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Making Endo-Cyclizations Favorable Again: Conceptually New Synthetic Approach to Benzotriazoles via Azide Group Directed Lithiation/Cyclization of 2-Azidoaryl Bromides

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Abstract

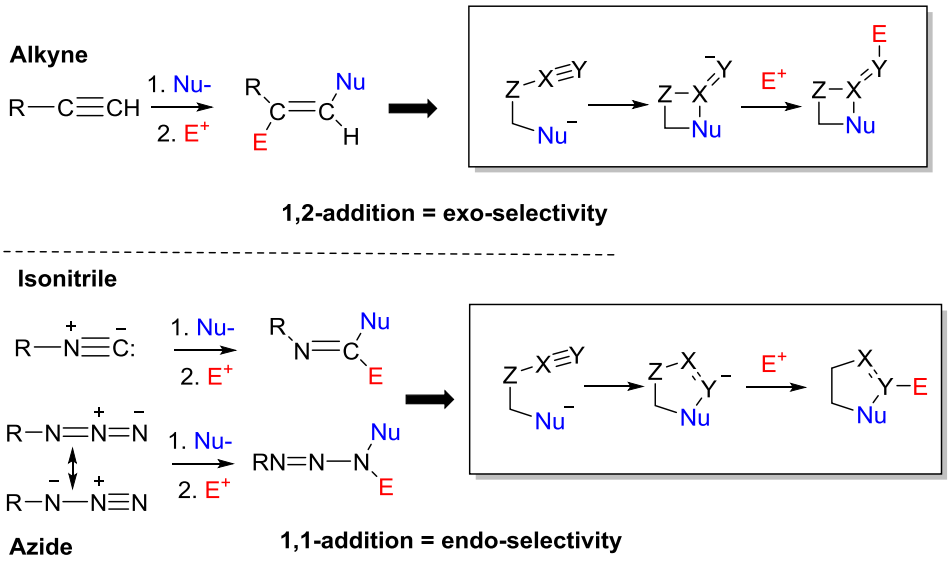
Although benzotriazoles are important and ubiquitous, currently there is only one conceptual approach to their synthesis: bridging the two ortho-amino groups with an electrophilic nitrogen. Herein, we disclose a new practical alternative – the endo-cyclization of 2-azidoaryl lithiums obtained in situ from 2-azido-aryl bromides. The scope of the reaction is illustrated by twenty-four examples with a variety of alkyl, alkoxy, perfluoroalkyl, and halogen substituents. We found that the directing effect of the azide group allows selective metal–halogen exchange in aryl azides containing several bromine atoms. Furthermore, (2-bromophenyl)diazomethane undergoes similar cyclization to give indazole. Thus, cyclizations of aryl lithiums containing an *ortho*–X=Y=Z group emerge as a new general approach for synthesis of aromatic heterocycles.

DFT computations suggested that the observed endo-selectivity applies to the anionic cyclizations of other functionalities that undergo the "1,1-additions" (i.e., azides, diazo compounds, and isonitriles). In contrast, cyclizations with the heteroatomic functionalities that follow the "1,2-addition" pattern (cyanates, thiocyanates isocyanates, isothiocyanates, nitriles) prefer the exo-cyclization path. Hence, such reaction expands the current understanding of stereoelectronic factors in anionic cyclizations.

Introduction

The importance of cyclization reactions is underscored by the fact that the majority of molecules in nature are cyclic.[1] The success of a multi-step synthesis often depends on making the key cyclic structure precisely and efficiently. Conceptually, classic nucleophilic cyclizations can follow either an exo- or an endo-pathway.[2] The endo-path, where the breaking bond is inside of the forming cycle, is intrinsically unfavorable due to stereoelectronic penalty associated with the unfavorable orbital overlap of the nucleophile with either σ* or π* of the breaking bond.[3] Hence, the design of selective nucleophilic endo-cyclizations remains an important conceptual challenge.

The present manuscript shows that such challenge can be addressed by using the family of functional groups that undergo "1,1-addition" reaction (Scheme 1). High endo-selectivity in these reactions contrasts the usual preference for exo-cyclizations of the more common functionalities, e.g., alkenes and alkynes, that undergo "1,2-additions". In this work, we will explore the utility of selective endo-cyclizations in synthesis of benzotriazoles.



Scheme 1. Comparison of "1,1-additions" and "1,2-additions" in cyclization reactions. See Scheme 11 for additional details

Benzotriazoles (Bts) find a wide range of applications in medicinal chemistry as illustrated by such drugs as Vorozole and Alizapride.[4] The search for the new Bt-based drugs continues - a series of Bt derivatives have been identified as inhibitors of various kinases,[5] inactivators of severe acute respiratory syndrome 3CL protease,[6] photoactivated DNA cleaving agents[7] and agonists of human orphan G-protein-coupled receptor GPR109b.[8]

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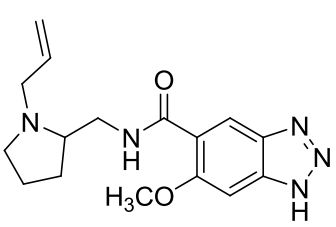
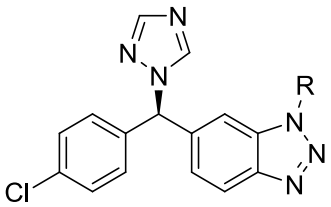


Alizapride

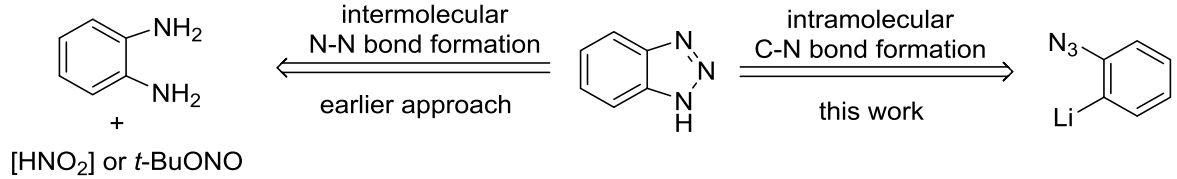


(S)-Vorazole R=Me
(S)-Norvorazole R=H

Besides, many Bt derivatives are important in pharmacology since they exhibit antidepressant,[9] antimicrobial,[10] antiviral,[11] antimalarial,[12] anti-inflammatory,[4, 13] and antimycobacterial activity.[14] Furthermore, benzotriazoles are versatile synthetic auxiliaries in diverse transformations[15] and ligands in cross-coupling reactions.[16]

Today, there are only a few general methods to synthesize N-unsubstituted benzotriazoles. The most common one is diazotization of *ortho*-phenylenediamines.[17] Despite its frequent use, the method has a number of drawbacks caused by limited availability and stability of substituted *ortho*-phenylenediamines.

In all of the methods mentioned above, the 1,2,3-triazole ring of a benzotriazole is assembled from an *ortho*-disubstituted benzene containing amino groups or its synthetic precursor (Scheme 2).



Scheme 2. Comparison of the traditional and the new approaches to N-unsubstituted benzotriazoles

Here, we present a new general synthetic approach to N-unsubstituted Bts from *ortho*-metalated aryl azides. A unique feature of our approach is the unprecedented *in situ* transformation of 2-azidophenyllithium into an *N*-lithium derivative of an unsubstituted benzotriazole. To the best of our knowledge, no cyclization of the kind has been reported in literature. Proposed reaction conditions are tolerant to a number of functional groups. Furthermore, synthetic approaches to the requisite 2-azidoaryl bromides (iodides) allow access to substitution patterns that are different and complementary to those available for *ortho*-phenylenediamines and their synthetic analogues (i.e., *ortho*-halogenated nitrobenzenes, *ortho*-nitroanilines, etc.). As the result, this method makes it possible to synthesize benzotriazoles that have been unavailable through the previously reported synthetic routes (*vide infra*).

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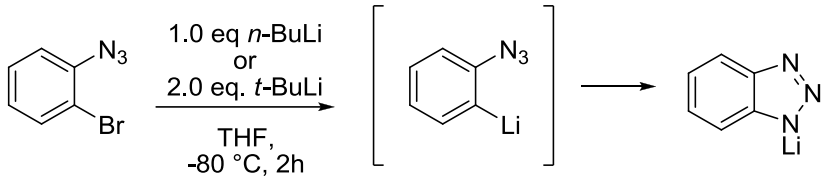
Results and Discussion

Azide cyclization

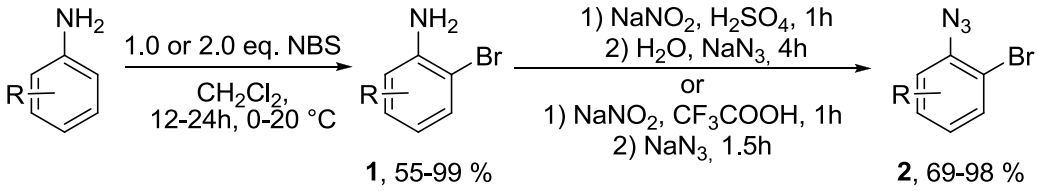
During the search for cyclization conditions, we tested different experimental approaches using 2-azidobromobenzene as a model compound (Scheme 3). The attempt to obtain 2-azidophenylmagnesium bromide by an excess of activated magnesium in refluxing THF failed; the initial azide was regenerated in 92% yield. On the other hand, halogen-lithium exchange with *n*-BuLi or *t*-BuLi in THF at –80 °C for 2h turned out to be more successful. Although application of *t*-BuLi was accompanied by formation of intensely colored side products, treatment of the reaction mixture with dilute hydrochloric acid resulted in the 62% yield of the benzotriazole. *n*-BuLi turned out to be the most appropriate reagent providing 66% yield of the target benzotriazole.



Scheme 3. The one-pot formation of benzotriazole via lithiation of 2-azidobromobenzene

Inspired by these results, we decided to test the scope and limitations of the lithiation-mediated cyclization with a wide range of readily available 2-azidobromobenzenes with various substituents compatible with Li-organic reagents.

Substituted 2-azidobromoarenes were synthesized following a two-step approach (Scheme 4): bromination of substituted arylamines with *N*-bromosuccinimide in dichloromethane allowed 2-bromoanilines **1** with yields 55–99%. Diazotization of 2-bromoanilines was performed according to one of the two ways. The easily soluble anilines were diazotized under standard conditions in aqueous solution of sulfuric acid,[18] whereas polyhalogenated anilines and fluorine-containing anilines were diazotized under water-free conditions, in trifluoroacetic acid.[19]



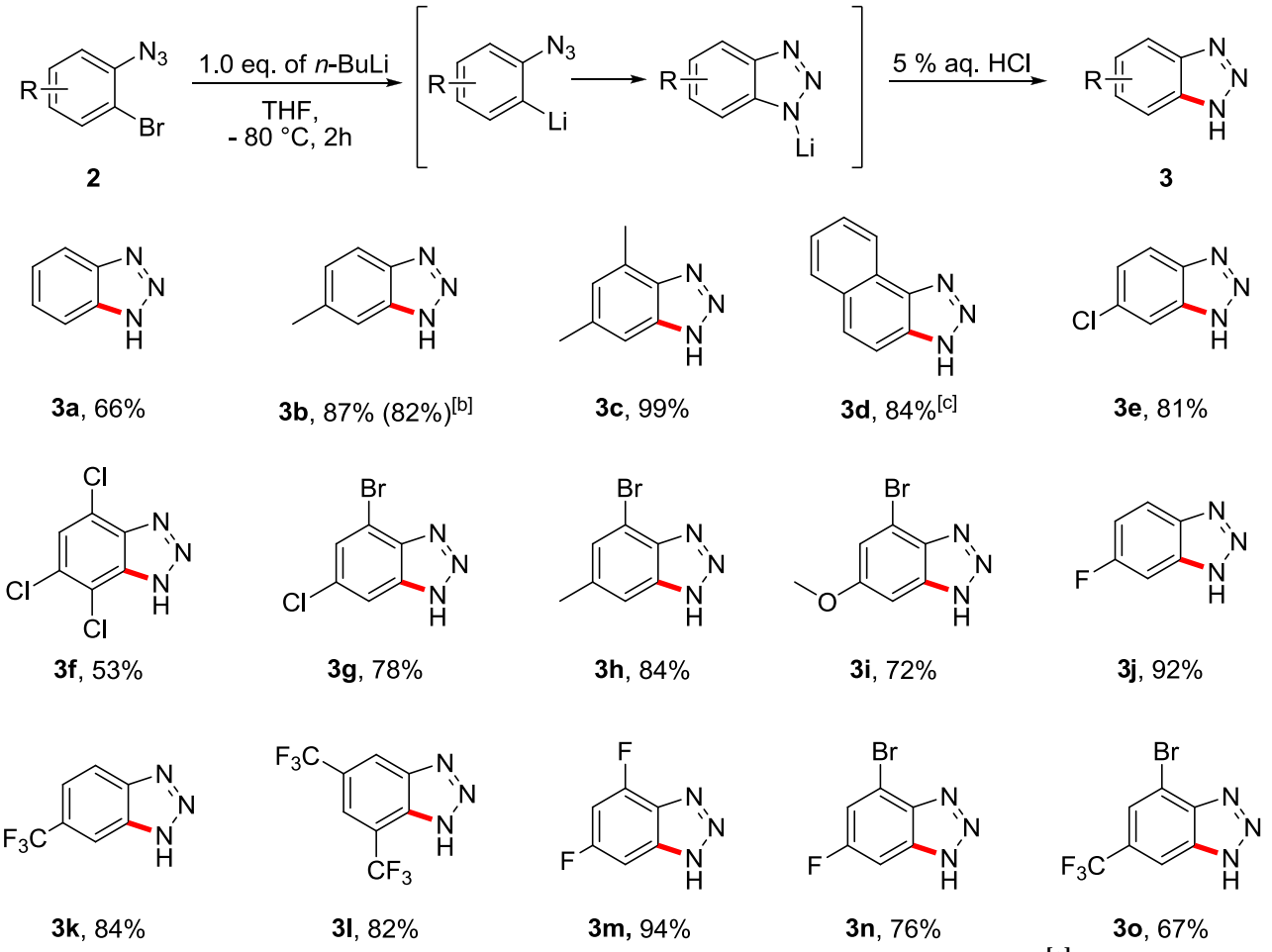
Scheme 4. General synthetic strategy for the preparation of substituted 2-azidobromoarenes

We found that 2-azidobromobenzenes containing alkyl substituents readily cyclized to provide 1*H*-benzotriazoles **3b** and **3c** in excellent isolated yields (Scheme 5). Cyclization of 1-azido-2-iodo-4-methylbenzene led to benzotriazole **3b** in a lower yield than in case of the bromo analogue. In the case of the iodo aryl precursor, isolation of the product was hampered by formation

of the *N*-butylated benzotriazole byproduct. In the course of metal–halogen exchange, an aryllithium derivative and corresponding *n*-butyl halide were formed. Under the reaction conditions, 1-bromobutane, formed from 2-azidobromoaryls, does not alkylate the lithium benzotriazole salt formed in the course of the reaction. In contrast, the more reactive 1-iodobutane produces small amounts of benzotriazole *N*-alkylation products (at N atoms 1 and 2).

Proposed method allows to synthesize polycyclic triazoles as demonstrated by the facile formation of naphthotriazole **3d** after Br-Li exchange of 2-bromo-1-azidonaphthalene **2d**. The tricyclic 3*H*-naphtho[1,2-d][1,2,3]triazole product was isolated in 84% yield.

1*H*-Benzotriazoles **3j**–**o** from fluorine-containing aryl azides were obtained in good yields.

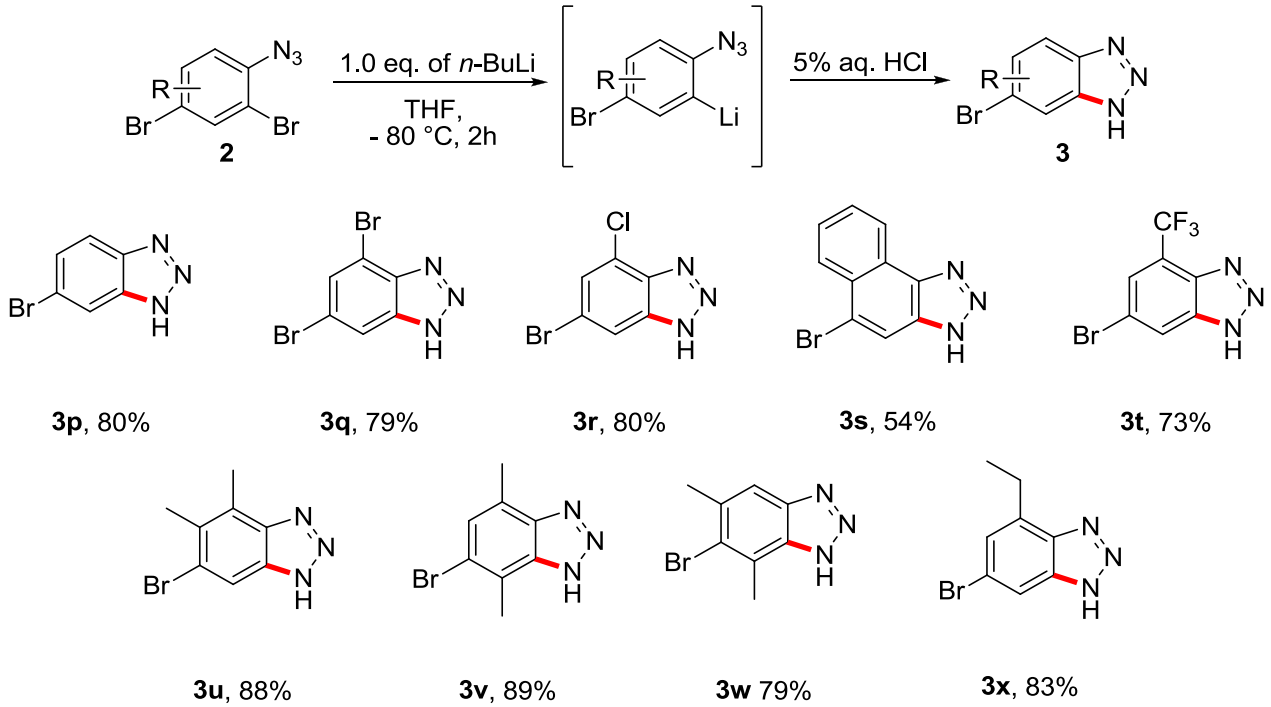


Scheme 5. Synthesis of benzotriazoles from 2-azidobromoaryls.[a]

[a] Reaction conditions: 2-azidoaryl bromide (5 mmol), 2.5M solution of *n*-BuLi (2.0 ml, 1.0 eq.) , THF (20 ml), –80 °C, 2h. Yields of isolated pure products are reported. [b] Cyclization 1-azido-2-iodo-4-methylbenzene. [c] For the reaction, 40 ml THF was used.

The presence of two bromine atoms at the *ortho*-position with respect to the azido group provided no complications - the bromo-substituted cyclic products **3g**–**i**, **3n** and **3o** were isolated in good yields (Scheme 5). Therefore, we decided to study the possibility of selective synthesis of

benzotriazoles from polybrominated azides. A series of nine bromo-substituted benzotriazoles was synthesized (Scheme 6).



[a] Reaction conditions: 2-azidoaryl bromide(5 mmol), 2.5M solution of *n*-BuLi (2.0 ml, 1.0 eq.) , THF (20 ml), –80 °C, 2h.

Scheme 6. Haloselective metal–halogen exchange in brominated aryl azides.[a]

Despite low solubility of alkyl-substituted azides **2u**–**w** under the reaction conditions at –80 °C, relevant benzotriazoles **3u**–**w** were isolated in high yields. We found that the lithium–halogen exchange is halogen- and regioselective in the presence of the *ortho*-azido substituent. Such selectivity allows to synthesize a number of previously unknown substituted bromobenzotriazoles in excellent yields. In cases when two halogens, bromine and chlorine, are located in *ortho*-positions, metal–halogen exchange occurs only at bromine. For the di- and tribromosubstituted substrates, only the bromine atom in *ortho*-position with respect to azide group was substituted with lithium (Scheme 6).

It should be noted that because of the prototropic tautomerism of H-benzotriazoles,[5b, 20] measurement of their ^{13}C NMR spectra was complicated by considerable signal broadening. The problem was solved by registering the NMR spectra in a 5:1 (by volume) mixture of DMSO-d_6 and D_2O, with the addition of excess of NaOH (15 equivalents with respect to a benzotriazole).

Therefore, we showed that the azide moiety can serve as a directing group in lithiation reactions. To the best of our knowledge, this directing effect has not been demonstrated previously in the literature. It stems from the presence of unpaired electrons at the nitrogen atoms of the azide group, which can coordinate the Lewis-acidic Li cation.

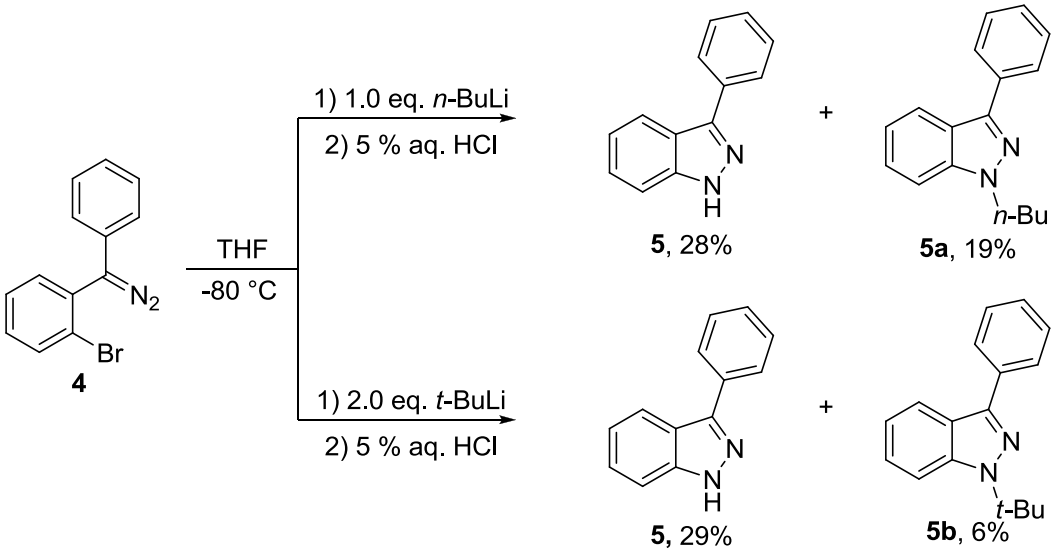
Thus, the proposed method opens broad prospects for synthesis of new biologically active substances. Many halogen-containing benzotriazoles are known to exhibit anticancer properties. For example, 4,5,6,7-tetrabromo-1*H*-benzotriazole (TBBT) is a reference compound among CK2 inhibitors.[21] Furthermore, the new method enables synthesis of benzotriazoles that could not be accessed via conventional methods. For example, SciFinder® found no literature reports of *ortho*-phenylenediamines needed for the synthesis of benzotriazoles **3v** and **3w** via diazotization.

The potential of the new bromobenzotriazoles in further functionalization via cross-coupling reactions or via lithium-bromine exchange followed by treatment with electrophiles (DMF, CO_2, B(O*i*-Pr)$_3$, etc.), is obvious.

Indazole formation

Guided by the analogy between azides and other heteroatomic groups of –X=Y=Z type, we have tested whether the *ortho*-lithiated benzenes substituted with such groups can undergo similar cyclizations.

Indeed, we found that indazole synthesis can be accomplished using this method staring from a diazo compound **4** (Scheme 7). 3-Phenylindazole **5** was isolated in a 28% yield along with the 19% of *N*-butyl-3-phenylindazole **5a** as a side-product.



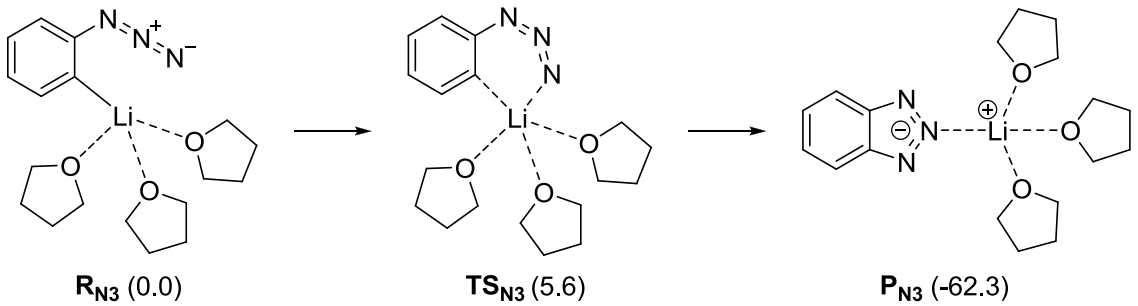
Scheme 7. Cyclization of diazoderivative 4

The side-product **5a** results from secondary reaction, alkylation of lithium salt **5** with 1-bromobutane formed in the course of metal–halogen exchange. To avoid formation of **5a**, we substituted *n*-BuLi with *t*-BuLi. Treatment of diazocompound **4** with 2 equivalents[22] of *t*-BuLi resulted in 3-phenylindazole **5** being isolated in 29% yield. Interestingly, *tert*-butylated side-product (*N*-*tert*-butyl-3-phenylindazole **5b**) was isolated from a complex mixture in 6% yield.

Theoretical analysis

Theoretical studies of the cyclization mechanisms were performed using DFT calculations with the PBE functional.[23] Valence electrons were treated using a TZ2P basis set, innermost electrons of Li, C, N, O, S atoms were emulated using effective core potentials ECP-SBKJC.[24] Stationary points were characterized as minima by calculations of normal modes of vibrations. Total energies including zero-point vibration energy corrections were calculated $E^0 = E + ZPVE$. All calculations were made using PRIRODA program.[25]

In order to obtain realistic energies of the reactant, transition state and the product (lithiated benzotriazole) for the reaction, we have included three molecules of THF coordinating to the Li atom in our computational model (Scheme 8). As a reference point, we have also evaluated the reaction energy profiles using the pure carbanion without the Li counterion and the solvent molecules.



Scheme 8. Mechanism of cyclization of ortho-azido phenyl lithium (E^0 in kcal/mol, relative to the starting material).

According to the computational data, the cyclization of *ortho*-azido phenyl lithium to the five-membered product $\mathbf{R_{N3}}$ is highly exothermic (-62.3 kcal/mol). Furthermore, the barrier for this process is very low (5.6 kcal/mol).

From the nature of Frontier Molecular Orbitals (FMOs) of the reagent, the cyclization can be described as a nucleophilic attack of the carbanionic lone pair (the HOMO) at the LUMO, delocalized between the three azide nitrogens (Figure 1). Hence, one can draw an analogy of this reaction with the known reactions of intermolecular nucleophilic addition of carbanions to organic azides.[26]

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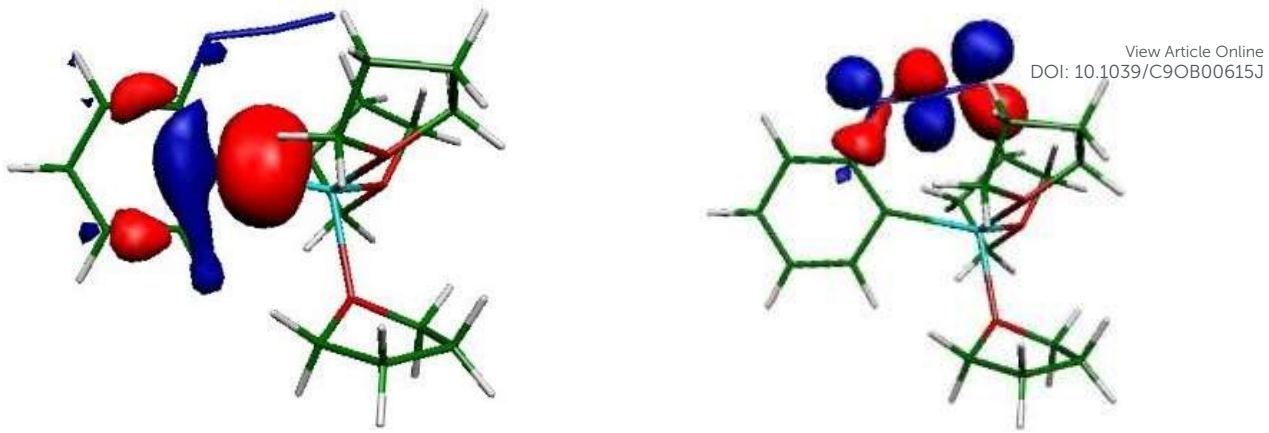
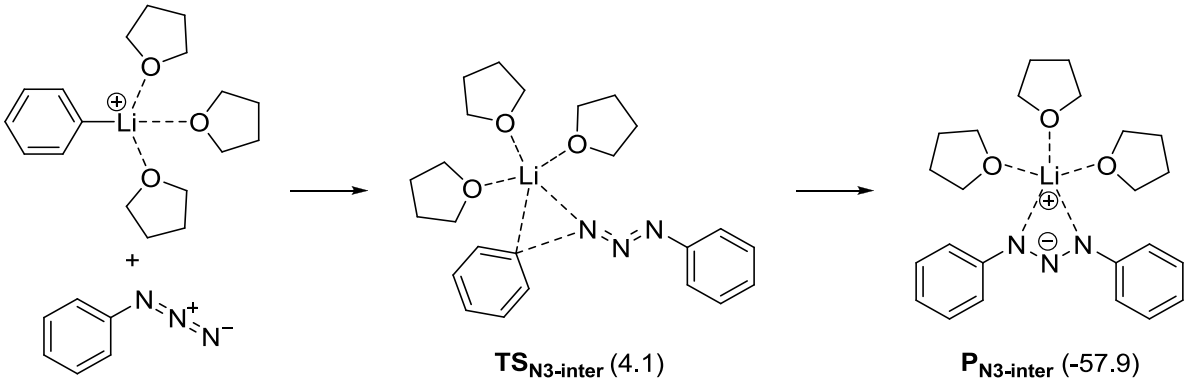


HOMO (-3.92) LUMO (-1.29)

Figure 1. The shape and energies of the frontier molecular orbitals of ortho-azido phenyl lithium (orbital energies in eV)

The low calculated reaction barrier (5.6 kcal/mol) agrees well with the fast reaction observed at the low temperatures used for the experimental metalation step. Considering how low the barrier is, it is possible that the observed reaction rate mostly reflects the rate of metalation. To further evaluate this scenario, we performed a series of experiments on lithium-halogen exchange of 2-azidobromobenzene followed by low temperature (-80 °C) treatment with various H-acids (CH_3OH, CF_3COOH). In every case, we did not observe even traces of dehalogenated azides. Either the 2-bromoazide reactant or the benzotriazole cyclization product was isolated depending on duration of the lithium-bromine exchange.

In order to understand the role of cyclic constraints in the 5-endo TS, we compared the energetic parameters of intramolecular reaction (Scheme 8) with the analogous intermolecular addition of PhLi to PhN_3 (Scheme 9).



Scheme 9. Mechanism of the intermolecular addition of PhLi to PhN_3 (E^0 in kcal/mol).

Comparison of reaction kinetics and thermodynamics provides important insights into the nature of cyclization barrier. In particular, intermolecular nucleophilic addition is characterized by even lower calculated energy barrier than in case if intramolecular reaction, 4.1 kcal/mol for $\mathbf{TS_{N3\text{-}inter}}$ vs. 5.6 kcal/mol for $\mathbf{TS_{N3}}$.

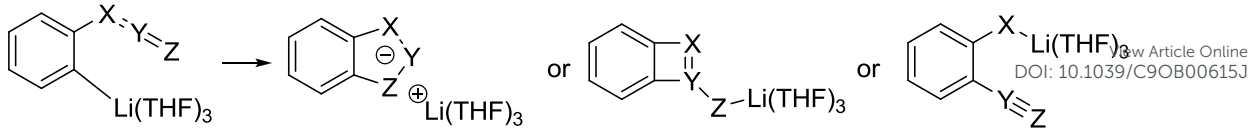
Interestingly, the two reaction energies trends show an opposite trend than the activation barriers. Although the product of the intermolecular reaction, the delocalized diphenyltriazenyl lithium $\mathbf{P_{N3\text{-}inter}}$, is stabilized by double coordination of the lithium cation with both terminal nitrogen centers, the exergonicity of the intermolecular reaction is lower (57.9 kcal/mol) in comparison to the exergonicity of the intramolecular process (62.3. kcal/mol for $\mathbf{P_{N3}}$). Such difference can be attributed to the greater stabilization associated the formation of the aromatic triazole π-system in the cyclization product $\mathbf{P_{N3}}$.

The intermolecular reaction also defines the general stereoelectronic requirement for the nucleophilic attack at the azide moiety. In particular, it provides the preferred angle of attack at the azide π-system. This geometric parameter has been used extensively in analysis of reactivity and selectivity of nucleophilic additions. For the alkene targets, such angle is called the Burgi-Dunitz angle[27] and usually lies in the region of 105-109 degrees. The angle of attack on alkynes has been controversial: it was suggested to be acute in the classic work on the rules for cyclizations by Baldwin[2, 28] but later shown to be obtuse.[29] Remarkably, the calculated angle of attack by PhLi at the terminal nitrogen atom of phenyl azide (C-N-N = 106.1) is the same as the Burgi-Dunitz angle, confirming that both geometric features originate from the generally preferred directionality for the interaction of a donor at a π*-orbital. The obtuse trajectory avoids interaction with the node between the two atoms in the p-target. Exo-cyclizations where the breaking bond is outside of the forming cycle can follow the obtuse trajectory and, thus, are generally stereoelectronically preferred.

In contrast, the C-N-N angle for the 5-endo TS is much smaller (C-N-N = 72.4), providing a possible explanation to why the intramolecular reaction has a higher barrier despite being more exothermic.

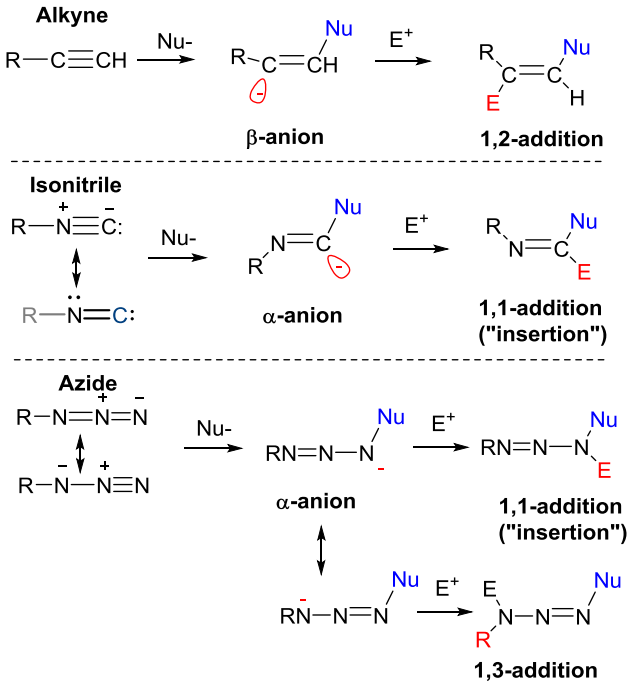
Notably, the only reaction route that we were able to localize on the potential energy surface corresponds to attack of phenyl anion to terminal nitrogen atom in $\mathbf{TS_{N3\text{-}inter}}$. No transition states were found for reactions corresponding to attack on nitrogen atoms in medium position, or the one attached to phenyl group. This is an important observation because it shows that 4-exo-cyclization is not a viable option.

Intrigued by these results, we explored whether the cyclization of aryl lithium derivatives with heteroatomic functionalities is general and whether it can be extended beyond the formation of benzotriazoles from aryl azides. For this purpose, we have analyzed cyclizations of a number of substrates with the general formula [Ph-X…Y…Z]Li(THF)$_3$ (Scheme 10). In each case, we considered both the 1,5-attack (5-endo) at the terminal atom Z and the 1,4-attack (4-exo) at the central atom Y.



Scheme 10. 1,5- vs 1,4-cyclizations in [Ph-X…Y…Z]Li(THF)$_3$.

Before discussing the specific findings, we have to mention the specific differences between the two main patterns for the addition of reactive species at a π-system: i.e., 1,2-addition vs. 1,1-addition. Such differences were clearly analyzed recently for radical additions to alkynes and isonitriles.[30] Although the two functionalities possess an analogous set of π-orbitals that combine in similarly looking HOMO and LUMO, the outcomes of their addition reactions are drastically different. We will discuss these differences below by using anionic addition, pertinent to the present discussion. Whereas addition to alkynes proceeds in a "1,2-manner" where the new bond and the anionic center are formed at the different alkyne carbons, isonitriles can react as "1,1-synthons" by forming *both* the new bond and the anionic center at the *same* terminal carbon of the isonitrile moiety (Scheme 11). Such outcome is consistent with the hidden carbene nature of the isonitrile functionality[30] and accounts for the key role of isonitriles in multicomponent transformations such as the Passerini and the Ugi reactions[31] as well as the many interesting radical cascades of isonitriles, sometimes described as an "insertion of isonitrile".



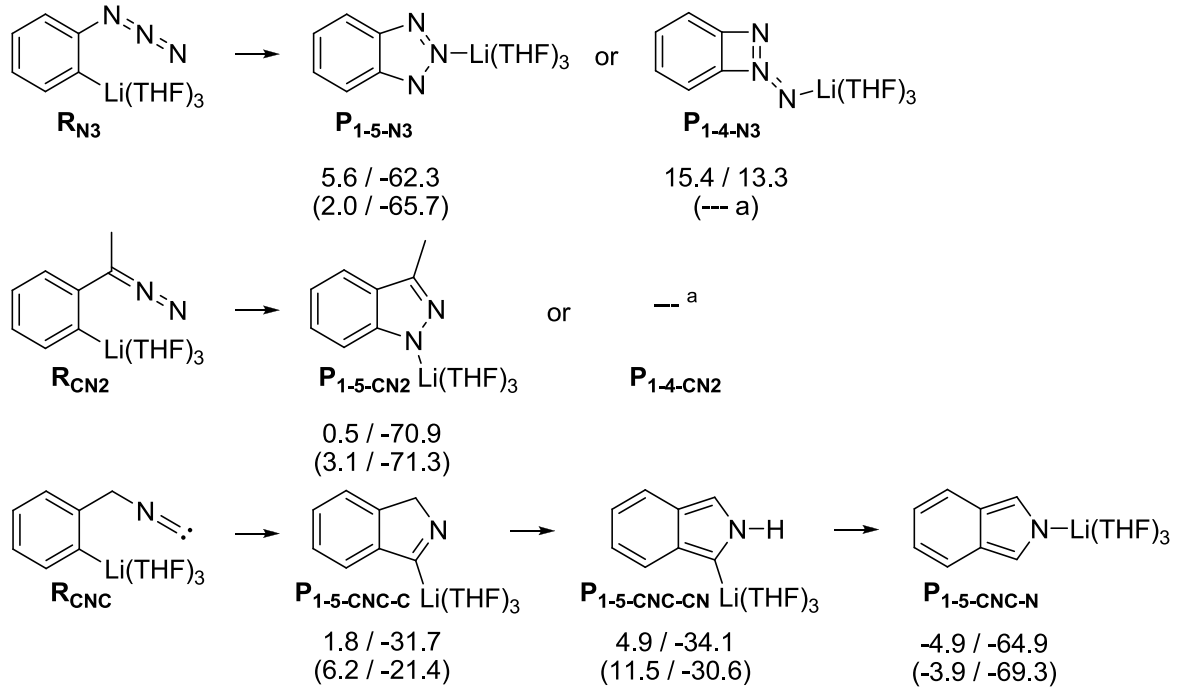
Scheme 11. Comparison of polar "1,1-", "1,2-" and "1,3-additions" to selected functional groups.

Although azides are electronically complex and have the potential of making either 1,1- or 1,3-products, the possibility of 1,1-products formation in addition to azides is the key feature that is

similar to the 1,1-addition to isonitriles. The 1,2-addition to azides would give a charge-separated zwitter-ionic product and is generally unfavorable. Also note that the "1,3" addition mode that is possible in the intermolecular additions to azides, is more difficult in the presence of intramolecular constraints in the *o*-Li-azidobenzene cyclization.

1,1-additions

As one could expect from the experimental preferences (vide infra), the preferred transformation of the azide reactant $\mathbf{R_{N3}}$ is the formation of benzotriazole $\mathbf{P_{1\text{-}5\text{-}N3}}$ (Scheme 12). Not only is the 1-4 activation barrier (~15 kcal/mol) is much higher but the putative product of the 1-4 reaction $\mathbf{P_{1\text{-}4\text{-}N3}}$ is 13.3 kcal/mol higher in energy than the reactant. Even if the 4-exo product were kinetically competitive, its formation would be reversible. The fact that the 4-exo activation barrier is only 2 kcal/mol higher than energy of the product suggests that this process is not stereoelectronically unfavorable.



Scheme 12. $[Ph\text{-}X\ldots Y\ldots Z]Li(THF)_3$ systems with preferred 1,1-additions (relative energies of activation barriers E^0_a, intermediates and products E^0 in kcal/mol, numbers in parenthesis corresponds to reactions of anions in absence of $Li^+(THF)_3$).

[a] no stationary points corresponding to transition states or products were found on potential energy surface.

Considering the 1,1-pattern of addition to azides, one can also suggest that the 1-5 (endo) preference is enhanced by the fact that the Li "counterion" does not need to migrate to an adjacent atom as in the usual additions to alkenes and alkyne (the "1,2-additions"). In order to address this

issue, we have also calculated the two cyclization potential energy profiles for the purely anionic version of this reaction. As expected, the "naked" anion is more reactive and the 1-5 cyclization barrier decreases noticeably (from 5.6 to 2.0 kcal/mol). Interestingly, the 1,4-product does not correspond to an energy minimum in the absence of Li cation.

According to the computations, the diazo derivative $\mathbf{R_{CN2}}$ can be transformed in the respective indazole $\mathbf{P_{1\text{-}5\text{-}CN2}}$ via negligible barrier of 0.5 kcal/mol and with high exothermicity (-62.3 kcal/mol). This finding suggested that the 1-5 reaction may be experimentally feasible. In contrast, we could not locate a minimum at the potential energy surface that corresponds to the 1-4 product $\mathbf{P_{1\text{-}4\text{-}CN2}}$. These findings agree well with the experimental observations.

In a similar manner, the endo-cyclization to an isonitrile proceeds via a low (1.8 kcal/mol) barrier and is highly exothermic. Subsequent proton migration leads to a highly stable isoindole, rendering the overall process to be 64.9 kcal/mol exergonic. The exo-cyclization does not provide a product that corresponds to an energy minimum.

1,2-additions

For comparison, we have also investigated the reactions of isocyanate and isothicyanate derivatives, $\mathbf{R_{NCO}}$ and $\mathbf{R_{NCS}}$ (Scheme 13). In these "1,2-additions" cases, exo-cyclizations become the favorable direction. Polarization of the π-bonds strongly favors nucleophilic attack at the carbon. As the result, we could not find an energetically feasible path to the 5-endo-product from the isocyanate. In contrast, the alternative 4-exo reaction has a low 8.0 kcal/mol activation barrier and is sufficiently exothermic (ΔE^0 = -9.0 kcal/mol) to suggests that such four-membered structures may be formed at the low temperature along with the products of their further transformations.

On the other hand, we have found both the 4-exo and the 5-endo products as energy minima for the isothiocyanate substrate. In both cases, the cyclization process is exothermic (-7.9 and -19.8 kcal/mol). However, the reactions display relatively high barriers (27.9 and 17.3 kcal/mol, respectively for $\mathbf{P_{1\text{-}5\text{-}NCS}}$ and $\mathbf{P_{1\text{-}4\text{-}NCS}}$) and the intermolecular processes are likely to become competitive because isothiocyanate groups are known to be highly reactive towards aryl lithiums.

We have also explored the transformation of cyanate $\mathbf{R_{OCN}}$ and thiocyanate derivatives $\mathbf{R_{SCN}}$. In both cases, the 5-endo-cyclizations have relatively low barriers (14.1 и 9.5 kcal/mol, respectively) and are quite exergonic (-32.0 и -32.7 kcal/mol, respectively) because they lead to the formation of aromatic benzoxazole $\mathbf{P_{1\text{-}5\text{-}OCN}}$ and benzothiazole $\mathbf{P_{1\text{-}5\text{-}SCN}}$. However, the 4-exo-dig cyclization was calculated to have even lower barriers (E^0_a = 5.6 и 5.3 kcal/mol, respectively). Hence, the "normal"[3a, 32] exo-preference for the "1,2-systems" is observed. Interestingly, the formation of the four-membered ring is transient, and the reacting systems evolves further with the migration of the cyano-group from the chalcogen to the *ortho*-carbon. The overall process results in

the formation of the stable *o*-cyano phenolate $\mathbf{P_{1\text{-}4\text{-}OCN}}$ and *ortho*-cyano thiophenolate $\mathbf{P_{1\text{-}4\text{-}SCN}}$, the likely final products at these conditions.

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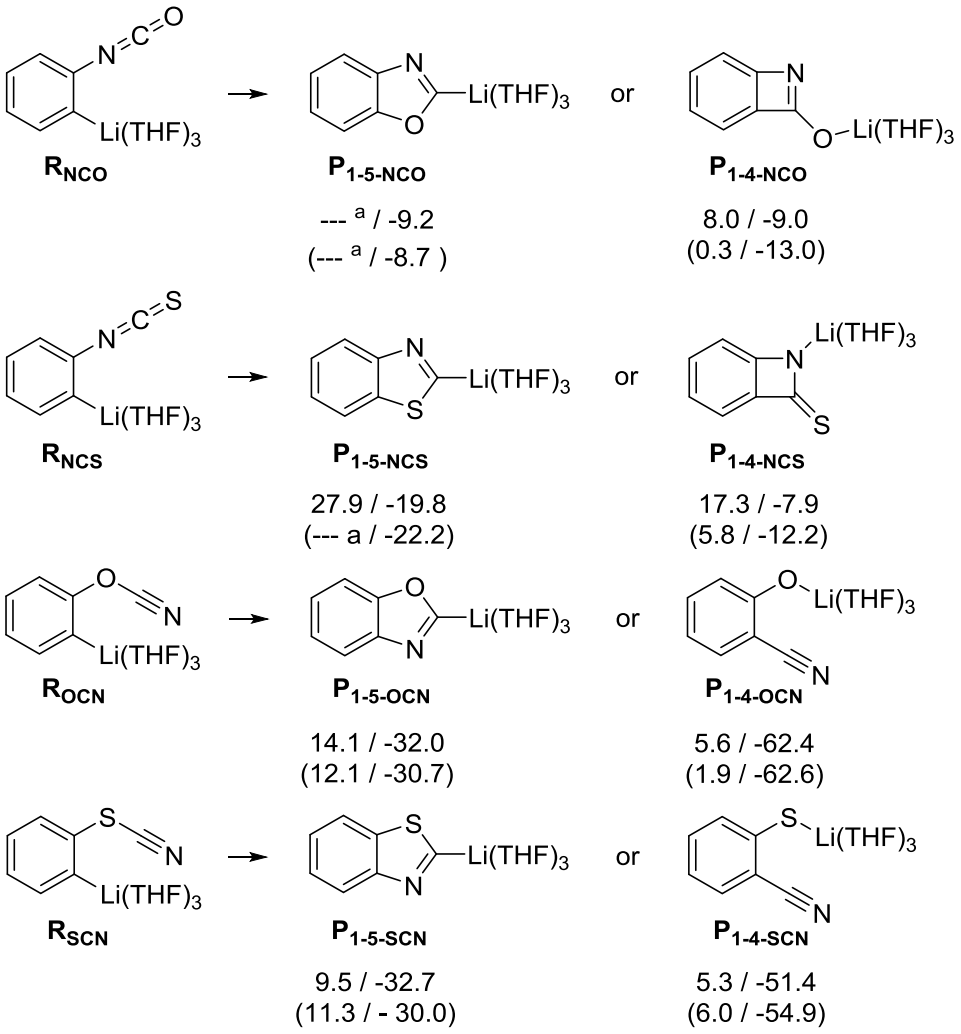

Scheme 13. $[Ph\text{-}N{=}C{=}Z]Li(THF)_3$ and $[Ph\text{-}X\text{-}C{\equiv}N]Li(THF)_3$ systems with preferred 1,2-additions (relative energies of activation barriers E^0_a, intermediates and products E^0 in kcal/mol, numbers in parenthesis corresponds to reactions of anions in absence of $Li^+(THF)_3$).

[a] no stationary points corresponding to transition states or products were found on potential energy surface.

An analogous kinetic preference for the 4-exo cyclization followed by a rearrangement was observed for the reaction of benzyl cyanide $\mathbf{R_{CCN}}$ (Scheme 14). The barrier for the cyclization is only 8.8 kcal/mol. In this case, the 4-exo product corresponds to an intermediate $\mathbf{P_{1\text{-}4\text{-}CCN}}$. The latter undergoes the C-C bond scission with the formation of *ortho*-cyano benzyl lithium via a low energy (4.5 kcal/mol) transition state. The process is quite favorable thermodynamically -17.6 kcal/mol) due to the strain relief and benzylic stabilization of the negative charge. The 5-endo product

formation is much more favorable thermodynamically (-47.6 kcal/mol) but disfavored kinetically (E^0_a = 16.4 kcal/mol).

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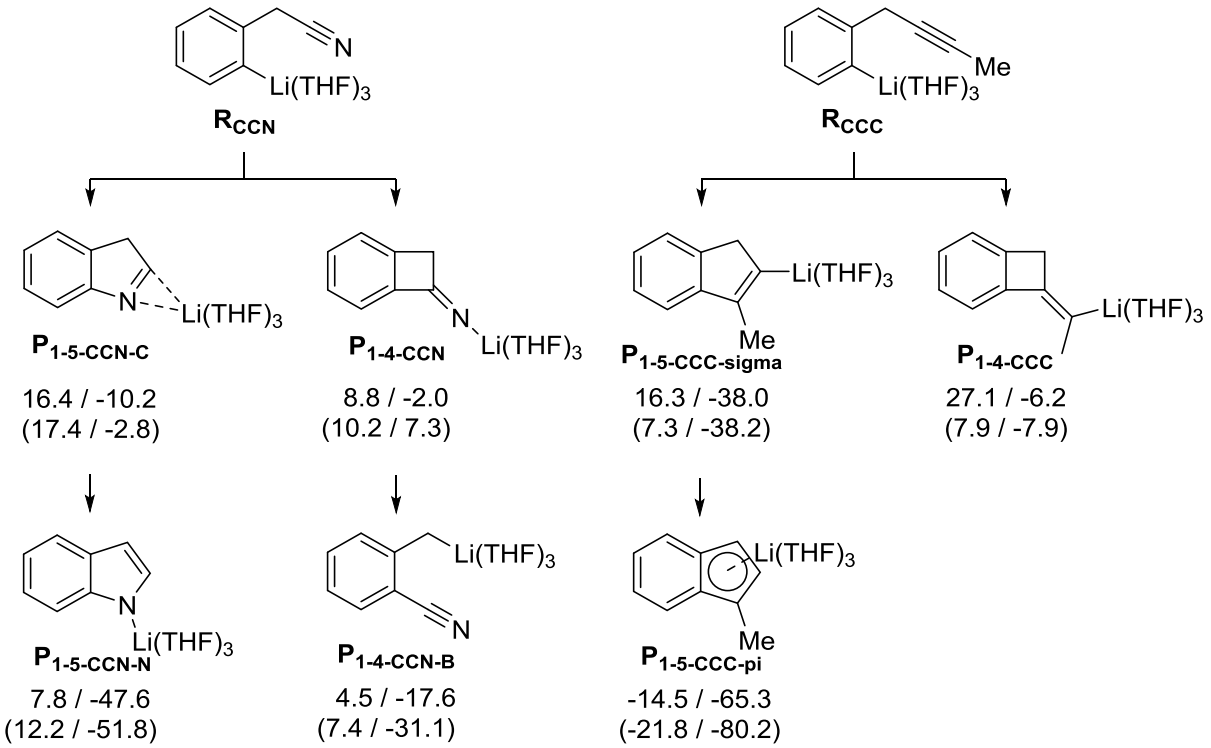


Scheme 14. Computational analysis of cyclizations of [Ph-CH_2-C≡Z]Li(THF)$_3$ systems following the 1,2-additions patterns (activation barriers E^0_a, relative energies of intermediates and products E^0 in kcal/mol, numbers in parenthesis corresponds to reactions of anions in absence of $Li^+(THF)_3$).

Finally, we have analyzed reaction of the *ortho*-lithium derivative containing a non-activated acetylene moiety **R_{CCC}**. In the absence of activating electronegative heteroatoms, the 4-exo barrier is significantly increased (27.1 kcal/mol). Much of this increase is due to the large decrease of thermodynamic contribution to the reaction barrier:[29b, 33] unlike the previous examples, this 4-exo- product is a C-centered anion and, hence, reaction energy is significantly less favorable (-6.2 kcal/mol).

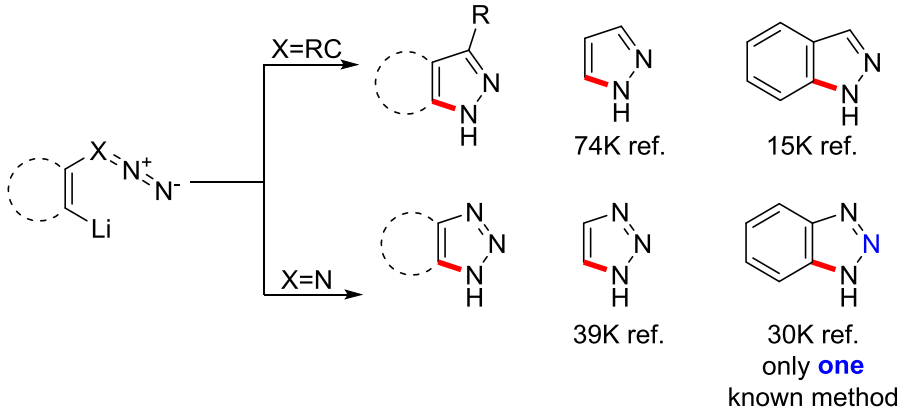
On the other hand, the 5-endo barrier remains sufficiently low (16.3 kcal/mol) for this path to remain kinetically viable at ambient temperatures. The initially formed indene **$P_{1\text{-}5\text{-}CCC\text{-}sigma}$** ($\Delta E^0$ = -38.0 kcal/mol) where the lithium is positioned at an sp^2-hybridized carbon undergoes (E^0_a = -14.5 kcal/mol) prototropic isomerization to a fully-conjugated aromatic anion **$P_{1\text{-}5\text{-}CCC\text{-}pi}$** ($\Delta E^0$ = -65.3 kcal/mol). Hence, such reaction can be potentially a source of indenyl lithium derivatives of this type.

Conclusions

A conceptually new method of benzotriazole synthesis by intramolecular cyclization of *ortho*-lithium aryl azides was developed. This method is based on robust lithium-halogen exchange which is followed by fast and selective cyclization with azide is fast and selective. Furthermore, the scope of the new method is broad - it was used to prepare a variety of polysubstituted benzotriazoles including those that were previously unavailable.

From the general perspective, the newly developed approach for the construction of the five-membered aromatic cycles opens synthetic access to four classes of heterocycles (benzotriazoles, triazoles, indazoles, pyrazoles. In particular, despite the fact that benzotriazoles are mentioned in ca. 30 thousand references,[1] This method was based on the introduction of the middle nitrogen atom to N,N'-orthodisubstituted benzenes (Scheme 15). The new method is based on the creation of a C-N bond from precursor that has the N_3-moiety already installed.

The new method also works well for the construction of indazoles, another popular heterocyclic scaffold as evident from ca. 15 thousands publications. In the future, the new method may open synthetic avenues for the preparation of triazoles and pyrazoles, all of each are very popular heterocycles.



Scheme 15

For the first time, directing effect of azide group in reactions of Li-Br exchange in aromatic ring was demonstrated. This effect allows selective activation of o-Br substituents in the presence of remote halogen atoms.

Computational analysis supports the possibility of intramolecular rearrangement at low temperatures and provides insights into the selectivity of these processes. Computed geometries for intermolecular addition to PhN_3 revealed that the preferred stereoelectronic trajectory for the

[1] The search for each heterocycle type was done using the following procedure – search for structures with at least one reference, search for structures with at any experimental property, then "find all publications"

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nucleophilic attack at the azide group is similar to the classic Burgi-Dunitz trajectory for nucleophilic addition to alkenes and alkynes.

However, the *intra*molecular reactions found dramatic differences between the functional groups that undergo the two distinct addition patterns: the 1,1-additions (azides, isonitriles, diazo compounds) and 1,2-additions (isocyanates, isothiocyanates, alkynes). Whereas exo-cyclizations are preferred for the 1,2-additions, endo-cyclizations become more favorable for the 1,1-addition, especially when the kinetic barrier is significantly lowered by thermodynamic contribution (e.g., from aromatic stabilization) and when the 4-exo-cyclizations are especially disfavored by the high strain.

The new reaction opens broad possibilities for development of synthetic approaches to heterocycles isoelectronic to benzotriazole through intramolecular cyclizations of the lithium–phenyl–XYZ fragment. In particular, the theoretical predictions paved the way to the experimental discovery of a new reaction, i.e., the indazole synthesis via cyclization of aryl-diazomethane lithium derivatives. More detailed studies of the new process will be reported in the due course.

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