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Title: Lithium-Bromide Exchange versus Nucleophilic Addition of Schiff's base: unprecedented tandem cyclisation pathways S. A. Orr[a], E. C. Border[b], P. C. Andrews*[a] and V. L. Blair*[a]

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FULL PAPER

Lithium-Bromide Exchange versus Nucleophilic Addition of Schiff's base: unprecedented tandem cyclisation pathways

S. A. Orr[a], E. C. Border[b], P. C. Andrews*[a] and V. L. Blair*[a]

Dedication ((optional))

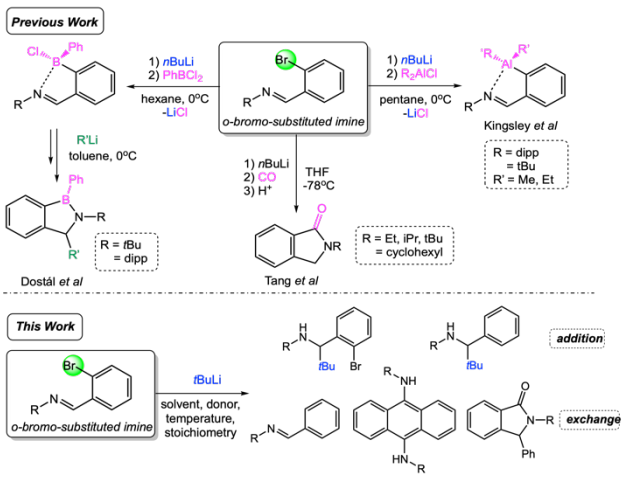
Abstract: By exploring lithium-bromide exchange reactivity of aromatic Schiff's bases with *tert*-butyllithium (*t*BuLi) we have revealed unprecedented competitive intermolecular and intramolecular cascade annulation pathways leading to valuable compounds such as *iso*-indolinones and N-substituted anthracene derivatives. A series of reaction parameters were probed including solvent, stoichiometry, sterics and organolithium reagent choice in order to understand the influences limiting such ring closing pathways. In the case of having two viable reactivity options for the organolithium on the imine; namely nucleophilic addition or lithium-bromide exchange, a surprising competitive nature was observed where nucleophilic addition dominated, even under cryogenic conditions. Considering the most commonly used solvents for lithium-bromide exchange, tetrahydrofuran (THF) and diethyl ether (Et_2O), contrasting reactivity outcomes were revealed with nucleophilic addition promoted in THF, while Et_2O yielded almost double the conversion of cyclic products than in THF.

Introduction

Imines, because of the reactivity of the carbon nitrogen double bond, are valuable precursors for the synthesis of many complex molecules. The simplicity in preparing functionalised azomethine derivatives in high yields, with minimal purification, from the condensation reaction between a primary amine and a carbonyl containing compound makes them both desirable and versatile precursors. Also known as Schiff's bases, they are typically employed in the preparation of amines,[1] in multifunctional ligand design for metal complexation,[2] in polymerisation[3] and in the construction of pharmaceutical-based scaffolds.[4] As a result, there is ongoing interest in developing and establishing new synthetic strategies for the adaptation and functionalisation of these valuable N-containing building blocks.

To generate new high value molecules, imines are often treated with an organolithium reagent. In the case of aryl imines, the carbon-nitrogen functionality is weakly directing hence *ortho*-directed lithiation is typically not observed, though it has been observed in some specific cases.[5] More commonly, aryl imines undergo 1,2 nucleophilic addition providing access to optically pure amines in the presence of a chiral, non-racemic ligand. The facile and thermodynamically favoured nature of this 1,2-addition reaction has been reinforced by recent studies from the groups of Hevia and Capriati showing such reactivity even in deep eutectic solvents and water.[6]

Given the challenge of ring metalation, specifically *ortho*-lithiation, an alternative methodology of lithium-bromide exchange at the *ortho*- site has been successfully employed. Recent studies from Tang, Kingsley and Dostál have shown this approach can generate *ortho*-lithiated aryl imines *in-situ*. These can be further functionalised to give new aluminium,[7] titanium[8] and benzaborole[9] compounds using simple metathesis pathways, and *iso*-indolinones from CO insertion followed by cyclisation[10] (Scheme 1). However, insight into the structural composition of the lithium intermediates have, to date, not been crystallographically determined. In these cases, the possible competing nucleophilic addition reaction was not observed, perhaps somewhat expected given the reported and often accepted rapid rate of lithium-bromide exchange, even at very low temperatures.[11] There is, though, a single example of alternative reactivity, where employing the bulky lithium reagent, $[(HMe_2Si)_3CLi]$, led to the formation of vinylbis(silanes) instead of facilitating lithium-halogen exchange. [12]



Scheme 1. Previously reported lithium-bromide exchange of imines and our work.

The lithium-halogen exchange reaction remains one of the most fundamental synthetic transformation strategies used to

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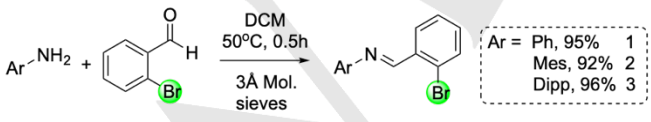
regioselectively form new C-C and C-X bonds allowing new organic molecules to be constructed from simpler organic scaffolds.[13] The highly facile nature of the reaction demands cryogenic conditions along with excess alkyllithium to control the equilibria.[11] As such, it is often invaluable for protecting sensitive functional groups, and increasing tolerance towards nucleophilic addition and/or metalation. The boundaries of lithium-bromide exchange are continually developing with flow chemistry now offering an alternative method to overcome any functional group sensitivity, with rapid transmetalation to more stable organometallic complexes which can be further functionalised.[14] Whilst specially designed organolithium systems allow the successful lithium-bromide exchange under non-cryogenic temperatures.[15] Surprisingly despite their synthetic relevance, the study of lithium-bromide exchange of aryl imines prior to further reactivity remains absent from the literature.

Herein we report the unforeseen reactivity of commonplace *ortho*-bromo-substituted aryl imine precursors with butyllithium, revealing an unanticipated competition pathway between the expected fast lithium-bromide exchange and normally unfavorable nucleophilic addition, resulting in synthetically valuable substituted *iso*-indolinones and anthracenes. *Iso*-indolinones are crucial heterocycles in pharmaceutical chemistry being abundant in numerous natural products and displaying a wide range of biological properties including activity towards drug resistant bacteria.[16] Whilst substituted polyaromatics have been reported to possess interesting material chemistry applications in OLEDs.[17] The sequential C-C bond forming mechanistic pathways for these one pot cascade reactivities are proposed, with a comprehensive study of reaction parameters.

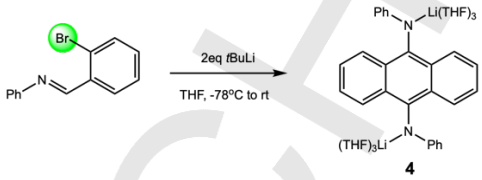
Results and Discussion

The benchmark imine used in this study was 2-bromophenylbenzylidene (**1**) which was prepared according to our previously reported microwave procedure in high yields from 2-bromobenzaldehdye and aniline in dichloromethane at 50°C for 30 minutes.[18] The resulting yellow oil, which displayed light sensitivity, was fully characterised by ^{1}H and ^{13}C NMR spectroscopy, with the distinct C*H*=N imine resonance at 8.87 ppm providing an NMR handle for nucleophilic addition reactivity. The mesityl (**2**) and diisopropyl (**3**) functionalised aniline derivatives were prepared in the same manner using the corresponding amine derivative (Scheme 2).



Scheme 2. Microwave synthesis of *ortho*-bromosubstituted imines.

The first reaction studied was that targeting specifically lithium-bromide exchange. Compound **1** was treated with two equivalents of *tert*-butyllithium (*t*BuLi) at -78°C in tetrahydrofuran (THF) and allowed to warm to room temperature (Scheme 3). After one week, a small crop of red needle crystals deposited from the red solution.



Scheme 3. Synthesis of Compound **4**.

Single crystal X-ray diffraction studies revealed the unexpected formation of monomeric [anthracene-9,10-(NPhLi.THF$_3$)$_2$] (**4**) Figure 1 in which an anthracene unit is substituted at the 9 and 10 positions with a lithium phenylamide moiety with the Li atoms solvated by three molecules of THF. The planar core of the anthracene unit confirms a fully delocalised system with average C=C bond lengths of 1.412 Å which is comparable to literature values.[19] The pendant amido group, C8-N1, is almost co-planar with the anthracene core (deviation from plane <5°), with the nitrogen atom sitting in a distorted trigonal planar arrangement (bond angles ∑ 357.58°), while the phenyl groups are orientated anti- to the plane of the central anthracene molecule. The lithium cations adopt a slightly distorted tetrahedral geometry (bond angles ∑ 653.69°) bonding to the nitrogen atom and three THF molecules.

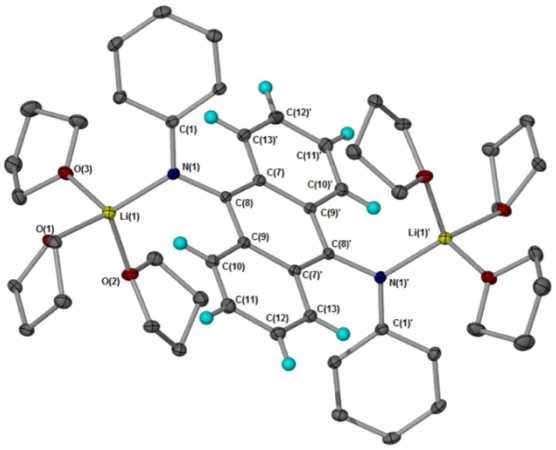


Figure 1. Molecular structure of [anthracene-9,10-(NPhLi.THF$_3$)$_2$] (**4**) with thermal ellipsoids drawn at the 50% probability level and hydrogen atoms omitted for clarity. Symmetry transformations used to generate equivalent atoms labelled ‘: 1-x, 1-y, 1-z. Bond lengths and angles; Li1-O1, 1.971(2), Li1-O2, 1.977(2), Li1-O3, 1.961(2), Li1-N1, 1.989(2), N1-C1, 1.3648(16), N1-C8, 1.4129(15), C8-C7, 1.4180(18), C8-C9, 1.4205(18), C9-C10, 1.4326(18), C10-C11, 1.3657(19), C11-C12, 1.4223(19), C12-C13, 1.3603(19), Li1-N1-C1, 124.50(10), Li1-N1-C8, 114.44(10), C1-N1-C8, 118.64(10), O1-Li1-O2, 104.45(10), O1-Li1-O3, 101.46(11), O2-Li1-O3, 97.55(11), O1-Li1-N1, 120.50(12), O2-Li1-N1, 113.63(11), O3-Li1-N1, 116.09(11), N1-C8-C7, 122.97(11), N1-C8-C9, 119.50(11).

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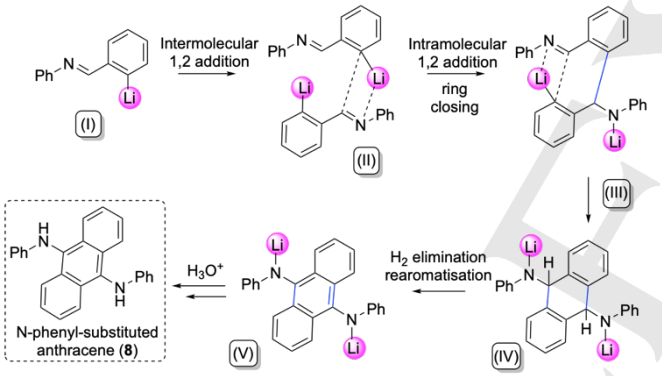
Scheme 4 illustrates the proposed formation of the anthracene compound (**4**). This can be termed as a 'head to tail' nucleophilic addition process. The *ortho*-lithiated molecule (Scheme 4, **I**) undergoes intermolecular 1,2-addition resulting in homocoupling between two imine molecules (Scheme 4, **II**), which can then ring close via a secondary intramolecular addition (Scheme 4, **IV**). However, it is also plausible that instead of a sequential two-step ring closing process a concomitant double addition could occur. Finally, hydrogen evolution driven by re-aromatisation results in the anthracene skeleton (Scheme 4, **V**) confirmed by the isolation of compound **4**. To the best of our knowledge this is the first report of a lithium-directed approach facilitating anthracene formation. The closest literature example is a serendipitous result arising from diorganodiselenides containing an iminoaryl group, which in the presence of sodium metal and zinc chloride results in the formation of a cis-9,10-bis(arylamino)-9,10-dihydroanthrancene species. This is believed to proceed via a radical intermediate.[20] A similar result, originating from an *ortho*-bromo substituted aryl imine, is the formation of a titanium 9,10-dihydrophenanthrenediamide accessed via *ortho*-lithiation and subsequent transmetallation with $TiCl_4$.[8] In our system no other metal salt is present for metathesis to occur and hence the reactive lithiated species couples with itself via 1,2 nucleophilic addition.



Scheme 4. Proposed mechanism for the formation of N-phenyl-substituted anthracene **4**.

The isolation of this unexpected product led us to probe the reaction process in more depth. The reaction was repeated using the same conditions and after 18 hours, hydrolysed. The crude product was then studied by GC-MS, revealing an array of cyclic and acyclic compounds shown in Figure 2. At least four classes of compounds could be identified: amines from nucleophilic addition (**5**+**5a**), imine (**6**) from Li/Br exchange, *iso*-indolinone derivatives (**7**) and anthracene species (**8**) both resulting from combined exchange and cyclisation pathways. For simplicity, the resultant cyclised products have been categorised as **7** and **8** although the composition of these mixtures are further detailed in the Supporting Information, including the characterisation of a hydroxyl *iso*-indolinone (**7a**) and a bromo-aryl substituted isoindolinone (**9**). Given the inherent rapid nature of lithium-bromide exchange, it is surprising that the major species from the reaction arises not from exchange process but from the 1,2 addition of *t*BuLi across the imine bond.

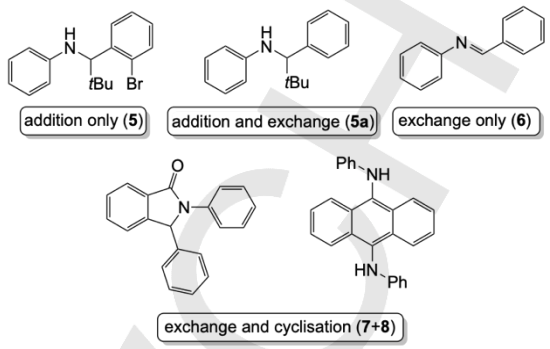
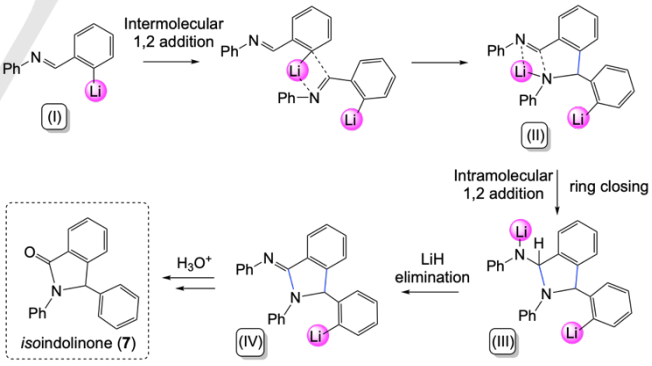


Figure 2. Identified products from the reaction of **1** and *t*BuLi.

Considering the resulting cyclised products, the major *iso*-indolinone **7** and minor N-substituted anthracene **8**, it can be concluded that two concurrent mechanisms are at play. Both follow the same initial step of Li/Br exchange resulting in species (Scheme 5, **I**), however following this, a second competitive pathway is available as proposed in Scheme 5. In the case of *iso*-indolinones, a 'head to head' intermolecular nucleophilic addition can occur to give species (Scheme 5, **II**), which can then undergo a further intramolecular addition resulting in ring closing step to yield species (Scheme 5, **III**). The elimination of lithium hydride (LiH) results in the formation of *iso*-indolinimine (Scheme 5, **IV**) which upon work-up undergoes hydrolysis to the desired *iso*-indolinone (**7**).



Scheme 5. Proposed mechanism for the formation of *iso*-indolinones.

Due to the importance of the *iso*-indolinone skeleton many methods have been described for their synthesis. Among the suite of synthetic methodologies available, two main approaches dominate namely; functionalisation of pre-constructed bicyclic scaffolds, such as phthalimide derivatives,[21] or the synthesis of a γ-lactam core via cyclisation reactions.[22] Relevant examples include lithiation and annulation methodologies,[23] with a recent report describing *ortho*-bromo-substituted aryl-alkyl imines as a route to *iso*-indolinones (Scheme 1).[10,24] In contrast to our

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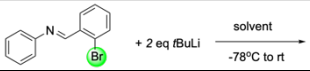
intermolecular cyclisation pathway, the imine undergoes selective lithium-bromide exchange to which toxic carbon monoxide inserts into the C-Li bond which upon rearrangement yields an *iso*-indolinone. Interestingly no evidence of a competing nucleophilic addition pathway was described suggesting Schiff bases display differing reactivity dependent on their substituents being alkyl or aromatic. The cascade reactivity observed in this work is also reliant upon the *ortho*-position of the bromine. This is demonstrated by previous studies whereby *t*BuLi will undergo clean nucleophilic addition of a *para*-bromo-substituted diarylimine with no lithium-bromide exchange observed.[6] Alternatively increasing the sterics surrounding the bromine atom, such as a bromo-substituted bis(imino)phenyl NCN ligand, can switch off the nucleophilic addition site for reactivity and facilitate solely lithium-bromide exchange.[25] Given the importance of the resultant cyclised products, a range of reaction parameters were probed in a bid to understand the reaction pathways.

Solvent studies

To determine the effect solvent may have on both the diversity and ratio of final products obtained, we studied a range of solvents with differing polarities (ε = 1.9 - 7.6) alongside the addition of Lewis bases, including TMEDA (N,N,N',N'-tetramethylethylenediamine) and PMDETA (N,N,N',N''-pentamethyldiethylenetriamine), as co-solvents, as summarised in Table 1.

Table 1. Influence of solvent on Li/Br exchange of compound **1**.[a]



Entry	Solvent	**5** (%)	**5a** (%)	**6** (%)	**7** and **8** (%)[b]	Other (%)
1	THF	6	56	0	38	0
2	Et_2O	0	23	1	72	4
3	toluene	0	29	0	64	7
4	hexane/ PMDETA[c]	0	37	0	61	2
5	hexane/ TMEDA[c]	16	39	0	45	0
6	hexane	14	30	0	53	3

[a] Determined by GC-MS. [b] Combined conversion of cyclic derivatives, see SI for full ratios. [c] Reaction in bulk hexane with 2 equivalents of donor. [d] Commercial solution of *t*BuLi (1.7M in pentane).

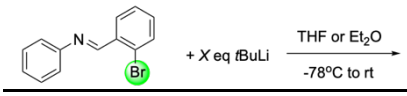
All reactions were performed under the same conditions only varying the bulk solvent. The resulting mixtures were hydrolysed and the organic components extracted and analysed by GC-MS. The outcomes of these reactions emphasise the competing nature of the nucleophilic addition pathway, whereby all systems resulted in a considerable amount of amine products **5** and **5a** being isolated in the range of 23 - 62%, with the lowest formation being in diethyl ether (entry 2, Table 1). THF is typically the solvent of choice for typical Li/Br exchange reactions in the literature,[11,26] hence it was surprising to find that the highest conversion to addition products (combined 62% yield of amines **5** and **5a**, entry 1, Table 1) was observed for THF. A point to note is once the addition or exchange step has occurred, neither site being lithiated limits the other process from occurring. From the initial results, it is possible to observe the effects of several competing reaction pathways. Lithium-bromide exchange is the fastest to occur, however the consequent intermolecular cyclisation step is slower and thus ends up in competition with nucleophilic addition. This is problematic since once the imine has undergone nucleophilic addition the two-step cyclisation pathway is inhibited. Relating these outcomes to the choice of solvent medium, it can be deduced that there are two possible factors at play; polarity and Lewis donor stabilisation.

In relatively polar solvents homogeneous solutions help facilitate cyclisation, whereas with less polar solvents, such as hexane (entry 6, Table 1), lower solubility and precipitation of reaction intermediates impedes the cyclisation pathway. However, the outcome is not wholly attributed to the solubility. The strength of the metal-donor interaction in solution appears to be crucial as it can shut down the metal atom site for reactivity. In the presence of strongly coordinating Lewis donor solvents, such as monodentate THF (entry 1, Table 1) and bidentate TMEDA (entry 5, Table 1), it would appear the lithiated intermediate is stabilised thereby hindering cyclisation. In the case of bulkier tridentate PMDETA (entry 4, Table 1) an increase in cyclised product is observed. Interestingly, diethyl ether, which is a low polarity, labile, monodentate Lewis donor, provides the best solvent for inhibiting addition reactivity while promoting lithium-bromide exchange and subsequent cyclisation (entry 2, Table 1).

Stoichiometric effect

To validate the observation that the addition and exchange processes are competitive and not stepwise due to using two equivalents of *t*BuLi, studies investigating the effect of stoichiometry were carried out. Reactions using the two most contrasting solvents - THF and Et_2O - were conducted using both a 2:1 and1:1 ratio of *t*BuLi:imine, as summarised in Table 2.

Table 2. Varying stoichiometry of *t*BuLi with compound **1** in Et_2O and THF.[a]



Entry	*X*	solvent	**5** (%)	**5a** (%)	**6** (%)	**7** and **8** (%)[b]	Other (%)
1	1	Et_2O	3	12	0	77	8
2	2	Et_2O	0	23	1	72	4
3	1	THF	71	17	0	12	0
4	2	THF	6	56	0	38	0

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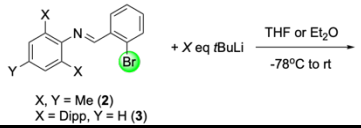
[a] Determined by GC-MS. [b] Combined conversion of cyclic derivatives, see SI for full ratios. [c] Commercial solution of *t*BuLi (1.7M in pentane).

Even when only one equivalent of *t*BuLi was used the addition-only product **5** was observed for both systems, revealing the addition and exchange pathways to be truly competitive, and hence detrimental to the cyclisation pathway. The high yield of cyclised products for both reactions in Et_2O (entries 1 and 2, Table 2) indicates that the exchange process dominates over addition of the lithium reagent, while the relatively low yields of cyclised products from the THF reactions indicate the addition reaction to be more favourable, as highlighted by when only one equivalent of *t*BuLi is employed (entry 3, Table 2). Thus, in THF the addition occurs faster than Li/Br exchange on the same molecule, and the addition step then prevents cyclisation.

Steric influences

To confirm that the suppression of the addition pathway allows the Li/Br exchange to occur successfully we prepared two substituted imines, compounds **2** and **3**, bearing a mesityl (Mes) or diisopropylphenyl (Dipp) group as the aniline moiety. The reaction was then performed in the same manner as previous studies employing both one and two equivalents of *t*BuLi in Lewis base donor solvents THF and Et_2O (Table 3).

Table 3. Effect of varying sterically protected imines **2** and **3** with 1 and 2 eq of *t*BuLi in Et_2O and THF.[a]



X, Y = Me (**2**)
X = Dipp, Y = H (**3**)

Entry	imine	*X*	Solvent	**5** (%)	**5a** (%)	**6** (%)	**7** and **8** (%)[b]	Other (%)
1	**2**	1	Et_2O	0	0	48	35	17
2	**2**	2	Et_2O	0	31	42	20	7
3	**2**	1	THF	33	6	45	0	16
4	**2**	2	THF	3	89	2	0	6
5	**3**	1	Et_2O[c]	0	0	99	0	1
6	**3**	2	Et_2O	0	10	85	4	1
7	**3**	1	THF	0	2	89	4	5
8	**3**	2	THF	0	6	88	2	4

[a] Determined by GC-MS. [b] Combined conversion of cyclic derivatives, see SI for full ratios. [c] Commercial solution of *t*BuLi (1.7M in pentane).

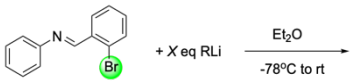
In the case of the mesityl functionality (**2**), in diethyl ether (entries 1 and 2, Table 3), nucleophilic addition was not notably different in comparison to the non-substituted imine **1**. The addition occurs concurrently with Li/Br exchange when two equivalents of *t*BuLi are used. Interestingly when only one equivalent is used no addition is observed which would suggest that the competing addition step is slow in Et_2O. In the case of THF (entries 3 and 4, Table 3) when two equivalents of *t*BuLi are employed, almost selectively the addition and exchange product **5a** was observed (89%). Alternatively using a 1:1 ratio a mixture of products was obtained, 33% of which addition product **5** was observed highlighting the rapidness of the addition pathway. Comparing these two solvents it can be seen that THF promotes the addition pathway and is quicker than in Et_2O, confirmed by the presence of species **5** in THF reactions. There is also no cyclisation observed with THF, whereas in Et_2O the slower addition pathway is less competitive, and facilitates cyclisation.

As the mesityl group was not sterically demanding enough to protect the C=N functionality, the bulkier diisopropyl substituted imine **3** was tested. The reaction in Et_2O, (entries 5 and 6, Table 3) revealed almost exclusively Li/Br exchange as the major product with 99% of **6** being obtained when one equivalent of *t*BuLi was employed. This was consistent in THF (entries 7 and 8, Table 3) with 88% of **6** recorded. As predicted, providing steric protection of the imine functionality reduced or completely inhibited 1,2 nucleophilic addition, however this also blocked the site for intermolecular cyclisation.

Importance of organolithium reagent

Finally, a series of experiments were conducted to determine whether the ratio of addition, exchange, and cyclisation products could be varied based on the nucleophilicity of the organolithium reagent. The results are summarised in Table 4, with the outcome using *t*BuLi under optimised conditions for cyclisation presented in entries 1 and 2. Using two equivalents of *n*BuLi in diethyl ether at -78°C, product *n*Bu-**5a** dominates, resulting from nucleophilic addition and Li/Br exchange on the same molecule (entry 6, Table 4). Using only one equivalent of *n*BuLi (entry 5, Table 4) led almost exclusively to the addition product (*n*Bu-**5**), confirming that addition is favoured over exchange in this case. Comparatively, *s*BuLi, offering an in-between nucelophilicity and basicity of *t*BuLi and *n*BuLi, behaves similarly to *t*BuLi in the presence of 1 equivalent (entry 3, Table 4). Although, in the presence of 2 equivalents a trend is observed for the addition and exchange product **R-5a** which gradually decreases from *n*Bu>*s*Bu>*t*Bu (entries 2, 4 and 6, Table 4).

Table 4. Effect of varying organolithium reagents with **1** in Et_2O.[a]



Entry	R	*X*	**R-5** (%)	**R-5a** (%)	**R-6** (%)	**R-7** and **8** (%)[b]	Other (%)
1	*t*Bu	1	3	12	0	77	8
2	*t*Bu	2	0	23	1	72	4
3	*s*Bu	1	4	13	0	78	4

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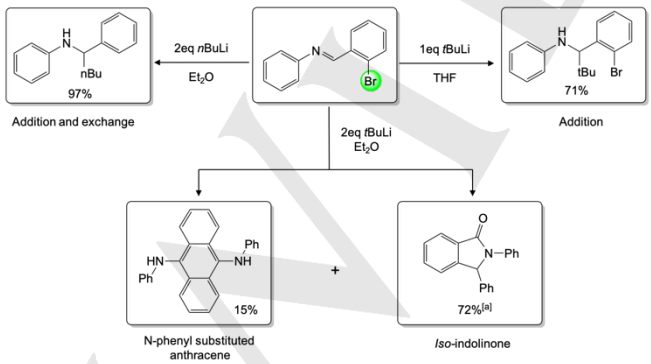
4	*s*Bu	2	0	36	0	58	6
5	*n*Bu	1	91	2	0	7	0
6	*n*Bu	2	0	96	0	0	4
7	CH_2SiMe_3	1	68	0	0	0	32[c]
8	CH_2SiMe_3	2	64	36	0	0	0
9	Mes	1	83	7	0	10	0
10	Mes	2	68	21	0	2	9

[a] Determined by GC-MS. [b] Combined conversion of cyclic derivatives, see SI for full ratios. [c] Starting material. [d] Commercial solution of *t*BuLi (1.7M in pentane), *n*BuLi (1.6M in hexanes), *s*BuLi (1.4M in cyclohexane), $LiCH_2SiMe_3$ (1M in hexanes).

Interestingly, with (trimethylsilyl)methyllithium, employing both one and two equivalents of organolithium reagent, nucleophilic addition dominates over Li/Br exchange with no cyclisation observed (entry 7 and 8, Table 4). In an attempt to inhibit nucleophilic addition of the organolithium reagent and to preserve the imine functionality for ring closing, a less nucleophilic aryl lithium reagent was studied, mesityllithium. However, on treating the imine with mesityllithium the addition product (Mes-**5**) was again identified as the major species, suggesting sterics of the lithium reagent has little influence in hindering the addition pathway (entry 9 and 10, Table 4). In summary, employing either one or two equivalents of *t*BuLi in diethyl ether at -78°C remains the optimum reaction conditions for obtaining the highest ratio of *iso*-indolinone products.

Overall, a powerful solvent, stoichiometric and nucleophilic dependence is apparent in determining the resulting products in what would appear a simple textbook organolithium transformation. From this lithium-bromide exchange study of *ortho*-bromo-substituted diaryl imines, we can generalise reaction conditions to obtain various products as summarised in Scheme 6. Future work within our group will probe the scope of the cyclisation pathways to introduce further functionality on the imine precursors to access a range of privileged N-heterocycles.



Scheme 6. Summary of reaction conditions for obtaining desired product. [a] = combined conversion of *iso*-indolinone derivatives.

Conclusions

In this fundamental study of the lithium-bromide exchange reaction in bromo-substituted diaryl imines, it is revealed that the expected superior chemoselectivity of the Li/Br exchange is challenged by competitive addition pathways. In the presence of traditionally used THF, the unprecedented amine product is a result of the unsaturated functionality of the imine moiety undergoing nucleophilic addition, even under cryogenic conditions. Alternatively employing diethyl ether the rapidity of Li/Br exchange versus nucleophillic addition is generally maintained. Remarkably, in this case the lithiated imine is consumed in cascade cyclisation pathways. The new C-C bond formation arises through a two-step 1,2-nucleophilic addition process of the lithiated imine; either in a 'head to head' or a 'head to tail' manner forming *iso*-indolinones and N-phenyl-anthracenes, respectively.

Experimental Section

General considerations

All reactions and manipulations were carried out under a protective nitrogen atmosphere using either standard Schlenk techniques or an MBraun glove box fitted with a gas purification and recirculation unit. NMR measurements were conducted in a J. Youngs tube oven dried and flushed with nitrogen prior to use. Solvents were obtained from an MBraun SPS-800 solvent purification system and stored over 4 Å molecular sieves under nitrogen.

NMR spectra were recorded on a Bruker AVANCE DRX 400 spectrometer operating at 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 155.5 MHz for ^{7}Li. All ^{13}C spectra were proton decoupled. ^{1}H and ^{13}C NMR spectra were referenced against the appropriate solvent signal.

Crystallographic data of compound **4** was collected at the MX1 beamline at the Australian Synchrotron, Melbourne, Victoria, Australia (γ = 0.71073 A). All data was collected at 100 K, maintained using an open flow of nitrogen. The software used for data collection and reduction of the data was performed using XDS. Multi-scan absorption corrections (SADABS) were applied. Crystallographic data for compound **9** were collected on a Bruker X8 Nonius Kappa CCD diffractometer with graphite-monochromated Mo Kα (λ_0 = 0.71073 Å) radiation at 123 (1) K. Data was collected and processed using the Bruker Apex2 v.2012.2.0 software; Lorentz, polarisation and absorption corrections (multi-scan – SADABS[1]) were applied. Structures were solved and refined using SHELX-2016 or Olex2. All non-hydrogen atoms were refined using anisotropic thermal parameters. Selected crystallographic details and refinements are provided in table S5. CCDC 1914306 and 1914307 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General reaction method

To a flame dried Schlenk flask 5 mL of the desired solvent was added along with the corresponding imine (**1**-**3**). The reaction mixture was then cooled to -78°C and the lithium reagent was added. The reaction mixture was left to stir for approximately 18 hours warming to room temperature. The reaction mixture was then hydrolysed with 10 mL of deionised water and extracted (3 x 15 mL) with diethyl ether. The organic layer was dried with anhydrous $MgSO_4$ and volatiles removed, the crude sample was analysed by GC-MS.

Full details are provided in the electronic supporting information.

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Keywords: lithium-bromide exchange • nucleophilic addition • imines • cyclisation • *iso*-indolinones

[1] (a) R. Bloch, *Chem. Rev*. 1**998**, *98*, 1407-1438; (b) K. Yamada, K. Tomioka, *Chem. Rev*. **2008**, *108*, 2874-2886; (c) S. E. Denmark, C. M. Stiff, *J. Org. Chem.* **2000**, *65*, 5875-5878; (d) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc*. **1994**, *116*, 8797-8798; (e) T. Franz, M. Hein, U. Veith, V. Jäger, E.-M. Peters, K. Peters, H. G. von Schnering, *Angew. Chem. Int. Ed*. **1994**, *33*, 1298-1301; (f) K. Higashiyama, H. Inoue, T. Yamauchi, H. Takahashi, *J. Chem. Soc. Perkin Trans.* **1995**, 111-115; (g) G. Wu, M. Huang, *Chem. Rev*. **2006**, *106*, 2596-2616. (h) S. Kobayashi, H. Ishitani, *Chem. Rev*. **1999**, *99*, 1069-1094.

[2] (a) J. F. Beck, J. A. R. Schmidt, *Dalton Trans*. **2012**, *41*, 860-870; (b) A. M. Preda, C. I. Rat, C. Silvestru, H. J. Breunig, H. Lang, T. Rüffer, M. Mehring, *Dalton Trans*. **2013**, *42*, 1144-1158; (c) M. Novák, L. Dostál, J. Turek, M. Alonso, F. De Proft, A. Ružička, R. Jambor, *Chem. Eur. J*. **2016**, *22*, 5620-5628; (d) D. L. Davies, F. Lelj, M. P. Lowe, K. S. Ryder, K. Singh, S. Singh, *Dalton Trans*. **2014**, 43, 4026-4039.

[3] (a) T. R. Forder, M. D. Jones, *New J. Chem*. **2015**, *39*, 1974-1978; (b) M. C. Joseph, A. J. Swarts, S. F. Mapolie, *Dalton Trans*. **2018**, *47*, 12209-12217; (c) C. Bariashir, Z. Wang, H. Suo, M. Zada, G. A. Solan, Y. Ma, T. Liang, W.-H. Sun, *European Polymer Journal* **2019**, *110*, 240-251.

[4] S. F. Martin, *Pure Appl. Chem*. **2009**, *81*, 195-204.

[5] (a) F. E. Zieglar, K. W. Fowler, *J. Org. Chem.* **1976**, 41, 1564-1566; (b) J. F. Beck, A. Neshat, J. A. R. Schmidt, *Eur. J. Inorg. Chem*. **2010**, 5146-5155; (c) A. Neshat, C. L. Seambos, J. F. Beck, J. A. R. Schmidt, *Dalton Trans*. **2009**, 4987-5000.

[6] (a) C. Vidal, J. García-Álvarez, A. Hernán-Gómez, A. R. Kennedy, E. Hevia, *Angew. Chem. Int. Ed*. **2016**, *55*, 16145-16148; (b) G. Dilauro, M. Dell'Aera, P. Vitale, V. Capriati, F. M. Perna, *Angew. Chem. Int. Ed*. **2017**, *56*, 10200-10203.

[7] N. B. Kingsley, T. J. Doyon, L. E. Shephard, *J. Organomet. Chem*. **2016**, 48-53.

[8] D. Zhao, W. Gao, Y. Mu, L. Ye, *Chem. Eur. J*. **2010**, *16*, 4394-4401.

[9] M. Hejda, A. Lyčka, R. Jambor, A. Ružička, L. Dostál, *Dalton Trans*. **2014**, *43*, 12678-12688

[10] (a) H.-J. Li, Y.-Q. Zhang, L.-F. Tang, *Tetrahedron* **2015**, *71*, 7681-7686; (b) Y. Xi, X.-Y. Liu, Z. -H. Wang, L.-F. Tang, *Tetrahedron* **2017**, *73*, 7245-7253.

[11] *Organolithiums: selectivity for synthesis*, Chapter 3, *Vol. 23* (Ed.; J. Clayden), Elsevier, Oxford, **2002**.

[12] Y. M. Oskoei, A. Mousavi-azar, A. Madram, A. Hassanpour, M. Hayaty, *Silicon* **2012**, *4*, 251-257.

[13] (a) L. Bonnafoux, F. R. Leroux, F. Colobert, *Beilstein J. Org. Chem*. **2011**, *7*, 1278-1287; (b) M. Schlosser, *Angew. Chem. Int. Ed*. **2005**, *44*, 376-393.

[14] (a) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770-12773; (b) H. Kim, H.-J. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2015**, *54*, 1877-1880; (c) H. Kim, A. Nagaki, J.-I. Yoshida, *Nat. Commun*. **2011**, 2, 264-269.

[15] P. C. Gros, F. Elaachbouni, *Chem. Commun*. **2008**, 4813-4815.

[16] M. Dutta, S. M. Mandal, R. Pegu, S. Pratihar, *J. Org. Chem*. **2017**, *82*, 2193-2198.

[17] Y.-H. Yu, C.-H. Huang, J.-M. Yeh, P.-T. Huang, *Organic Electronics* **2011**, *12*, 694-702.

[18] E. C. Border, V. L. Blair, P. C. Andrews, *Aust. J. Chem*. **2015**, *68*, 844-848.

[19] (a) C. Lambert, C. Risko, V. Coropceanu, J, Schelter, S. Amthor, N. E. Gruhn, J. C. Durivage, J.-L. Brédas, *J. Am. Chem. Soc*. **2005**, *127*, 8508-8516; (b) T. Nishiumi, Y. Chimoto, Y. Hagiwara, M. Higuchi, K. Yamamoto, *Macromolecules* **2004**, *37*, 2661-2664.

[20] A. Pöllnitz, C. Silvestru, J.-F. Carpentier, A. Silvestru, *Dalton Trans*. **2012**, *41*, 5060-5070.

[21] (a) J. M. Dennis, C. M. Calyore, J. S. Sjoholm, P. Lutz, J. J. Gair, J. B. Johnson, *Synlett* **2013**, *24*, 2567-2570; (b) R. K. Dempster, F. A. Luzzio, *Tetrahedron Letters* **2011**, *52*, 4992-4995; (c) A. B. Nejma, M. Znati, A. Daich, M. Othman, A. M. Lawson, H. B. Jannet, *Steroids* **2018**, *138*, 102-107.

[22] A. Di Mola, I. Palombi, A. Massa, *Curr. Org. Chem*. **2012**, *16*, 2302-2320.

[23] (a) C. K. Bradsher, D. A. Hunt, *J. Org. Chem*. **1981**, *46*, 327-330; (b) J. B. Campbell, R. F. Dedinas, S. A. Trumbower-Walsh, *J. Org. Chem*. **1996**, *61*, 6205-6211; (c) K. Smith, G. A. El-Hiti, A. S. Hegazy, *Chem. Commun*. **2010**, *46*, 2790-2792.

[24] Y. Xu, X.-Y. Liu, Z.-H. Wang, L.-F. Tang, *Tetrahedro*n **2017**, *73*, 7245-7253.

[25] (a) S.-P. Chia, H.-W. Xi, Y. Li, K. H. Lim, C.-W. So, *Angew. Chem. Int. Ed.* **2013**, *52*, 6298-6301; (b) M. T. Nguyen, B. Gabidullin, G. I. Nikonov, *Dalton Trans*. **2018**, *47*, 4607-4612; (c) I. Vránová, R. Jambor, A. Ružička, R. Jirásko, L. Dostál, *Organometallics* **2015**, *34*, 534-541.

[26] (a) L. Bonnafoux, F. Leroux, F. Colobert, *Beilstein J. Org. Chem*. **2011**, *7*, 1278-1287; (b) K. S. Feldman, I. Y. Gonzalez, J. E. Brown, *Tetrahedron Lett*. **2015**, *56*, 3564-3566.

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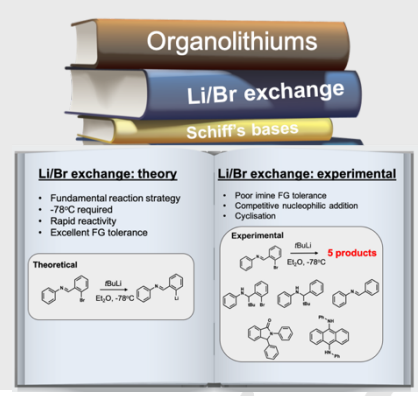

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