) the sp^2 geometry of the deprotonated α-C centre, including the location of the remaining hydrogen atom and, (ii) the lengths of the arene–(α-C) bond and those that form the aromatic system. An analysis of the C–C bond lengths shows that, in contrast to all previously reported benzylic lithiates, the secondary carbanion in **6**-Li$_l$·PMDTA shows both a short arene–(α-C) distance as well as a flat, essentially unperturbed aromatic ring. Similar observations pertain for **6**-Li$_l$·DGME. Whereas these data contrast with those reported recently for structurally authenticated tertiary carbanions, significant similarities are seen insofar as the connectivity of the alkali metal is concerned when changing tridentate Lewis bases. Thus, whereas **6**-Li$_l$·PMDTA fails to show a Li–(α-C) interaction in the solid state, in Li$_l$·DGME the corresponding distance (2.406(6) Å) suggests an interaction with the amide-arene torsional angle reduced accordingly. DFT analysis successfully reproduces both the bonding patterns seen experimentally in the anionic component of **6**-Li$_l$·L and also the varying propensity of the metal for involvement with the formally deportonated C-centre in the presence of different Lewis bases.

In contrast to previous work on carbanion formation in the presence of an aromatic N+O directing group, **6**-Li$_l$·L dissolves in hydrocarbon media to reveal two structures in solution. Based on previous work and new DFT studies, we ascribe these as being *cis* (minor) and *trans* (major) isomers based on partial double bond character in the arene–(α-C) bond. ^{1}H,^{7}Li-HOESY on the PMDTA complex supports this view by revealing a correlation between the metal and the remaining benzylic hydrogen atom in this system. However, the observation that this correlation is substantially stronger than that between the metal and the remaining *ortho* hydrogen centre suggests that the structure of the major solution isomer of **6**-Li$_l$·PMDTA may involve the metal approaching the benzylic position more closely than is seen in the solid-state structure. These data therefore suggest that, as was recently noted for the analogous tertiary carbanion complexes [20], the major form of **6**-Li$_l$·PMDTA in solution shows strong similarities to the solid-state structure of **6**-Li$_l$·DGME.

Further studies will seek to further probe the solution behaviour observed for **6**-Li$_l$·L to better understand the relationship between the identity and structure of the tridentate Lewis base and the propensity of the metal and deprotonated α-C centre to interact. In particular, tandem theoretical and NMR spectroscopic studies will seek to elucidate whether polydentate Lewis bases may exhibit dynamic and variable hapticity with respect to the lithium ion in solution, potentially leading to the interconversion of different solution structures. Synthetic work will focus on employing the reported lateral metallates synthetically using a range of electrophiles. Of major interest will be the study of how steric encumbrance controls applications, particularly in the field of generating aromatics with chiral substituents at the 2-position.

Experimental

General synthetic and analytical details

Reactions and manipulations were carried out under dry N$_2$ using standard double manifold and glove box techniques. Solvents were distilled off from sodium (toluene) or sodium-potassium amalgam (hexane) immediately before use. PMDTA and DGME were distilled from sodium at reduced pressure and stored over molecular sieves (4 Å) and *t*-BuLi (1.7 M in pentane) was purchased from Aldrich and used as received. NMR data were collected on a Bruker 500 (500.20 MHz for ^{1}H, 125.80 MHz for ^{13}C and 194.40 MHz for ^{7}Li) FT NMR spectrometer. Spectra were obtained at 300 K and chemical shifts are internally referenced to the deuterated solvent and calculated relative to TMS for ^{1}H and {^{1}H}^{13}C. For ^{7}Li a LiCl (1 M in D$_2$O) reference was employed. Chemical shifts are expressed in δ ppm. [D$_8$]toluene was stored under N$_2$ over a Na mirror. The following abbreviations are used for NMR spectra: s = singlet, d = doublet, t = triplet, sept = septet, (v) br = (very) broad and m = multiplet.

General crystallographic details

Single crystal data were collected using the 'oil drop technique' [68] to mount crystals on a Nonius Kappa-CCD equipped with an Oxford Cryostream low-temperature device. Structures were solved using direct methods [29], with refinement, based on F^2, by full-matrix least squares [30]. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-853884 and -853885. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; email: deposit@ccdc.cam.ac.uk).

6-H: *N*,*N*-Diisopropyl-2-propylbenzamide was prepared from *N*,*N*-diisopropylbenzamide using a modified literature method [25]. Yield 1.11 g (90%); ^{1}H NMR (500 MHz, [D$_8$]toluene, 300 K) δ 7.13–7.00 (m, 4H, Ar), 3.54 (sept, ^{3}J(H,H) = 7 Hz, 1H, NCH), 2.99 (sept, ^{3}J(H,H) = 7 Hz, 1H, NCH), 2.73–2.61 (m, 2H, ArC*H*$_2$), 1.92–1.80 (m, 1H, ArCH$_2$C*H*$_2$), 1.70–1.58 (m, 1H, ArCH$_2$C*H*$_2$), 1.66 (d, ^{3}J(H,H) = 7 Hz, 3H, NCMe), 1.64 (d, ^{3}J(H,H) = 7 Hz, 3H, NCMe), 1.00 (d, ^{3}J(H,H) = 7 Hz, 3H, ArCH$_2$CH$_2$*Me*), 0.68 (d, ^{3}J(H,H) = 7 Hz, 6H, NCMe$_2$) ppm; {^{1}H}^{13}C NMR (500 MHz, [D$_8$]toluene, 300 K) δ 169.6 (C=O), 138.9 (C-Ar), 138.7 (C-Ar), 129.5 (CH-Ar), 127.9 (CH-Ar), 125.7 (CH-Ar), 125.0 (CH-Ar), 50.1 (NCH), 45.4 (NCH), 35.4 (Ar*C*H$_2$), 24.7 (ArCH$_2$*C*H$_2$), 20.4 (NCMe), 20.2 (NCMe), 20.0 (NCMe$_2$), 14.4 (ArCH$_2$CH$_2$*Me*) ppm.

6-Li$_l$·PMDTA: *t*-BuLi (0.15 mL, 1.7 M in pentane, 0.25 mmol) was added to a solution of **6**-H (0.07 g, 0.25 mmol) in toluene/hexane (0.5:0.1 mL) containing freshly distilled *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA, 0.05 mL, 0.25 mmol) under nitrogen at −78 °C. The purple solution which resulted was warmed to room temperature before being stored at −30 °C for 3 days to yield red crystals of **6**-Li$_l$·PMDTA. Yield 60 mg (56%); mp 101–103 °C; ^{1}H NMR (500 MHz, [D$_8$]toluene, 273 K, #1 **6**-Li$_l$·PMDTA major isomer, #2 **6**-Li$_l$·PMDTA minor isomer, #3 **6**-H) δ 7.13–7.00 (m, 0.4H, Ar#3), 6.90 (ddd, *J*(H,H) = 8, 7, 1 Hz, 1H, Ar#1), 6.73 (dd, *J*(H,H) = 8, 1 Hz, 0.09H, Ar#2), 6.69 (ddd, *J*(H,H) = 9, 6, 2 Hz, 0.09H, Ar#2), 6.65 (dd, J(H,H) = 9, 1 Hz, 0.09H, Ar#2), 6.38 (dd, *J*(H,H) = 8, 2 Hz, 1H, Ar#1), 6.36 (d, *J*(H,H) = 8 Hz, 1H, Ar#1), 5.77 (ddd, *J*(H,H) = 8, 6, 1 Hz, 0.09H, Ar#2), 5.58 (dd, *J*(H,H) = 7, 7 Hz, 1H, Ar#1), 4.78 (sept, ^{3}J(H,H) = 6 Hz, 0.09H, NCH#2), 4.3–3.7 (v br m, 2H, NCH#1), 3.55 (sept, ^{3}J(H,H) = 7 Hz, 0.1H, NCH#3), 3.22 (dd, ^{3}J(H,H) = 6, 4 Hz, 0.09H, ArC*H*#2), 3.10 (t, ^{3}J(H,H) = 6 Hz, 1H, ArC*H*#1), 3.06 (m, 0.2H, NCH#2 + NCH#3), 2.71–2.60 (m, 0.2H, ArC*H*$_2$#3), 2.41 (m, 2H, ArCHC*H*$_2$#1), 2.25–1.60 (v br m, 9.52H, CH$_2$-PMDTA), 2.08 (s, 17.85H, Me-PMDTA), 2.02 (v br m, ~0.22H, ArCHC*H*$_2$#2 or ArCHCH$_2$*Me*#2), 1.92–1.80 (m, 0.1H, ArCH$_2$C*H*$_2$#3), 1.70–1.58 (m, 0.1H, ArCH$_2$C*H*$_2$#3), 1.63 (d, ^{3}J(H,H) = 5 Hz, 0.3H, NCMe#3), 1.62 (d, ^{3}J(H,H) = 4 Hz, 0.3H, NCMe#3), 1.60 (d, ^{3}J(H,H) = 7 Hz, 0.27H, NCMe#2), 1.47 (v br m, ≈0.22H, ArCHC*H*$_2$#2 or ArCHCH$_2$*Me*#2), 1.45 (d, ^{3}J(H,H) = 7 Hz, 0.27H, NCMe#2), 1.44 (t, ^{3}J(H,H) = 6 Hz, 3H, ArCHCH$_2$*Me*#1), 1.32–1.10 (br m, 12H, NCMe#1), 1.06 (d, ^{3}J(H,H) = 6 Hz, 0.27H, NCMe#2), 0.98 (t, ^{3}J(H,H) = 7 Hz, 0.3H, ArCH$_2$CH$_2$*Me*#3), 0.84 (d, ^{3}J(H,H) = 7 Hz, 0.27H, NCMe#2), 0.73 (d, ^{3}J(H,H) = 7 Hz, 0.3H, NCMe#3), 0.72 (d, ^{3}J(H,H) = 7 Hz, 0.3H, NCMe#3) ppm; {^{1}H}^{13}C NMR (125 MHz, [D$_8$]toluene, 273 K, #1 **6**-Li$_l$·PMDTA major isomer, #2 **6**-Li$_l$·PMDTA minor isomer, #3 **6**-H) δ 179.4 (C=O#1), 177.4 (C=O#2), 169.5 (C=O#3), 146.6 (C-Ar#2), 144.7 (C-Ar#1), 138.9 (C-Ar#3), 138.7 (C-Ar#3), 130.1 (CH-Ar#2), 130.0 (CH-Ar#1), 129.4 (CH-Ar#3), 127.8 (CH-Ar#3), 127.0 (CH-Ar#1), 126.7 (CH-Ar#2), 125.6 (CH-Ar#3), 124.9 (CH-Ar#3), 123.1 (CH-Ar#2), 113.9 (C-Ar#1), 112.0 (CH-Ar#1), 108.8 (C-Ar#2), 99.9 (CH-Ar#2), 96.3 (CH-Ar#1), 71.9 (Ar*C*H#2), 67.1 (Ar*C*H#1), 57.1 (CH$_2$-PMDTA), 53.8 (CH$_2$-PMDTA), 51.2 (NCH#1), 50.0 (NCH#3), 45.3 (NCH#3), 45.0 (Me-PMDTA), 43.8 (Me-PMDTA), 35.3 (Ar*C*H$_2$#3), 26.3 (ArCH*C*H$_2$#2), 24.5 (ArCH2*C*H$_2$#3), 22.6 (ArCH*C*H$_2$#1), 22.5 (NC*Me*#2), 21.2 (NC*Me*#1), 21.0 (NC*Me*#1), 20.4 (NC*Me*#3), 20.2 (NC*Me*#3), 20.0 (NC*Me*#3), 17.4 (ArCHCH$_2$*Me*#2), 16.8 (ArCHCH$_2$*Me*#1), 14.2 (ArCH$_2$CH$_2$*Me*#3) ppm; ^{7}Li NMR (194 MHz, [D$_8$]toluene, 273 K, #1 **6**-Li$_l$·PMDTA major isomer, #2 **6**-Li$_l$·PMDTA minor isomer) δ 0.51 (s, #1), 0.15 (s, #2) ppm; anal. calcd for $C_{25}H_{47}LiN_4O$: C, 70.38; H, 11.10; N, 13.13; found: C, 70.34; H, 10.83; N, 12.33; crystal data for **6**-Li·PMDTA: $C_{25}H_{47}LiN_4O$, $M = 426.61$, monoclinic, space group $P2_1/n$, $a = 9.6194(2)$, $b = 29.1721(8)$, $c = 10.0296(3)$ Å, $\beta = 102.643(2)°$, $V = 2746.24(13)$ Å^3, $Z = 4$, $\rho_{\mathrm{calcd}} = 1.032$ g cm^{-3}; Mo Kα radiation, $\lambda = 0.71070$ Å, $\mu = 0.063$ mm^{-1}, $T = 180$ K; 14239 data (4461 unique, $R_{\mathrm{int}} = 0.0477$, $\theta < 24.40°$) were collected on a Nonius Kappa CCD diffractometer. Structure solved by direct methods and refined by full-matrix least-squares on F^2 values of all data giving $wR2 = \{\Sigma[w(F_o^2\text{-}F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2} = 0.1261$, conventional $R = 0.\ 0493$ for F values of 2591 reflections with $F_o^2 > 2\sigma(F_o^2)$, $GoF = 0.976$ for 310 parameters. Residual electron density extrema 0.159 and −0.141 eÅ^{-3}.

6-Li$_l$·DGME: *t*-BuLi (0.15 mL, 1.7 M in pentane, 0.25 mmol) was added to a solution of **6**-H (0.07 g, 0.25 mmol) in toluene/hexane (0.3:0.1 mL) containing diglyme (DGME, 0.04 mL, 0.25 mmol) under nitrogen at −78 °C. The resulting purple solution was warmed to room temperature and stored at −30 °C for 3 days to yield red crystals of **6**-Li$_l$·DGME. Yield 44 mg (45%); mp <25 °C; ^{1}H NMR (500 MHz, [D$_8$]toluene, 253 K, #1 **6**-Li$_l$·DGME major isomer, #2 **6**-Li$_l$·DGME minor isomer, #3 **6**-H) δ 7.13–7.00 (m, 12H, Ar#3), 6.88 (dd, ^3J(H,H) = 7, 8 Hz, 1H, Ar#1), 6.74 (d, ^3J(H,H) = 8 Hz, 0.15H, Ar#2), 6.63 (m, 0.3H, Ar#2), 6.46 (d, ^3J(H,H) = 7 Hz, 1H, Ar#1), 6.38 (d, ^3J(H,H) = 9 Hz, 1H, Ar#1), 5.69 (m, 0.15H, Ar#2), 5.63 (dd, ^3J(H,H) = 6, 7 Hz, 1H, Ar#1), 4.4–3.6 (v br m, 2H, NCH#1), 3.54 (m, 3H, NCH#3), 3.39 (t, ^3J(H,H) = 4 Hz, 16H, CH$_2$-DGME), 3.27 (t, ^3J(H,H) = 5 Hz, 16H, CH$_2$-DGME), 3.15 (s, 24H, Me-DGME), 3.08 (m, 3H, NCH#3), 3.05 (m, 1H, ArC*H*#1), 2.69–2.58 (m, 6H, ArC*H*$_2$#3), 2.35 (m, 2H, ArCHC*H*$_2$#1), 1.79 (m, 3H, ArCH$_2$C*H*$_2$#3), 1.62 (m, 3H, ArCH$_2$C*H*$_2$#3), 1.61 (d, ^3J(H,H) = 7 Hz, 9H, NCMe#3), 1.60 (d, ^3J(H,H) = 7 Hz, 9H, NCMe#3), 1.36 (t, ^3J(H,H) = 7 Hz, 3H, ArCHCH$_2$*Me*#1), 1.24 (br m, 6H, NCMe#1), 1.13 (br m, 6H, NCMe#1), 0.97 (t, ^3J(H,H) = 7 Hz, 9H, ArCH$_2$CH$_2$*Me*#3), 0.73 (d, ^3J(H,H) = 7 Hz, 18H, NCMe#3) ppm; {^{1}H}^{13}C NMR (125 MHz, [D8]toluene, 273 K, #1 **6**-Li$_l$·DGME major isomer, #2 **6**-Li$_l$·DGME minor isomer, #3 **6**-H) δ 179.5 (C=O#1), 177.2 (C=O#2), 169.6 (C=O#3), 145.9 (C-Ar#1), 138.7 (C-Ar#3), 138.6 (C-Ar#3), 137.5 (C-Ar#1), 130.8 (CH-Ar#2), 130.1 (CH-Ar#1), 129.4 (CH-Ar#3), 127.8 (CH-Ar#3), 127.1 (CH-Ar#1), 126.5 (CH-Ar#2), 125.6 (CH-Ar#3), 125.0 (CH-Ar#3), 122.6 (CH-Ar#2), 112.4 (CH-Ar#1), 99.2 (C-Ar#2), 97.6 (CH-Ar#1), 71.5 (CH$_2$-DGME), 70.1 (CH$_2$-DGME), 64.6 (Ar*C*H#1), 58.4 (Me-DGME), 50.1 (NCH#3), 45.4 (NCH#2), 35.3 (Ar*C*H$_2$#3), 24.4 (ArCH$_2$*C*H$_2$#3), 22.3 (ArCH*C*H$_2$#1), 20.4 (NC*Me*#3), 20.2 (NC*Me*#3), 20.0 (NC*Me*$_2$#3), 16.6 (ArCHCH$_2$*Me*#1), 14.2 (ArCH$_2$CH$_2$*Me*#3) ppm; ^{7}Li NMR spectroscopy (194 MHz, [D$_8$]toluene, 273 K, #1 **6**-Li$_l$·DGME major isomer, #2 **6**-Li$_l$·DGME minor isomer) δ 0.62 (s, #2), 0.26 (s, #1) ppm; anal. calcd for $C_{22}H_{38}LiNO_4$: C, 68.19; H, 9.88; N, 3.61; found: C, 68.00; H, 9.62; N, 4.12; crystal data for **6**-Li$_l$·DGME: $C_{22}H_{38}LiNO_4$, M = 387.47, monoclinic, space group $P2_1/n$, a = 7.8821(16), b = 18.975(4), c = 15.737(3) Å, β = 92.84(3)°, V = 2350.8(8) Å^3, Z = 4, ρ_{calcd}= 1.095 g cm^{-3}; Mo Kα radiation, λ = 0.71073 Å, μ = 0.073 mm^{-1}, T = 173 K. 13765 data (4238 unique, R_{int} = 0.0425, θ < 25.31°) were collected on a Nonius Kappa CCD diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 values of all data to give $wR2 = \{\Sigma[w(F_o{}^2 - F_c{}^2)^2]/\Sigma[w(F_o{}^2)^2]\}^{1/2}$ = 0.2729, conventional R = 0. 0938 for F values of 2961 reflections with $F_o{}^2 > 2\sigma(F_o{}^2)$, GoF = 1.040 for 253 parameters. Residual electron density extrema 0.729 and −0.616 eÅ^{-3}.

Computational details

Geometry optimisation of *cis*/*trans*-**6**-Li$_l$·L (L = PMDTA, DGME) was carried out using the B3LYP density functional and a 6-311++G(2d,2p) basis and Gaussian 09 (see Supporting Information File 3). To give free energy differences relevant to the solid state, thermodynamic corrections (at the B3LYP/6-311G(2d,2p) level) and condensed phase effects, using the CPCM model (at the B3LYP/6-311++G(2df,2dp) level) with a dielectric constant of 2.37, were included.

Supporting Information

Supporting Information File 1

Crystallographic data for **1**-Li·PMDTA.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-5-S1.cif]

Supporting Information File 2

Crystallographic data for **1**-Li·DGME.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-5-S2.cif]

Supporting Information File 3

NMR spectroscopic data and DFT calculations for **6**-Li$_l$·L (L = PMDTA, DGME).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-5-S3.pdf]

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