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Controlling Diastereoselectivity in Dearomatizing Diels-Alder Reactions of Nitroarenes with 2-Trimethylsilyloxycyclohexadiene

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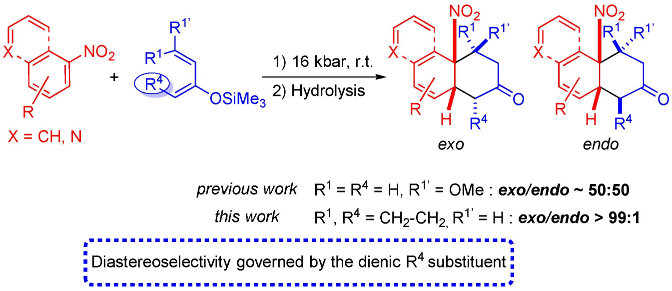
Dearomative Diels-Alder cycloadditions between nitroarenes and 2-trimethylsilyloxycyclohexadiene are carried out under high pressure at room temperature in the absence of any chemical promoter. Reactions are performed with different arenes, including the highly aromatic naphthalenes and quinolines. They lead to 3D-scaffolds with exquisite *exo*-diastereoselectivity. The *exo* approach is characterized by lower distortion of the substrates in a late TS and by more favorable orbital interactions presumably between the nitro group and the dienic part, explaining the stereoselectivity.

Introduction

Dearomatization strategies have the potential to convert planar substrates into complex (poly)cyclic three-dimensional molecules in a single step by disruption of the planar aromatic π-system.[1] Cycloaddition reactions involving aromatic C=C bonds as 2π-electron partners have become increasingly popular in recent years,[2] one of the most prevalent being transformations involving (3+2) and (4+2) annulations with the C2=C3 double bond in 3-nitroindoles.[3] This has led to the development of several elegant dearomatizing processes towards indole-based scaffolds, with most relying on an initial addition of a highly nucleophilic anionic species (*O*, *N* or *C*-centered anions) followed by a 5- or 6-ring closure through intramolecular capture of the resulting nitronate intermediate. [4+2] Cycloadditions involving electron-rich neutral dienes are much scarcer due to their lower reactivity.[4] Although known with electrophilic 3-nitroindoles, such reactions usually require strong activation which in turn induces rearomatization of the resulting cycloadducts through elimination of nitrous acid.

Recently, we reported that Diels-Alder cycloaddition reactions between nitroarenes and Danishefsky's diene, 1-methoxy-3-trimethylsilyloxy-1,3-butene **2a**, could be induced under high pressure activation (Scheme 1).[5] This non-invasive method[6] allowed the reaction to be performed at room temperature. This in turn preserved the three-dimensionality of the scaffolds generated by their reduced propensity for re-aromatization through elimination.[7] The ease with which these complex and functionalized 3D-structures were accessed from common starting materials was notable, though reactions were compromised to some extent by the poor ~1:1 ratio of *endo*/*exo* diastereomers observed in most cases.

DFT studies previously performed with 1-nitronaphthalene and Danishefsky's diene **2a** at the (SMD:CH_2Cl_2) M06-2X/6-31+G(d,p) level of theory,[8] had revealed quasi isoenergetic transition states (TSs) for both the *endo* and *exo* approaches,[9] in line with the aforementioned experimental results.[5] It is generally believed that for normal electron demand Diels-Alder cycloadditions the *endo* approach is favoured due to stabilizing interactions between the internal carbon atoms of the reacting 1,3-diene and the electron-withdrawing substituent of the dienophile through secondary orbital interactions (SOIs).[10] By way of contrast, an *exo* approach is promoted when there are unfavorable steric interactions between the diene and dienophile. In the case highlighted above, the poor diastereoselectivity was attributed to these factors operating discordantly rather than in concert.



Scheme 1. Dearomative [4+2] cycloadditions of nitroarenes with silyloxy dienes.

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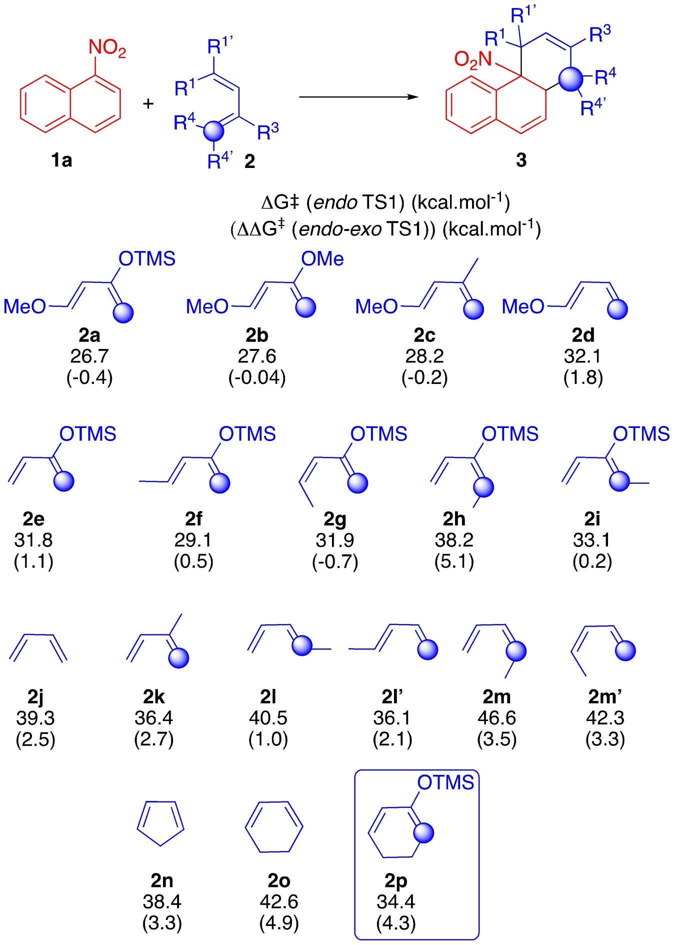
Results and Discussion

With 1-nitronaphthalene, DFT computations were performed on a series of dienes, substituted with electron-donating groups at different positions (Scheme 2). The activation energy required for both the *endo* and *exo* TSs were evaluated and compared, in order to examine the influence of the substitution on the diastereoselectivity of the process. Calculations were performed with dienes in their *s-cis* conformations (see supporting information (S.I.) for details). With oxydienes, calculations using an implicit solvation suggested that the cycloaddition occurs in a two-steps process, involving the formation of a zwitterionic primary adduct or a cyclic nitronate in the first step and its cyclisation to generate the cycloadduct in the second. Considering the higher energy barrier for the first dearomatizing addition compared to the second step (TS2 of ~3 kcal.mol^{-1} for the cyclisation of the *endo* primary adduct and ~21 kcal.mol^{-1} from the cyclic nitronate in the *exo* approach), it was clearly the rate determining step. Assuming that the first adduct had no time to rearrange before cyclization, the diastereoselectivity of the formal cycloaddition reflects the preferential approach in the first step of the sequence. The results displayed here relate this first determining addition step.



Scheme 2. Calculated Free Gibbs activation energy ($\Delta G^{\neq}$) and energy difference between the *endo* and *exo* approaches ($\Delta\Delta G^{\neq}$) in the first step (TS1) of the cycloadditions involving 1-nitronaphthalene and electron-rich dienes (at the (SMD:CH$_2$Cl$_2$) M06-2X/6-31+G(d,p) level). The shaded blue circle depicts the reacting center considered in this step, with unsymmetrical dienes.

Considering first the series of 1*E*-methoxybutadienes with different groups at C3 (**2a**–**2c**), calculations revealed that this variation has only a small impact on diastereoselectivity, leading to almost isoenergetic *endo* and *exo* pathways in each case. This is in line with experimental observations when changing a silyloxy group on the diene with a more sterically hindered substituent.[5] In the absence of a substituent at this position (**2d**), the *exo* path becomes slightly more favorable (by 1.8 kcal.mol^{-1}) and the activation energy is raised ($\Delta G^{\neq}$ = 32.1 kcal.mol^{-1}). Likewise, modifying the diene at position 1 while preserving the trimethylsilyloxy group at position 3 (**2e**–**2g**) has only a small impact on diastereoselectivity.[11] In stark contrast, a strong preference for the *exo* pathway is predicted with **2h** which bears a methyl group at position 4, in a *Z* configuration ($\Delta\Delta G^{\neq}$ = 5.1 kcal.mol^{-1}).[12] For the *E*-configured diene **2i** the difference between the *endo* and *exo* approaches is small, exposing the greater impact of substituents positioned internally over those positioned externally (*Z vs E*) in the TS.

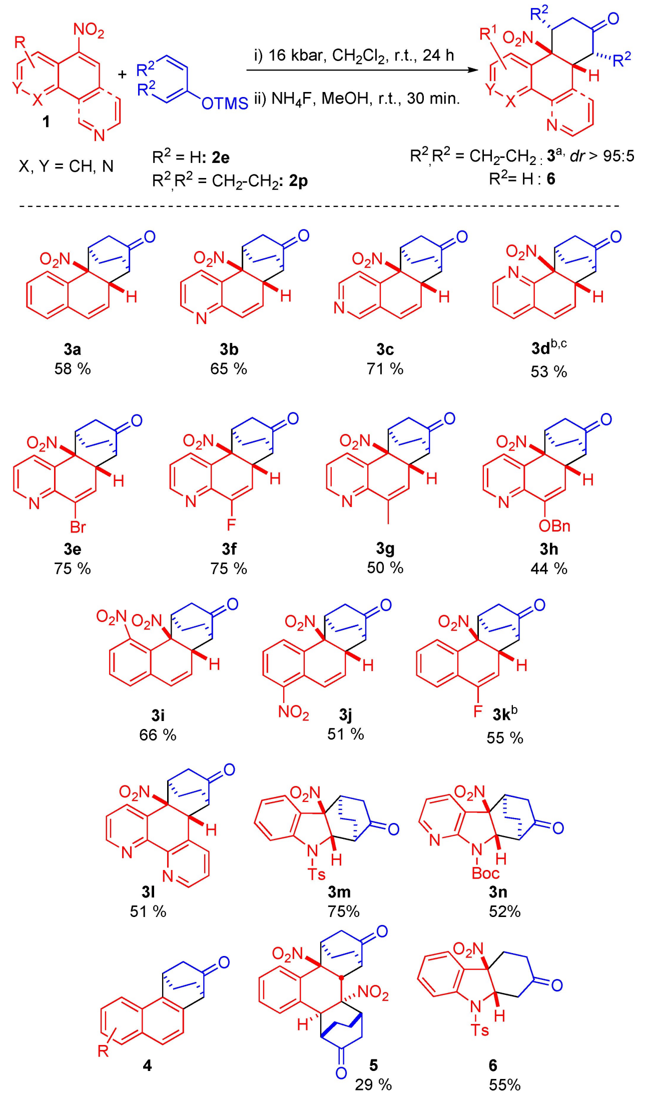
As expected, calculated activation energies were raised (to above 36 kcal.mol^{-1}) for dienes (**2j**–**2m**) with no ether groups attached, with each favoring an *exo* approach ($\Delta\Delta G^{\neq}$ = 1.0 to 3.5 kcal.mol^{-1}). As before, the highest diastereoselectivity predicted in the series was for **2m** bearing a substituent at position 4 with a *Z*-configuration.

Finally, cyclic dienes (**2n**–**2p**) gave improved diastereoselectivity in favor of the *exo* adduct ($\Delta\Delta G^{\neq}$ = 3.3 to 4.9 kcal.mol^{-1}) with the activation energy, as expected, higher for cyclohexadiene (**2o**) than for cyclopentadiene (**2n**) and trimethylsilyloxycyclohexadiene (**2p**) ($\Delta G^{\neq}$ = 42.6, 38.4 and 34.4 kcal.mol^{-1}, respectively).

The high activation energies calculated for these cycloaddition reactions are in line with the activation required experimentally for successful dearomatizing cycloadditions. Condensing classical alkylated dienes such as isoprene **2k**, cyclopentadiene **2n** or cyclohexadiene **2o** with 1-nitronaphthalene under high pressure led to an intractable polymeric mixture mainly resulting from diene polymerization. We turned our attention to 2-trimethylsilyloxycyclohexadiene **2p**, for which the calculated energetic barrier and diastereoselectivity were among the best. From a practical point of view, this diene benefitted from commercial availability, a low tendency for polymerization and would give access to highly functionalized cycloadducts with interesting molecular architectures.

Though **2p** is much less reactive than Danishefsky's diene, we were pleased to observe, experimentally, that it reacted well with 1-nitronaphthalene **1a** under 16 kbar pressure at room temperature (Table 1). A complete conversion of the nitroarene was observed within 24 h when it was condensed with an excess of diene. The effectiveness of high pressure activation in allowing nitronaphthalenic aromatics to serve as electron-poor dienophiles is notable. The corresponding tetracyclic cycloadduct **3a** was isolated after solvolysis with NH$_4$F at −30 °C. Pleasingly, only the *exo*-diastereomer was observed (which was assigned by NMR NOESY experiments on compound **3b**, see SI for details). Though the result confirmed the higher diastereose-

Table 1. High pressure activated [4+2] dearomatization reactions of nitroheteroaromatics with silyloxydienes **2p** and **2e.**



[a] Isolated yield. [b] compression at 16 kbar for 48 h instead of 24 h. c. 85 % conversion.

lectivity predicted by DFT calculations, the cycloadduct proved unstable on silica giving the eliminated product **4** through rearomatization by loss of nitrous acid. Indeed, this side reaction accounts for the discrepancy between the high conversion and modest 58% isolated yield. Once isolated, it however proved stable for weeks in the freezer.

With these results in hand, we evaluated the scope of this dearomative Diels-Alder cycloaddition with an array of nitro(hetero)arenes (Table 1). The electron-poor heteroaromatics 5-nitroquinoline and 5-nitroisoquinoline each furnished the expected cycloadducts **3b** and **3c** in 65 and 71% yield, respectively with exquisite *exo*-diastereoselectivity. By contrast, 8-nitroquinoline proved less reactive, leading to incomplete conversion after 24 h (~60%) which translated into a low 36% isolated yield. Pleasingly, extending compression to 48 h enhanced both conversion (85%) and yield (53%).

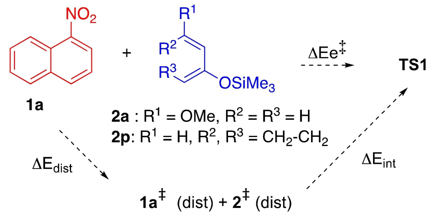
Various substituents were also tolerated on the nitroaromatic. Thus, in the 5-nitroquinoline series, 8-bromo- and 8-fluoro- analogues each gave the respective *exo*-cycloadducts, **3e** and **3f**, in 75% yield with no observed side reactions arising from S_NAr. The electron-releasing 8-methyl and 8-benzyloxy analogues proved less reactive, giving *exo*-cycloadducts **3g** and **3h** in ~50 and 44% isolated yield, respectively.[13] 1-Nitronaphthalenes bearing an additional nitro group, either at position 8 or 5, similarly gave the corresponding cycloadducts **3i** and **3j** in 66 and 51% isolated yield respectively. For the latter, the reaction was performed at higher dilution due to poor solubility (see S.I. for details). 4-Fluoro-1-nitronaphthalene was slow to react and required 48 h compression to achieve full conversion, giving adduct **3k** in 55% isolated yield.

1,3-Dinitronaphthalene, with two electron-withdrawing nitro groups on the same ring, behaved slightly differently giving *bis*-cycloadduct **5** through sequential cycloadditions to each nitrated double bond. Full conversion to one diastereomer was observed by ^1H NMR of the crude product mixture, but the high sensitivity of the adduct towards work-up and chromatographic purification led to a severe drop in the isolated yield (29%). Though less efficient, this cycloaddition is notable for producing in a single step a hexacyclic compound bearing 8 stereogenic centers from readily available starting materials.

Other substrates examined included 5-nitro-1,10-phenanthroline which reacted well to give adduct **3l** in 51% yield. 3-Nitroindole, which has been shown to react with Danishefsky's diene at room temperature and ambient pressure,[4h] gave no reaction with diene **2p** under those conditions. However, high pressure activation again proved effective, transforming this electrophilic substrate into the *exo*-diastereomer of tetracyclic indoline **3m** in 75% yield. As the diastereomer obtained is identical to the compound synthesized differently and characterized by X-ray diffraction studies,[3m] this supports the stereochemistry assignment in this case. Similarly, 7-aza-3-nitroindole led to the corresponding azaindoline **3n** in 52% yield.

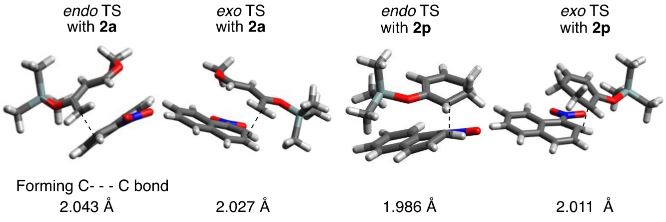
In the same way, the unsubstituted diene **2e** proved much less reactive than Danishefsky's diene and no reaction occurred at atmospheric pressure with 3-nitroindole. Here again, high pressure activation promoted cycloaddition to give adduct **6** was obtained in 55% yield after hydrolysis.

To gain a better understanding of the selectivity of these reactions, we compared the geometry of *endo* and *exo* transition states obtained with dienes **2a** and **2p** (Scheme 3). The first C–C bond formed is slightly shorter with the cyclic diene **2p** (1.986 and 2.011 Å for the *endo* and *exo* TSs respectively) than with the acyclic diene **2a** (2.043 and 2.027 Å for the *endo* and *exo* TSs respectively), indicating later transition states, in accordance with the higher activation barriers. In line with this observation, the pyramidalization of the reacting nitronaphthalenic C2 atom is more marked with the cyclic diene (sum of the 3 angles around the reacting C2 (C1 C2 C3, C1 C2H and C3 C2H) of 346.0–347.9°) than with Danishefsky's diene (349.7–349.3°).



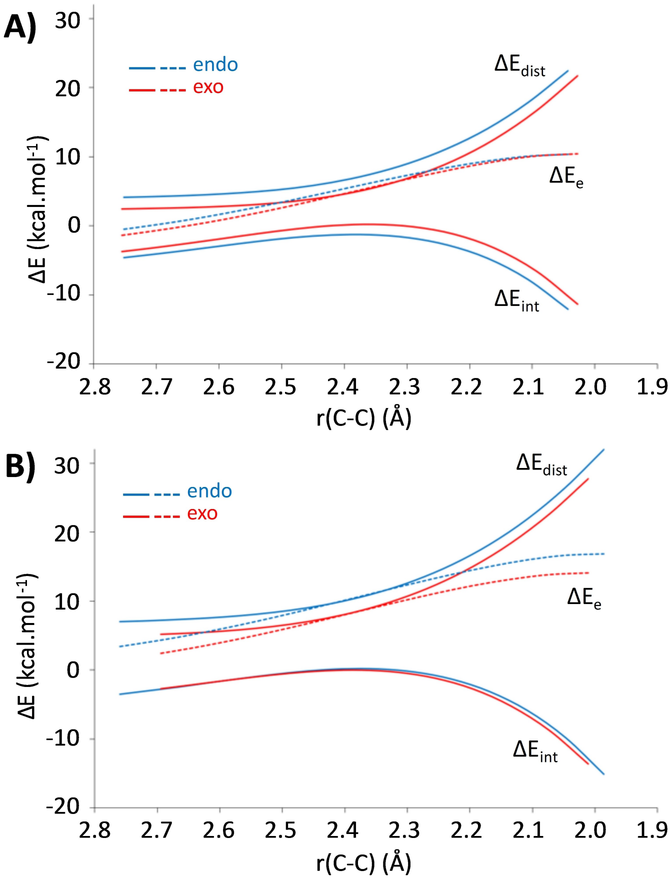
	endo TS with **2a**	*exo* TS with **2a**	*endo* TS with **2p**	*exo* TS with **2p**
$\Delta Ee^{‡}$	**10.3**	**10.4**	**16.8**	**14.1**
ΔE_{dist}	**22.4**	**21.7**	**31.9**	**27.7**
ΔE_{int}	-12.1	-11.3	-15.1	-13.6

ΔE (in kcal.mol^{-1})



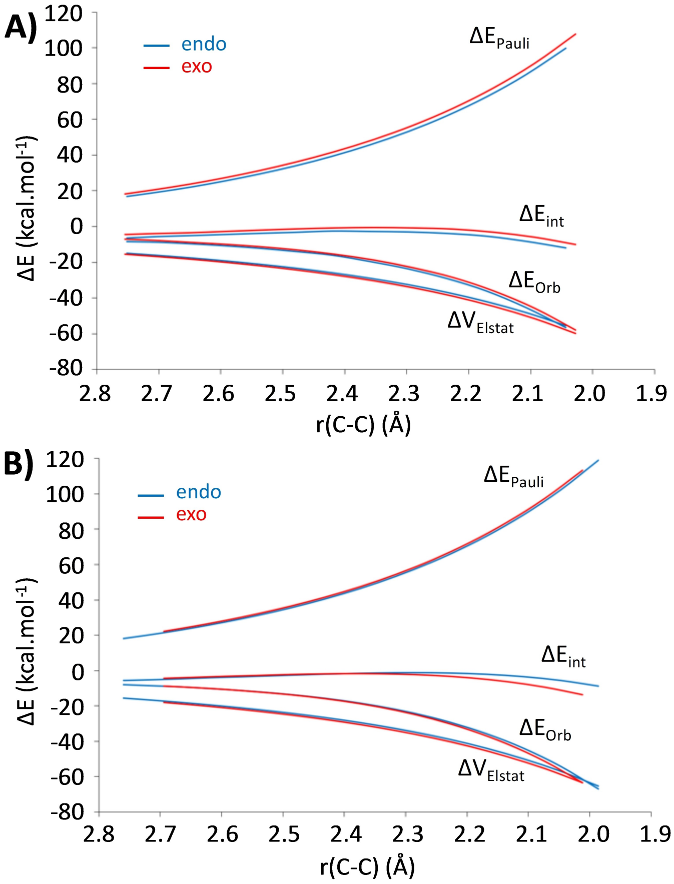
Scheme 3. D/I AS analysis scheme for the reaction involving 1-nitronaphthalene **1 a** and dienes **2 a** and **2 p**. Energies were calculated at the (SMD: CH_2Cl_2) M06-2X/6-31 + G(d,p) level.

Does this result, suggesting differences in deformation of the two substrates at the transition states, explain the *endo*/*exo* selectivity difference? To clarify this point, a distortion/interaction activation-strain (D/I AS) analysis was initiated.[14] Our hope was that it would provide new insights into the influence of steric and other factors on the transition states for the Diels-Alder cycloaddition reaction between 1-nitronaphthalene **1 a** and Danishefsky's **2 a** or cyclic diene **2 p** (Scheme 3). In this approach, the potential energy surface is separated into two contributions along the reaction path: the distortion energy (ΔE_{dist}) and interaction energy (ΔE_{int}) terms. ΔE_{dist} represents the energetic cost to deform the ground state geometries of the reactants into their geometries during the reaction, while the ΔE_{int} represents the energetic benefit resulting from stabilizing interactions between fragments at the same geometries. Scheme 4A shows a plot of the distortion and interaction energies along the intrinsic reaction coordinate (IRC) for the *endo* and *exo* paths of the reactions between **1 a** and **2 a**, from forming C–C bond distance of 2.8 Å to the transition states. Both the interaction energy and the distortion energy are larger along the *endo* path compared to the *exo* one, resulting in similar energy barriers ($\Delta\Delta G^{\neq} = -0.4$ kcal.mol^{-1}) and low selectivity. For the reaction between **1 a** and **2 p** (Scheme 4B), the interaction energies are nearly identical for both approaches, whereas the distortion energy remains larger along the reaction coordinates to the *endo* TS, resulting in the *exo* stereoselectivity with this diene. This suggests that the main difference would arise from a lower distortion to attain the *exo* TS with the cyclic diene.



Scheme 4. Plots of the distortion (ΔE_{dist}), interaction (ΔE_{int}) and total electronic (ΔE_e) energies along the intrinsic reaction coordinates for the *endo* (blue) and *exo* (red) approaches for the reactions involving 1-nitronaphtalene **1 a** and diene **2 a** (A) or **2 p** (B). Energies were calculated at the (SMD:CH_2Cl_2) M06-2X/6-31 + G(d,p) level.

To gain a more precise understanding of the factors influencing the interaction energy, we further conducted an Energy Decomposition Analysis (EDA).[15] This method breaks down the interaction energy into three components: Pauli repulsion (ΔE_{Pauli}), attractive electrostatic (ΔV_{elstat}) and orbital (ΔE_{orb}) terms. The calculations were performed with the Amsterdam Density Functional (ADF) program with the same functional, but without considering solvent effect. In scheme 5, the EDA terms are plotted along the IRC for the *endo* and *exo* reactions involving **2 a** and **2 p** dienes. For both dienes, the electrostatic interactions favour the *exo* transition states to the same extent, whereas the Pauli repulsion is smaller for the *endo* transitions states, in particular for **2 a**. The difference between the two dienes arises mainly from the orbital interactions that favour the *endo* transition state for **2 a** while, in contrast, it slightly favors the *exo* approach for diene **2 p**. This, combined with a relatively weaker Pauli repulsion, explains the *exo* diastereoselectivity. This is somehow unexpected as it means that the orbital interactions between the dienic part and the dienophile would involve preferably the naphthalenic part when **2 a** is considered whereas they would involve the nitro group with **2 p**.



Scheme 5. Plots of the electrostatic (ΔV_{Elstat}) orbital (ΔE_{Orb}), Pauli (ΔE_{Pauli}) interactions and interaction energies (ΔE_{int}) along the intrinsic reaction coordinates for the *endo* (blue) and *exo* (red) approaches for the reaction involving 1-nitronaphtalene **1 a** and dienes **2 a** (A) or **2 p** (B). The plots end at the transition stage geometries. Energies were calculated at the M06-2X/TZ2P level.

Conclusions

In conclusion, simple nitroarenes such as nitronaphthalenes and nitroquinolines smoothly undergo diastereoselective dearomatizing [4+2] cycloadditions with cyclic silyloxydienes under 16 kbar pressure at room temperature. These mild thermal conditions preserve 3-dimensionality in the polycyclic adducts by reducing the propensity for rearomatization by nitrous acid elimination. DFT calculations proved effective in determining the suitability of the dienic component for such reactions and correctly predicted the observed diastereoselectivity. They revealed that diene substitution at the reacting carbon atom (R^4 in Scheme 1) is a key factor determining the favorability of *endo* or *exo* approaches. With diene **2 p**, late TSs are localized computationally, with a lower distortion of the substrates in the *exo* approach. The latter is also characterized by more favorable orbital interactions, presumably between the nitro group and the dienic part, leading to the exclusive formation of the *exo* diastereomer in this case. We are currently looking to extend the methodology to enantioselective processes through use of chiral catalysts.

Supporting Information

Supporting Information (Ref. [16–20]).

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: [4+2] cycloaddition · nitroarene · silyloxydiene 3 · high pressure · DFT calculations

[1] See for instance: a) W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996–8017; b) J. M. Saya, E. Ruijter, R. V. A. Orru, *Chem. Eur. J.* **2019**, *25*, 8916–8935; c) C. J. Huck, D. Sarlah, *Chem* **2020**, *6*, 1589–1603; d) H. Zhu, S. Fujimori, A. Kostenko, S. Inoue, *Chem. – Eur. J.* **2023**, *29*, e202301973.

[2] See for instance: a) D. Antoniak, M. Barbasiewicz, *Org. Lett.* **2019**, *21*, 9320–9325; b) M. Okumura, D. Sarlah, *Chimia* **2020**, *74*, 577; c) J. Wang, H. Luo, X. Wang, D. Wei, R. Tian, Z. Duan, *Org. Lett.* **2022**, *24*, 4404–4408; d) S. Pradhan, F. Mohammadi, J. Bouffard, *J. Am. Chem. Soc.* **2023**, *145*, 12214–12223; e) L. Peng, Z. Zeng, K. Li, Y. Liu, Y. Lan, H. Yan, *Sci. Adv.* **2023**, *9*, eadg1645; f) S. Ben Salah, M. Othman, M. Sanselme, A. Daïch, I. Chataigner, A. M. Lawson, *J. Org. Chem.* **2023**, *88*, 12265–12275.

[3] See for instance: a) B. Rkein, A. Bigot, L. Birbaum, M. Manneveau, M. De Paolis, J. Legros, I. Chataigner, *Chem. Commun.* **2021**, *57*, 27–44; b) D. Cao, G. Chen, D. Chen, Z. Xia, Z. Li, Y. Wang, D. Xu, J. Yang, *ACS Omega* **2021**, *6*, 16969–16979; c) P.-H. Dou, S.-P. Yuan, Y. Chen, J.-Q. Zhao, Z.-H. Wang, Y. You, Y.-P. Zhang, M.-Q. Zhou, W.-C. Yuan, *J. Org. Chem.* **2022**, *87*, 6025–6037; d) H.-Z. Tian, S.-F. Wu, G.-Q. Lin, X.-W. Sun, *Tetrahedron Lett.* **2022**, *103*, 153969; e) H.-Z. Tian, S.-F. Wu, G.-W. Zhuang, G.-Q. Lin, X.-W. Sun, *Org. Biomol. Chem.* **2022**, *20*, 3072–3075; f) W.-C. Yuan, X.-M. Chen, J.-Q. Zhao, Y.-P. Zhang, Z.-H. Wang, Y. You, *Org. Lett.* **2022**, *24*, 826–831; g) J.-Q. Zhao, S. Zhou, H.-L. Qian, Z.-H. Wang, Y.-P. Zhang, Y. You, W.-C. Yuan, *Org. Chem. Front.* **2022**, *9*, 3322–3327; h) S. Pandit, V. K. Pandey, A. S. Adhikari, S. Kumar, A. K. Maurya, R. Kant, N. Majumdar, *J. Org. Chem.* **2023**, *88*, 97–105; i) W.-L. Zou, Y.-Q. Liu, Q.-Z. Li, X.-X. Kou, H. Huang, R.-S. Tong, J.-L. Li, B. Han, *Org. Chem. Front.* **2023**, *10*, 1237–1244; j) Y. Chen, J.-Q. Zhao, Y.-P. Zhang, M.-Q. Zhou, X.-M. Zhang, W.-C. Yuan, *Molecules* **2023**, *28*, 2765; k) M. Andreini, F. Chapellas, S. Diab, K. Pasturaud, S. R. Piettre, J. Legros, I. Chataigner, *Org. Biomol. Chem.* **2016**, *14*, 2833–2839; l) L. Birbaum, L. Gillard, H. Gérard, H. Oulyadi, G. Vincent,

X. Moreau, M. De Paolis, I. Chataigner, *Chem. Eur. J.* **2019**, *25*, 13688–13693; m) K. Pasturaud, B. Rkein, M. Sanselme, M. Sebban, S. Lakhdar, M. Durandetti, J. Legros, I. Chataigner, *Chem. Commun.* **2019**, *55*, 7494–7497.

[4] a) Ernest. Wenkert, P. D. R. Moeller, S. R. Piettre, *J. Am. Chem. Soc.* **1988**, *110*, 7188–7194; b) B. Biolatto, M. Kneeteman, P. Mancini, *Tetrahedron Lett.* **1999**, *40*, 3343–3346; c) T. L. S. Kishbaugh, G. W. Gribble, *Tetrahedron Lett.* **2001**, *42*, 4783–4785; d) B. Biolatto, M. Kneeteman, E. Paredes, P. M. E. Mancini, *J. Org. Chem.* **2001**, *66*, 3906–3912; e) M. Victoria Gómez, A. I. Aranda, A. Moreno, F. P. Cossío, A. De Cózar, Á. Díaz-Ortiz, A. De La Hoz, P. Prieto, *Tetrahedron* **2009**, *65*, 5328–5336; f) M. Andreini, M. De Paolis, I. Chataigner, *Catal. Commun.* **2015**, *63*, 15–20; g) Y. Li, F. Tur, R. P. Nielsen, H. Jiang, F. Jensen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2016**, *55*, 1020–1024; h) B. Rkein, M. Manneveau, L. Noël-Duchesneau, K. Pasturaud, M. Durandetti, J. Legros, S. Lakhdar, I. Chataigner, *Chem. Commun.* **2021**, *57*, 10071–10074.

[5] B. Rkein, R. Coffinier, M. Powderly, M. Manneveau, M. Sanselme, M. Durandetti, M. Sebban, G. Hamdoun, H. Oulyadi, D. Harrowven, J. Legros, I. Chataigner, *Chem. Commun.* **2022**, *58*, 11807–11810.

[6] For reviews on high pressure activation, see for instance: a) K. Matsumoto, H. Hamana, H. Iida, *Helv. Chim. Acta* **2005**, *88*, 2033–2234; b) *High Pressure Chemistry Synthetic, Mechanistic, and Supercritical Applications*, Wiley-VCH, Weinheim, **2008**; c) C. Hugelshofer, T. Magauer, *Synthesis* **2014**, *46*, 1279–1296. For a recent example, see for instance: d) M. Kopyt, M. Tryniszewski, M. Barbasiewicz, P. Kwiatkowski, *Org. Lett.* **2023**, 25, 6818-6822.

[7] 1-Nitronaphthalene had been shown previously to react with Danishefsky diene under thermal activation (120-150 °C). In this case, rearomatization of the cycloadducts is observed. See E. Paredes, B. Biolatto, M. Kneeteman, P. M. Mancini, *Tetrahedron Lett.* **2000**, *41*, 8079–8082.

[8] The M06-2X functional had shown good performance in similar processes. See for instance P. Vermeeren, M. Dalla Tiezza, M. E. Wolf, M. E. Lahm, W. D. Allen, H. F. Schaefer, T. A. Hamlin, F. M. Bickelhaupt, *Phys. Chem. Chem. Phys.* **2022**, *24*, 18028–18042.

[9] *Endo* cycloaddition can be defined as "that particular spatial arrangement of reactants in which the more bulky side of the diene is under the more bulky side of the dienophile". In this case, the naphthalene part is considered to be more bulky than the NO_2 group for the dienophile and the trimethylsilyloxydienic part is the more bulky of the diene. See for instance: F. Fringuelli, A. Taticchi, *Dienes in the Diels-Alder Reaction*, Wiley, New York, NY, **1990**, pp 1–44.

[10] See for instance a) K. N. Houk, *Tetrahedron Lett.* **1970**, *11*, 2621–2624; b) C. S. Wannere, A. Paul, R. Herges, K. N. Houk, H. F. Schaefer, P. Von Ragué Schleyer, *J. Comput. Chem.* **2007**, *28*, 344–361; c) B. J. Levandowski, T. A. Hamlin, F. M. Bickelhaupt, K. N. Houk, *J. Org. Chem.* **2017**, *82*, 8668–8675.

[11] Dienes **2e**, **2j** and **2k** do not bear any substituent at C1 and C4 and would lead to the formation of a single diastereomer, experimentally. The $\Delta\Delta G^{\neq}$ reported in these cases relate the energy differences between the computed values for the two endo/exo TSs.

[12] For consistency, we have used the same numbering throughout the series rather than strict IUPAC nomenclature.

[13] The cycloadducts **3g** and **3h** were isolated in the presence of a small amount of the corresponding re-aromatized adducts **4g** and **4h**. Noteworthy, the cycloadducts tendency to re-aromatize on silica proved dependent on their structures. The ones derived from nitro(aza)indoles or (iso)quinolines were, in general, much less prone to aromatization than the ones derived from nitronaphthalenes.

[14] See for instance: a) I. Fernández, F. M. Bickelhaupt, *Chem. Soc. Rev.* **2014**, *43*, 4953–4967; b) F. M. Bickelhaupt, K. N. Houk, *Angew. Chem. Int. Ed.* **2017**, *56*, 10070–10086.

[15] See for instance: L. Zhao, M. Von Hopffgarten, D. M. Andrada, G. Frenking, *WIREs Comput. Mol. Sci.* **2018**, *8*, e1345.

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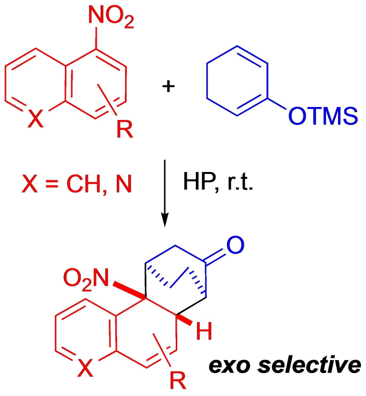
Dearomative Diels-Alder cycloadditions between simple nitroarenes and cyclic silyloxydienes are carried out under high pressure at room temperature in the absence of any chemical promoter to generate 3D-scaffolds with exquisite *exo*-diastereoselectivity, the *exo* approach being characterized by a lower distortion of the substrates and by more favorable orbital interactions presumably between the nitro group and the dienic part.



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Controlling Diastereoselectivity in Dearomatizing Diels-Alder Reactions of Nitroarenes with 2-Trimethylsilyloxycyclohexadiene