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Article

Interrupted S_NAr-Alkylation Dearomatization

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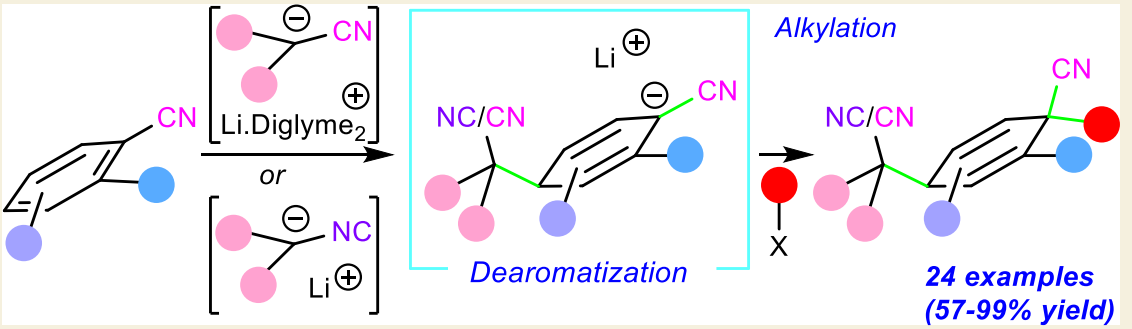


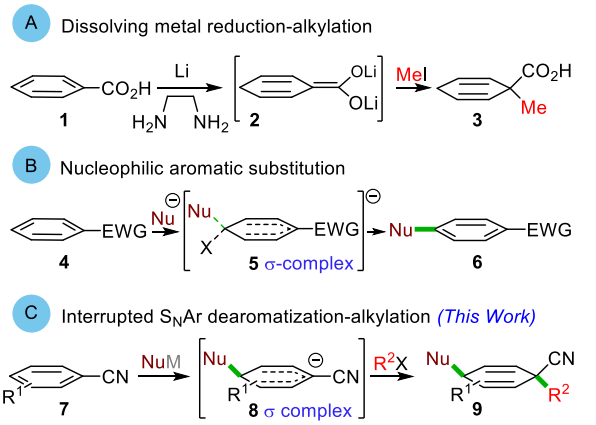
ABSTRACT: Dearomatizations provide powerful synthetic routes to rapidly assemble substituted carbocycles and heterocycles found in a plethora of bioactive molecules. Harnessing the advantages of dearomatization typically requires vigorous reagents because of the difficulty in disrupting the stable aromatic core. A relatively mild dearomatization strategy is described that employs lithiated nitriles or isocyanides in a simple S_NAr-type addition to form σ-complexes that are trapped by alkylation. The dearomatizations are diastereoselective and efficient and rapidly install two new carbon−carbon bonds, one of which is a quaternary center, as well as nitrile, isocyanide, and cyclohexadiene functionalities.

KEYWORDS: *dearomatization, interrupted S_NAr, σ-complexes, quaternary center, lithiated nitriles*

Aromatics rank among the most important organic molecules because of their high-volume deployment in industrial processes, their pervasive role in biological machinery, and their prevalence within active pharmaceutical ingredients.[1] The centrality of aromatics has spurred numerous strategies to transform readily available precursors into high value products. Several methods effectively dearomatize fused aromatics,[2] heteroaromatics,[3,4] and phenols,[3,5] whereas simple derivatives of benzene are more challenging because of the increased stability of the π-system.[6] Despite the strongly reducing conditions,[7] the classical dissolving metal reduction, and advantageous variants,[8] remain the gold standard to access complex cyclohexadienes (Scheme 1A, **1** → **2** → **3**).

Historically, nucleophilic aromatic substitutions have played a significant role in synthesis and in advancing the understanding of key σ-complexes **5** (Scheme 1B, **4** → **5** → **6**).[9] Originally posited as intermediates, σ-complexes **5** are now thought to more often occur as transition structures[10] which is guiding the development of new dearomatization manifolds.[11] Described here is a mild dearomatization strategy initiated by a nucleophilic dearomatization in which solvent effects are used to favor formation and trapping of intermediate σ-complexes **8** to assemble complex cyclohexadienes **9** (Scheme 1C, **7** → **8** → **9**). The method efficiently dearomatizes substituted benzenes, naphthalenes, anthracenes, and pyridine to rapidly assemble complex cyclohexadiene scaffolds that are valuable precursors for synthesis in general[12] and bioactive targets in particular.[13]

Scheme 1. Strategies for Dearomatization



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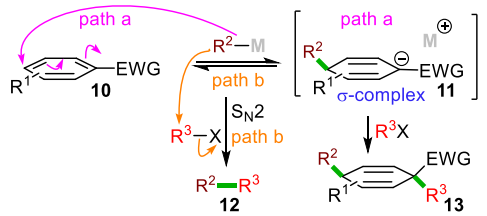
DISCUSSION

Nucleophilic addition to an aromatic followed by alkylation of the resulting anionic σ-complex requires overcoming several challenges (Scheme 2). Typically, S_NAr processes require

Scheme 2. Generalized Interrupted S_NAr Mechanism

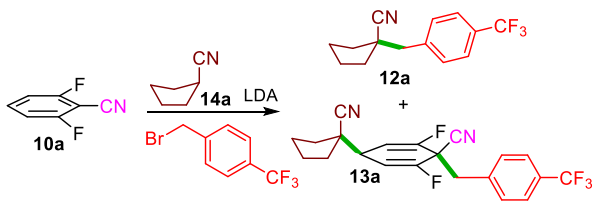


electron deficient aromatics **10** substituted with strongly electron withdrawing groups (EWG) tolerant of strong nucleophiles. In practice, the optimal electron withdrawing groups polarize the aromatic and stabilize the intermediate σ-complex via resonance because inductive electron withdrawal is usually insufficient.[11]

Among the best activating groups for S_NAr reactions are nitro-substituted aromatics (**10**, EWG = NO_2).[2] In fact, nucleophilic additions to nitroaromatics occur more rapidly at positions substituted by hydrogen than at positions occupied by halogens (**10** + R^2 M → **11**); subsequent ejection of the nucleophile from the σ-complex **11** to reform **10** is also fast which allows attack on carbons substituted with leaving groups leading to S_NAr.[14] Interrupting the dearomatization−rearomatization process requires that either the equilibrium between **10** and **11** (Scheme 2, path a) lies predominantly on the side of the σ-complex **11**, or that the rate at which **11** forms **13** is dramatically faster than the rate of electrophilic trapping by the nucleophile R^2 M to afford **12** (Scheme 2, path b).[15]

The feasibility of selectively trapping the intermediate σ-complex **11** was pursued with a lithiated nitrile and a substituted benzonitrile (Table 1). Lithiated nitriles are potent nucleophiles with a high charge density localized on the nucleophilic carbon which is ideal for disrupting the aromaticity.[16] Inexpensive 2,6-difluorobenzonitrile **10a** was selected as the aromatic because of the excellent ability of the nitrile and fluorine groups to stabilize the buildup of negative electron density in the σ-complex.[17] p-CF_3−$C_6H_4CH_2Br$ was selected as the electrophile because of the presumed requirement for a reactive electrophile to trap the modestly nucleophilic, delocalized, cyclohexadienyl anion (cf. **11** EWG = CN).,[18]

Table 1. Interrupted S_NAr Optimization Study[a]



entry	solvent	ratio **12a**:**13a**	yield **13a**
1	hexanes	1.0:0	0%
2	toluene	1.0:0	0%
3	Et_2O	1.0:0	0%
4	THF	2.2:1.0	48%
5	THF + 18-C-6	1.7:1.0	50%
6	DME	1.2:1.0	64%
7	diglyme	1.1:1.0	91%

[a]Conditions: Deprotonation of cyclopentanecarboniirile (2.0 equiv) with LDA (2.1 equiv) at −78 °C followed by addition of **10a** (1.0 equiv). After 1 h at-78 °C, added electrophile (2.1 equiv).

Exploratory forays revealed a significant solvent effect (Table 1). In hexanes, toluene, and ether (Table 1, entries 1−3, respectively), the only product was **12a** derived from the deprotonation and benzylation of **14a**. In THF, however, the 1,4-cyclohexadiene **13a** was clearly detected with the identity being unequivocally determined by X-ray crystallography (Scheme 3). Although the yield was modest, the crude reaction mixture was clean, with unreacted 2,6-difluorobenzonitrile and nitrile **12a** making up most of the remaining mass balance.

Efforts to promote full conversion focused on the temperature and time at which the electrophile, p-CF_3−$C_6H_4CH_2Br$, was added because of a strong dependence in a related dearomatization.[19] Reducing the reaction temperature from −78 to −100 °C completely shut down the dearomatization, whereas temperatures higher than −78 °C produced less cyclohexadiene **13a** and more of the benzylated nitrile **12a**. Changing the time at which p-CF_3−$C_6H_4CH_2Br$ was added from ten to less than 1 min led only to formation of the benzylated nitrile **12a**, whereas extending the time between the addition of 2,6-difluorobenzonitrile and p-CF_3−$C_6H_4CH_2Br$ substantially improved the conversion of **10a** to **13a**. The optimal time for aging the dearomatization in THF with **10a** and **14a** was 1 h, but the reaction did not go to complete conversion.

The aging was interpreted as the time required to establish the equilibrium in favor of the cyclohexadienyl anion (cf. Scheme 2, **10** → **11**). An additional equivalent of cyclopentanecarbonitrile (**14a**) was added to coax the equilibrium toward the cyclohexadienyl anion with the combination of 2.1 equiv of **14a**, 2.2 equiv of LDA, and a premixing time of 1 h affording a 48% yield of **13a** (Table 1, entry 4). Interpreting the beneficial effect of THF as creating a better nucleophile through lithium solvation led to the addition of 18-crown-6. Although the influence of 18-C-6 was minimal (Table 1, compare entries 4 and 5), changing the lithium solvation by switching from THF to DME to diglyme progressively improved the yield (Table 1, 48, 64, 91%, entries 7, 8, 9, respectively).[20]

Having identified optimized conditions, the reaction scope was probed with a series of commercially available benzonitriles and lithiated nitriles (Scheme 3). Lithiated nitriles derived by deprotonating acyclic (isobutyronitrile, 2-methylbutyronitrile) and cyclic 5- and six-membered nitriles followed by addition of 2-methoxybenzonitrile or 2,6-difluorobenzonitrile and trapping with BnBr efficiently afforded the corresponding cyclohexadienes **13b**−**13f**, respectively. Scaling the synthesis of **13e** to a one mmol scale proceeded in 69% yield, an efficiency similar to that of a small-scale reaction (77%). Electrophilic trapping of the σ-complex formed from the addition of lithiated cyclopentanecarbonitrile to 2-methoxybenzonitrile or 2,6-difluorobenzonitrile proved equally efficient with benzyl bromide (**13e** and **13f**), substituted benzyl bromides (**13g** and **13h**), allyl bromide (**13i**), and methyl iodide (**13j**).[21] Protonation with aqueous NH_4Cl occurred exclusively at the γ-position to afford **13k**, analogous

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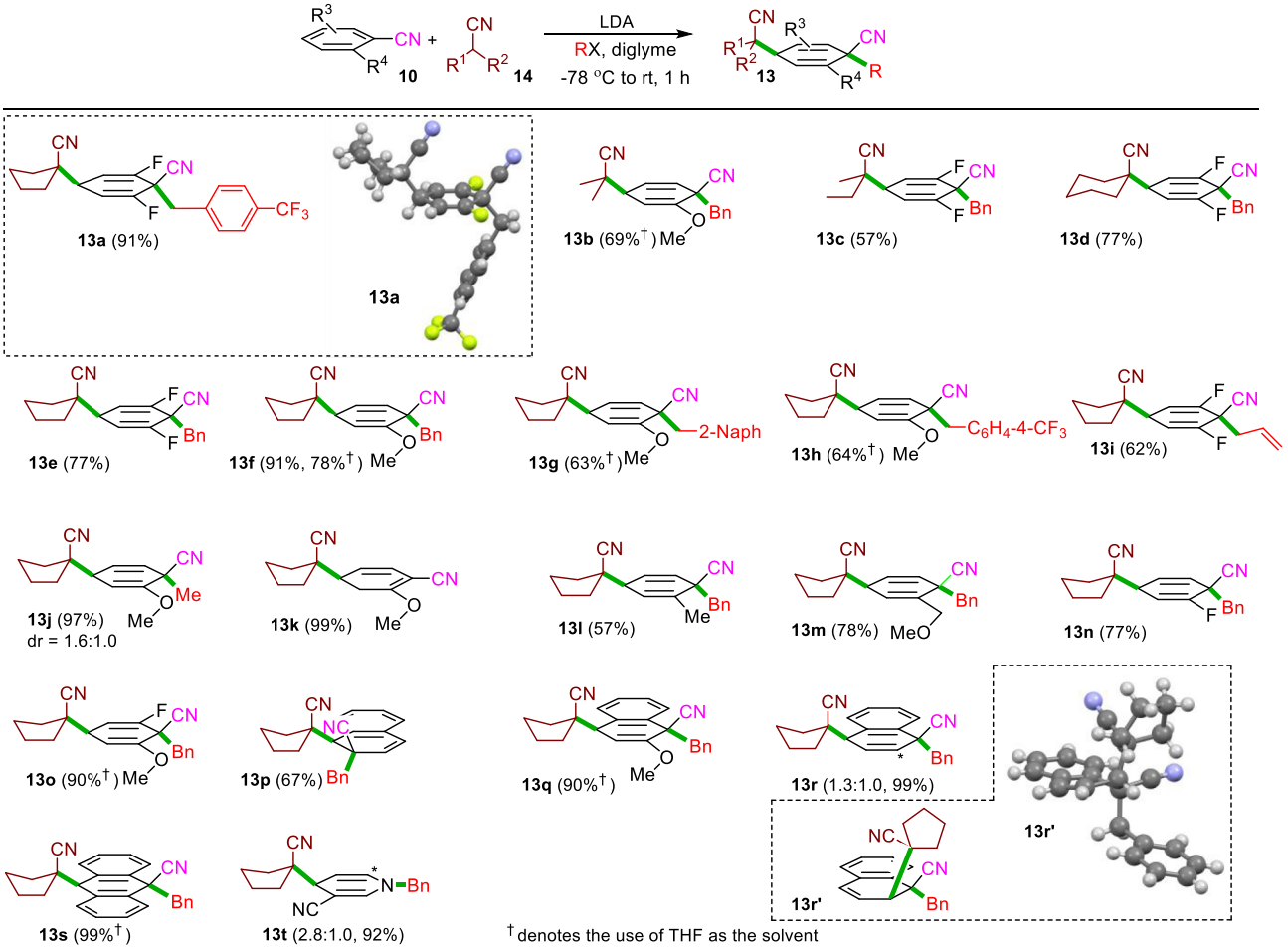
Scheme 3. Scope of the Interrupted SNAr-Alkylation of Substituted Benzonitriles with Nitrile Nucleophiles



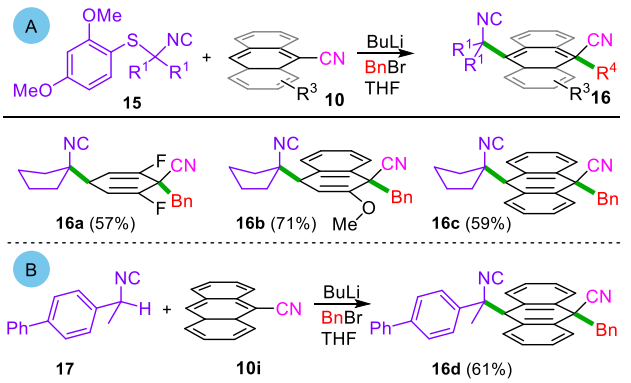
to related protonations of cyclohexadienecarbonitrile anions.[22] Only in the case of trapping with MeI were diastereomers observed resulting from attack on both faces of the cyclohexadienyl anion; in all other cases, a single diastereomer was obtained. Presumably, the small steric demand of MeI is insufficient to exert a large preference for addition to only one face of the σ-complex.

A range of substituted aromatic nitriles participate in the dearomatization.[23] In addition to 2-methoxy- and 2,6-difluorobenzonitriles (**13b**–**13k**), lithiated cyclopentane-carbonitrile efficiently dearomatized 2-methyl-, 2-methoxymethyl- and 2-fluorobenzonitrile to afford the cyclohexadienes **13l**, **13m**, and **13n**, respectively. The analogous dearomatization with 2-fluoro-6-methoxybenzonitrile very efficiently generated **13o**.

The dearomatization of 2-methylbenzonitrile demonstrates that neither electron deficient substituents nor chelating *ortho* substituents are required; attempts to add lithiated cyclopentanecarbonitrile to benzonitrile (**10**, $R^3 = R^4 = H$) afforded only minimal amounts of the corresponding cyclohexadiene (vide infra). Lithiated cyclopentanecarbonitrile efficiently added to several fused aromatics: 2-cyanonaphthalene and 1-cyano-2-methoxynaphthalene regioselectively afforded **13p** and **13q**, respectively, whereas the analogous addition to 1-cyanonaphthalene afforded a 1.3:1 ratio of regioisomers **13r** and **13r′**. For 9-cyanoanthracene, dearomatization occurred on the central ring to afford **13s**. The addition of lithiated cyclopentanecarbonitrile to 3-cyanopyridine afforded a mixture of regioisomers with divinylpyridine **13t** predominating.

The success of lithiated nitriles in the interrupted S_NAr-alkylation stimulated a search for other efficacious nucleophiles. While neither lithiated sulfides, sulfones, and sulfoxides nor the dianion derived from ethyl acetoacetate[24] participated in the dearomatization, lithiated nucleophiles derived by adding BuLi to the Asmic-like[25] isocyanide **15** efficiently afforded the corresponding isocyano-substituted cyclohexadienes **16a**–**16c** (Scheme 4A).[26] The lithiated benzylic

Scheme 4. Interrupted S_NAr-Alkylation Scope with Isocyanide-Containing Nucleophiles



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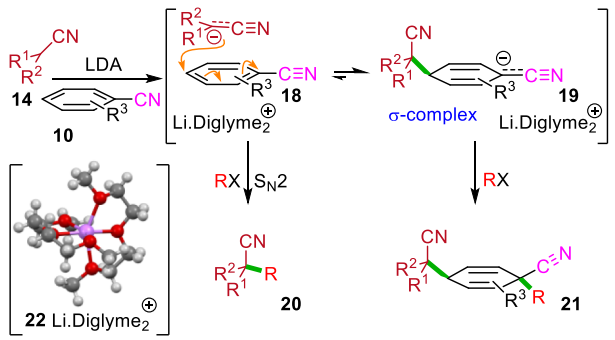
isocyanide derived by deprotonating **17** dearomatized 9-cyanoanthracene to afford **16d**; attempts to perform the analogous addition to 2,6-difluorobenzonitrile (**10a**) was not successful presumably because the delocalized, benzylic anion is insufficiently nucleophilic.[29]

DEAROMATIZATION MECHANISM

Mechanistic advances in nucleophilic aromatic substitution mechanisms have led to a revision of the classical S_NAr process.[14] Previously, the nucleophilic attack on an aromatic was thought to be particularly difficult, though now the nucleophilic addition is known to be facile with a faster attack at *ortho* and *para* positions occupied by hydrogen than at positions bearing leaving groups (cf. Scheme 5).[27,28]

Scheme 5. Mechanism of the Benzonitrile Dearomatization



Lithiated tertiary nitriles[15] and isocyanides[29] are exceptional nucleophiles because the electron density is localized on the nucleophilic carbon.[30] The nucleophilicity varies with solvation which dramatically accelerates the nucleophilic attack,[31] particularly when dissociated ion pairs are formed that localize electron density without dissipating charge into the solvent.[32] An attractive explanation for the efficacy of lithiated nitrile dearomatizations in diglyme is that diglyme encapsulates lithium cations in a cage-like structure **22**[33] creating a more nucleophilic nitrile anion than the lithium dimer favored in THF.[15] Support for the facile formation of the *σ*-complex **19** was obtained from a ^{19}F NMR experiment with lithiated cyclopentanecarbonitrile and 2,6-difluorobenzonitrile (**10a**) in which the initial signal for **10a** at −106.0 ppm was largely replaced by a signal at −105.4 ppm (6.4:1 ratio of the signals at −105.4 and −106.0, respectively).[34]

Conceptually, the conversion of the benzonitrile **10** to the cyclohexadiene **21** might arise by faster electrophilic trapping by **19** compared to the rate of trapping by the lithiated nitrile to give **20** (Scheme 5). The very efficient formation of **13k** (99% yield) obtained by protonating the putative *σ*-complex implies that the equilibrium lies strongly toward the side of the *σ*-complex because protonation is likely to be much faster than an equilibration between **18** and **19** (Scheme 5).

Computational analyses employing the local attachment energy were particularly beneficial in identifying the carbons most likely to be attacked in S_NAr processes;[35] the calculations point to a mechanism in which the formation of *σ*-complexes at aromatic sites substituted by hydrogen is faster than attack at a position substituted by a halogen. Calculations at the M06-2X/jun-cc-pVTZ level with an implicit SMD-PCM solvation correction for the attack of cyclopentanecarbonitrile anion on the para position of 2,6-difluorobenzonitrile show an exergonic attack passing through a transition structure TS1 with a free energy of 5.5 kcal/mol at −78 °C in THF solution (Figure 1, top left). Incorporating a lithium cation in the analogous calculation raises the energy of the transition structure considerably to 12.1 kcal/mol [TS1(Li$^+$)], consistent with the putative lithium solvation for the experiments in diglyme (Figure 1, bottom left). The lithium cation is not destabilizing TS1 or the anionic intermediate per se but the barrier is lower because lithium binds more strongly to deprotonated cyclopentanecarbonitrile than to the TS; this is the result of the negative charge being more localized in the anion than in TS1.

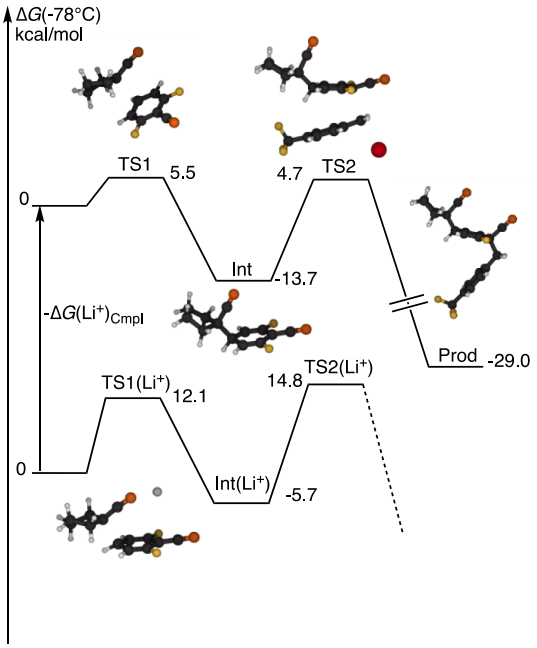


Figure 1. Stationary points for the dearomatization of 2,6-difluorobenzonitrile by deprotonated cyclopentylcarbonitrile followed by nucleophilic substitution with *p*-CF_3benzyl bromide in THF at −78 °C. Free energies have been computed at the M06-2X/jun-cc-pVTZ level with the implicit SMD-PCM solvation correction. The lower potential surface is for complexes with Li$^+$, where $DG(Li^+)_{Cmpl}$ is the free energy of complexation between deprotonated cyclopentylcarbonitrile and Li$^+$ in THF at −78 °C. The latter energy is very difficult to estimate accurately by computational means, because of a high dependence on the solvation energy of the bare Li$^+$ ion, which varies strongly with the radius assigned to Li$^+$.

Thus, the rate enhancing effect of diglyme derives from the favorable complexation to the lithium cation which activates the deprotonated nitrile toward attack on the *π*-cloud; the subsequent attack of the *σ*-complex onto *p*-CF_3−$C_6H_4CH_2Br$ is calculated to be the most favorable through an electrophilic trajectory TS2 to the face opposite the cyclopentylcarbonitrile substituent, i.e. an S_N2 type mechanism with the *σ*-complex as the nucleophile (Figure 1, top right).[36] Noteworthy is that the second step was identified to be rate-determining with a computed activation free energy of 18.4 kcal/mol at −78 °C relative to the *σ*-complex and free *p*-CF_3−$C_6H_4CH_2Br$.

Calculations using the local electron attachment energy[33] to predict the regioselective attack on the aryl nitriles are largely consistent with the observed addition−alkylations. For nitriles **10a** and **10s**, attack at the position para to the nitrile was predicted, whereas for **10f** and **10l**, attack at the positions ortho and para to the nitrile was calculated to be favorable

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(Figure 2); attack on the parent benzonitrile (**10z**) and **10q** were predicted to occur at the ortho position, though

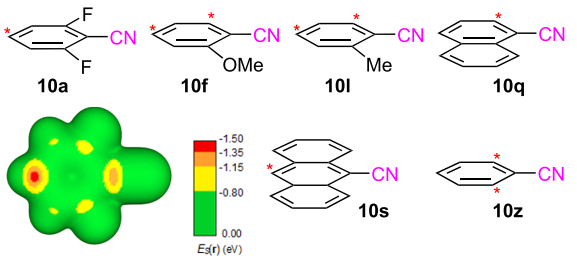


Figure 2. Arylnitriles evaluated with the local electron attachment energy ($E_S(\mathbf{r})$) to determine the addition regioselectivity. The asterisk marks the preferred position(s) for nucleophilic attack according to $E_S(\mathbf{r})$. The figure on the right shows $E_S(\mathbf{r})$ on the molecular surface of **10a**. The lowest $E_S(\mathbf{r})$ (red) is found at the *para*-position, which is also the position of the initial attack during the dearomatization. More information about the predictions of the $E_S(\mathbf{r})$ calculations are found in Table S1.

experimentally **10z** afforded minimal dearomatization−alkylation under all the conditions examined. Potentially, the attack preference as predicted by the electron attachment energy is accurate, but if alkylation of the nitrile-stabilized cyclohexadienyl anion is rate-determining, then the regioselectivity is independent of the initial *ortho* or *para* attack on the aromatic (cf. Scheme 5). Consequently, the reaction pathways for forming cyclohexadiene from **10l** by initial attack at both the *ortho* and *para* positions were computed to provide a point of comparison with **10a**.

Table 2 reports the relative free energies at −78 °C of the stationary points along the potential energy surfaces of **10l**

Table 2. Computed Relative Free Energies (in kcal/mol) of the Stationary Points for the Dearomatization of 10 Followed by Nucleophilic Substitution with *p*-CF_3benzylbromide to Form 13 in THF at −78 °C

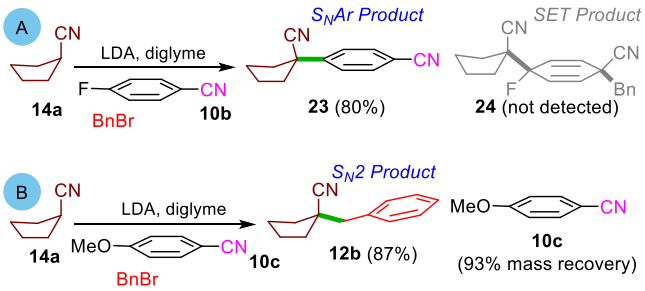
entry	EWG	position	TS1	int	TS2	product
10a	2,6-diF	para	5.5	−13.7	4.7	−29.0
10l	2-Me	ortho	12.0 (12.3)[a]	−0.7	15.1	−23.4
10l	2-Me	para	11.2	−2.9	10.4	−27.9

[a]The energy in parentheses refers to a TS conformer that will proceed directly to the lowest energy intermediate. The lowest energy TS proceeds to a conformer of higher energy, and the barrier of the conformational transition between the intermediate structures have not been computed.

together with the corresponding energies for **10a**. The activation free energy of the initial attack of **10l** is of similar magnitude for the *ortho* and *para* pathways, but the latter is slightly favored, i.e., by 0.8 kcal/mol. In contrast, the σ-complex resulting from attack at the *para* position is stabilized by 2.2 kcal/mol relative to the *ortho* σ-complex. The stabilization is the result of a more favorable solvation of the *para* σ-complex; the solvation energy of the *para* σ-complex is lower than that of the *ortho* σ-complex by 4.8 kcal/mol. The difference in solvation energy is reduced to 2.7 kcal/mol for the rate determining TS2, a difference that can only partially explain the lower free energy (−4.7 kcal/mol) of TS2 for the *para* pathway compared to the *ortho* pathway. The origin of the additional stabilization of TS2 in the *para* pathway by 2 kcal/mol is difficult to deduce but is speculated to stem from the increased steric compression for conversion of the *ortho* sp^2 hybridized carbon into an sp^3 center in the resulting σ-complex.

The regioselectivity of the dearomatizations was probed with a series of monofluorobenzonitriles. Addition of lithiated cyclopentanecarbonitrile to *o*-fluorobenzonitrile and trapping with BnBr afforded **13n** (Scheme 3), whereas *p*-fluorobenzonitrile **10b** afforded **23**, the product of anionic S_NAr (Scheme 6A); no dearomatization was observed with *m*-fluorobenzonitrile. Collectively, activation with an ortho or para fluorine substituent appears to be required, consistent with an S_NAr process, whereas the absence of a reaction with *m*-fluorobenzonitrile implies that an SET mechanism is unlikely. Probing the potential for SET-generated radical intermediates by performing the addition of lithiated cyclopentanecarbonitrile with 2,6-difluorobenzonitrile in the presence of TEMPO, and separately with diphenylethylene, decreased the yield from 91 to 48% (see **13a** in Table 1) but did not completely suppress the reaction.[37]

Scheme 6. Mechanistic Experiments



A related reaction with lithiated cyclopentanecarbonitrile and *p*-methoxybenzonitrile (**10c**) gave only nitrile **12b** arising from alkylation and no dearomatization, consistent with a more difficult attack at the *para* position (Scheme 6B). Consequently, benzylation of the lithiated nitrile becomes faster, leading to only formation of **12b**.

CONCLUSIONS

Lithiated nitriles add to variously substituted benzonitriles, triggering an unusual interrupted dearomatization−alkylation to afford complex cyclohexadienes. Use of diglyme as the solvent is particularly effective in facilitating the dearomatization which correlates with encapsulation of the lithium cation, thereby creating a potent nucleophile that readily disrupts the aromaticity. Calculations and mechanistic experiments indicate that the lithiated nitrile addition establishes an equilibrium between lithiated nitrile and a σ-complex. Subsequent rate-determining trapping of the σ-complex is efficient and highly diastereoselective with activated electrophiles, such as benzyl bromide and allyl bromide. The facile dearomatization of readily accessible arylnitriles makes the process potentially valuable for rapidly accessing complex cyclohexadienes.

METHODS

General Dearomatization Procedure

Neat benzonitrile (1.0 equiv) was rapidly added to a −78 °C, THF solution (0.1 M) of the lithiated nitrile [prepared by deprotonating the nitrile (2.0 equiv) with LDA (2.1 equiv)] or the lithiated isocyanide [prepared by adding BuLi (1.1 equiv) to a −78 °C, THF solution (0.1 M) of the isocyanide]. After 1 h at −78 °C for the

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lithiated nitrile or 60 s for the lithiated isocyanide, a neat electrophile (2.1 equiv) was rapidly added. The cooling bath was removed and after 1 h, saturated, aqueous NH_4Cl was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extract was dried (Na_2SO_4) and concentrated. The crude cyclohexadiene was dry loaded onto Celite and purified by automated flash column chromatography on silica gel using a Reveleris X2 purification system with 0−10% EtOAc/hexanes as the mobile phase.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00813.

Experimental procedures, compound characterization, computational data, and copies of NMR spectra (PDF)

Dearomatization (PDF)

Crystal data of **13a** (CIF)

Crystal data of **13r′** (CIF)

FAIR data which includes the primary NMR FID files for compounds **i−ii**, **12b**, **13a−13t**, **15**, **16a−16d**, and **23** (ZIP)

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Author Contributions

‡B.A. and J.-P.R.M. contributed equally. T.B. for computational analysis. The manuscript was written through contributions of all authors who have given approval to the final version of the manuscript. CRediT: **Bilal Altundas** formal analysis, investigation, writing-review & editing; **John-Paul R. Marrazzo** investigation, methodology, writing-review & editing; **Tore Brinck** conceptualization, software, validation, writing-review & editing; **Christopher Absil** data curation, formal analysis, resources, visualization; **Fraser F. Fleming** conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

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