

COMMUNICATION

High Pressure promoted Dearomatization of Nitroarenes by [4+2] Cycloadditions with Silyloxydienes

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Batoul Rkein,^a Romain Coffinier,^a Marian Powderly,^a Maxime Manneveau,^a Morgane Sanselme,^b Muriel Durandetti,^a Muriel Sebban,^a Ghanem Hamdoun,^a Hassan Oulyadi,^a David Harrowven,^c Julien Legros,^a and Isabelle Chataigner*^{a,d}

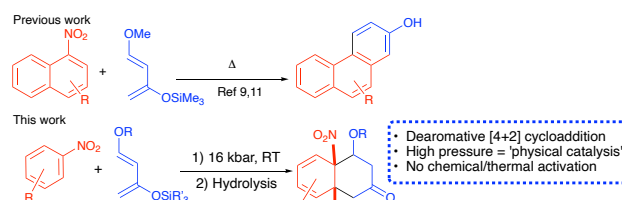
Simple nitroarenes such as nitronaphthalenes and nitroquinolines smoothly undergo dearomatizing [4+2] cycloadditions with silyloxydienes under 16 kbar. Highly functionalized 3-dimensional polycyclic adducts bearing a tetrasubstituted carbon centre at the ring junction are obtained in one step from simple raw materials. This unprecedented dearomative Diels-Alder process is performed at room temperature without any chemical promoter, illustrating the exceptional role of high pressure as physical promoter.

One of the current challenges in organic synthesis is to find ways of producing functionalized three-dimensional molecules with “high exploratory power”.¹ In this context, dearomatization strategies are able to convert planar substrates into elaborate 3D-molecules in a single step, by disruption of the aromatic π -system.² Oxidation of phenols constitutes an archetypal dearomatization process,³ and despite its limitations, the transformation has provided convenient routes to an array of valuable molecules. Indole dearomatization strategies have also been used in elegant alkaloid syntheses, with most taking advantage of the nucleophilicity of C3 in this electron-rich heterocycle.⁴

Nucleophilic dearomatization additions of organometallic reagents to electron deficient arenes also have a long history.⁵ More powerful still are dearomative cycloaddition reactions as they provide chemists with the means to synthesise complex (poly)cyclic 3D-molecules in a single operation.⁶ For example, [4+2] cycloadditions between electron-depleted arenes and electron-rich 1,3-dienes have been reported by us and by others.^{7,8} The most commonly used substrates are nitroarenes, where harsh conditions are often needed to promote the

cycloaddition process. For example, the reaction of 1-nitronaphthalene with Danishefsky diene **1a** requires heating in benzene at 150 °C over several days and, unfortunately, leads to subsequent re-aromatization to furnish the corresponding phenanthrenol.^{9,10} The reaction can also be performed at a lower temperature in ionic liquids but also leads to phenanthrenols.¹¹ Rearomatization can be prevented by nucleophilic activation of the dienic component.¹² For example, reaction of the enolate derived from methoxybutenone with 1,5-dinitronaphthalene yields the corresponding Michael adduct, which then undergoes ring closure to give the formal [4+2] cycloaddition product.

Herein, we report a direct dearomative [4+2] cycloaddition of nitroaromatic compounds promoted by high pressure (16 kbar). This unprecedented reaction requires no further chemical or thermal activation, and furnishes highly functionalized polycyclic structures with a tetrasubstituted carbon centre at the ring junction (Scheme 1).



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

High Pressure (HP) activation in the liquid phase has been shown to promote Diels-Alder cycloaddition reactions that have been impossible to achieve using standard procedures. Such [4+2] cycloadditions have very negative activation volumes, $\Delta V^\ddagger \sim -25$ to -40 mol. L⁻¹, such that their kinetics are almost always accelerated under HP.¹³ One of the first examples, and arguably the most emblematic, was by Dauben et al. who used furan as a diene in their synthesis of cantharidine.¹⁴ Since then, HP activation has proven useful when performing [4+2] cycloadditions with sterically hindered and electronically deactivated substrates, and in circumstances where the adducts are prone to elimination reactions (as these generally have a positive ΔV^\ddagger). The ability to perform reactions at room temperature or under gentle heating is also beneficial

^a Normandie Université, UNIROUEN, CNRS, INSA Rouen, COBRA laboratory, F-76000 Rouen, France
E-mail: isabelle.chataigner@univ-rouen.fr

^b Normandie Univ, UNIROUEN, SMS EA3233, F-76000 Rouen, France

^c Chemistry, University of Southampton, Highfield, Southampton, UK.

^d CNRS, Sorbonne Université, LCT UMR 7616, F-75005 Paris, France.

† Footnotes relating to the title and/or authors should appear here.

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for preserving the integrity of both the substrates and the resulting cycloadducts.

Our study began with the reaction of Danishefsky's diene **1a** (6 equiv) and 1-nitronaphthalene (**2a**) in dichloromethane (Table 1). After 24 h at room temperature under 16 kbar pressure, the dearomatized adduct **3a** was given in 50% yield after hydrolysis of the silyl enol ether intermediate. Increasing the reaction time to 72 h elevated that yield to 96%, with the product given as a 1:1 mixture of diastereoisomers in each case. Attempts to eliminate methanol while keeping the tetrasubstituted nitro center failed. As anticipated, a *cis*-relationship was observed between the proton and nitro group at ring junction. Notably, the outcome was in stark contrast to that given by thermal activation, where re-aromatization was observed through elimination of methanol and nitrous acid.⁹

To delineate the scope of the reaction, we next applied it to a series of nitro- and dinitro-arenes **2b-e**. Under the aforementioned conditions, fluoronitronaphthalene **2b** gave the analogous cycloadduct **3b** in 96% isolated yield (entry 2). Indeed, even in the presence of a large excess of diene **1a**, the fluorinated double bond proved resistant to both S_NAr and cycloaddition reactions. The structure was confirmed by X-ray analysis on a single crystal of the minor isomer of compound **3b-cis** (See E.S.I.). Similarly, 2,7-dinitronaphthalene **2c**, proved resistant to tandem cycloaddition, giving cycloadduct **3c** in 65% yield as a 1:1 mixture of diastereoisomers after 24 h. The reduced yield was traced to the sensitivity of the product on silica (entry 3).

Notably, 1,3-dinitronaphthalene **2d** behaved differently towards diene **1a**, giving the *bis*-cycloadduct **3d** in 92% yield. In this case, the initial cycloaddition produces an intermediate nitroalkene rather than a nitroarene making the second cyclisation facile. The *bis*-adduct was formed as a mixture of 3 diastereomers, in a ratio of 55:25:20 (entry 4) (See E.S.I. for details on the relative stereochemistry). The same tandem [4+2] cycloaddition reaction was also given by 1,3-dinitrobenzene **2e**, leading to tricyclic *bis*-cycloadduct **3e** in 45% isolated yield, formed as a mixture of 4 diastereomers (entry 5). Although full conversion of the starting materials was observed after compression, the intermediate proved sensitive to hydrolysis such that the isolated yield could not be improved. Nonetheless, it is significant as the first example of an uncomplexed benzene derivative acting as 2π electron-poor component in a [4+2] cycloaddition process.

The methodology was next extended to heteroaromatic systems through the dearomative [4+2] cycloaddition of various quinoline derivatives. Reacting 5-nitroquinoline **4a** with Danishefsky's diene **1a** resulted in the formation of adduct **5a**, where cycloaddition had occurred exclusively on the carbocycle (Scheme 2), in line with the regioselectivity observed in related (3+2) cycloaddition reactions.⁶ The regioisomeric 6-, 7- and 8-nitroquinolines **4b-4d** also proved reactive towards Danishefsky's diene at room temperature under pressure, furnishing cycloadducts **5b-5d** in high yields with comparable diastereoselectivities. In each case only one regioisomer was observed. For 5- and 7-nitroquinolines, **4a** and **4c** respectively, complete consumption was observed

within 24 h. By contrast, with 6- and 8-nitroquinoline, **4b** and **4d** respectively, some remained after 72 h of compression. In the latter of these diastereoselectivity was marginally higher, which we presume to be due to steric effects.

Table 1. High pressure activated dearomatizing [4+2] cycloadditions with nitronaphthalenes and 1,3-dinitrobenzene.

Entry	Substrate	time (h)	Cycloadduct ^b	Yield (%) ^c
1		24	 3a , <i>dr</i> ~ 50:50	50
		72		96
2		72	 3b , <i>dr</i> ~ 60:40	96
3		24	 3c , <i>dr</i> ~ 50:50	65
4		24	 3d , <i>dr</i> ~ 55:25:20	92
5		24	 3e , <i>dr</i> ~ 40:30:20:5	45

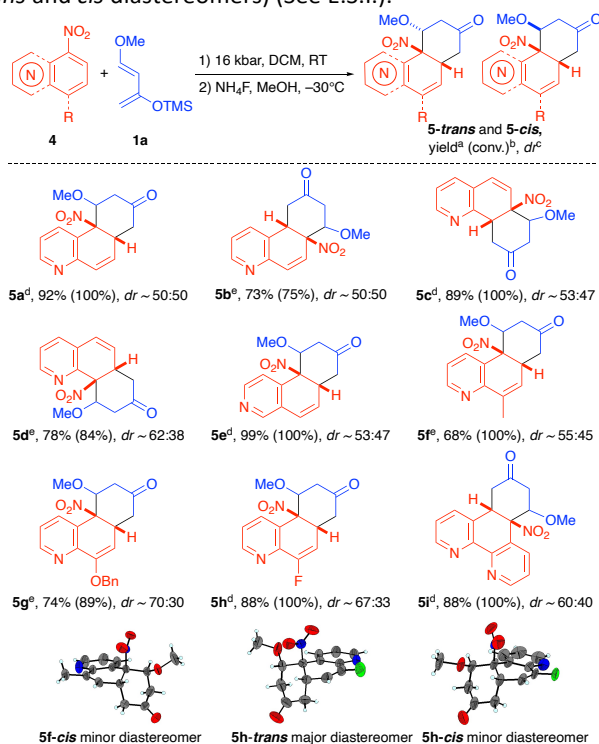
a. In the presence of 6 equiv of diene **1a** relative to the nitroarene.

b. Diastereomeric ratio determined by ¹H NMR on the hydrolyzed crude mixture.

c. Isolated yield.

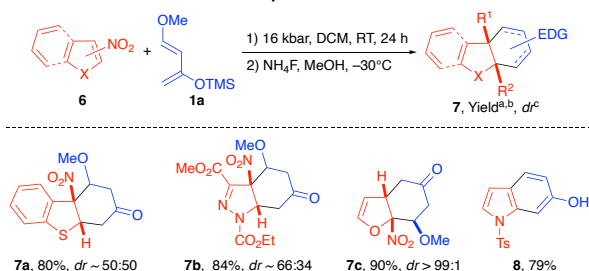
5-Nitroisoquinoline (**4e**) furnished the expected cycloadduct **5e** in a nearly quantitative yield, suggesting that the position of the nitrogen atom within the heteroarene had no impact on the course of the reaction. Various substituents on the carbocycle were also tolerated. Electron-releasing methyl and benzyloxy groups positioned at C8 produced less reactive substrates, with **4f** and **4g** both requiring an extended reaction time (72 h) to achieve high conversions and yields. Diastereoselectivity remained low but was better in the case of the more hindered benzyloxy substrate. The presence of a fluoro-substituent at C8 resulted in a more reactive dienophile with nitroarene **4h** entirely consumed within 24 h of compression with diene **1a**. The resulting cycloadduct **5h** was given in 88% yield as a 2:1 mixture of diastereomers after hydrolysis. Similarly, nitrophenanthroline **4i** furnished **5i** in 88% yield as a 3:2 mixture of diastereomers. The structures and relative stereochemistry were confirmed by X-ray analysis

on single crystals for **5f-cis** (minor diastereomer) and **5h** (both *trans* and *cis* diastereomers) (See E.S.I.).



Scheme 2. High pressure activated [4+2] dearomatization reactions of 6-membered nitroheteroareomatics **4** with diene **1a**. a. Isolated yield. b. Conversion of the nitroarene. c. Diastereomeric ratio, determined by ¹H NMR on the hydrolyzed crude mixture. d. compression for 24h. e. compression for 72h.

Next, we applied these cycloaddition reactions to nitrated five-ring heterocycles (Scheme 3). Although 3-nitro-indoles and benzofurans were reported to be sufficiently electrophilic to react with **1a** at ambient temperature and pressure,⁷ⁱ 3-nitrobenzothiophene **6a** was not. Here again, application of high pressure activation proved its worth giving the dearomatized cycloadduct **7a** in 80% isolated yield as a 1:1 mixture of diastereomers. Similarly, pyrazole **7b** bearing electron-withdrawing groups at positions N-1, C-3 and C-4 reacted smoothly to furnish bicyclic adduct **7b** in high yield with a 2:1 diastereoselectivity.

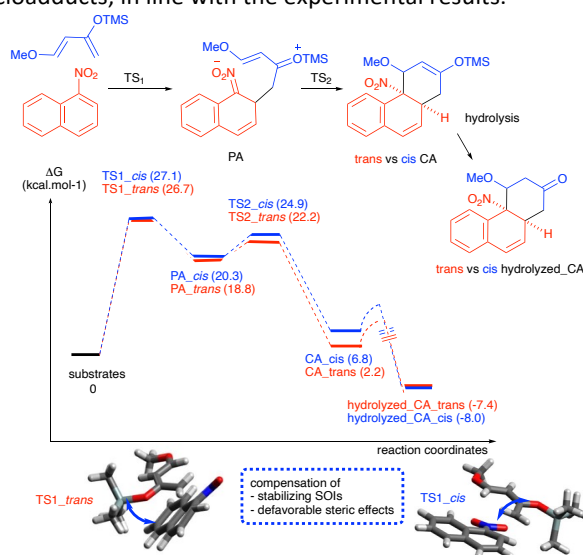


Scheme 3. High pressure activated [4+2] dearomatization reactions of five-membered nitroheteroareomatics **6** with **1a**. a. Isolated yield. b. 100% conversion of the nitroarene. c. Diastereomeric ratio determined by ¹H NMR.

2-Nitrofurans **6c** also gave the reaction in high yield (90%), and unexpectedly gave cycloadduct **7c** as a single *cis* diastereoisomer. 3-Nitropyrrrole **6d** also reacted well with

diene **1a** under HP, though the resulting cycloadduct proved unstable giving hydroxyindole **8** in 79% upon hydrolysis.

The modest diastereoselectivity witnessed in the reactions of Danishefsky's diene **1a** with most nitro-arenes and heteroarenes is probably a reflection of the similar transition state (TS) activation energies for both *endo* (leading to the *trans* isomer) and *exo* (leading to the *cis* isomer) approaches.¹⁵ In general, *endo*-TSs are promoted by stabilizing secondary orbital interactions (SOI) between the internal carbon atoms of the reacting 1,3-diene (HOMO) and the electron-withdrawing substituent(s) borne by the dienophile (LUMO). Under HP, this *endo* preference is generally more marked.¹⁶ By way of contrast, an *exo* mode is promoted when there are unfavourable steric interactions between the diene and dienophile. Here, the diene component can have stabilizing SOIs with both the arene *and* the nitro group of the dienophile. Only modest diastereoselectivity is observed as there is no intrinsic steric effect to bias the stereochemical course of the reaction. DFT calculations suggest that the cycloaddition occurs in a two-steps process (see E.S.I for details), involving the elusive formation of a zwitterionic primary adduct (**PA**) in the first step and its rapid cyclisation *via* a Michael addition to generate the cycloadduct (**CA**), before hydrolysis of the silyl enol ether moiety (Scheme 4). Considering the much higher energy barrier for the first dearomatizing addition compared to the cyclization step (~27 vs ~4 kcal.mol⁻¹), it is clearly the rate determining step. Assuming that the **PA** has no time to rearrange before cyclization, the diastereoselectivity of the formal cycloaddition reflects the preferential approach in the first step of the sequence. The low energy difference witnessed between the *trans* and *cis* approaches ($\Delta\Delta G^\ddagger = 0.4$ kcal.mol⁻¹), thus translates into a low *trans/cis* diastereoselectivity in the cycloadducts, in line with the experimental results.



Scheme 4. Energy profiles for the cycloadditions of **2a** with diene **1a**; *trans* (*endo*) approach (blue); *cis* (*exo*) approach (red), computed at the (SMD:CH₂Cl₂) M062X/6-31+G(d,p) level of theory.

Table 2. (4+2) Dearomatization reactions of 5-nitroquinoline with silyloxy dienes.

Entry	diene	R	R'	Yield (Conv.) ^a	dr ^b
1	1b	Me	SiEt ₃	75% (100%)	59:41
2	1c	Me	SiEt ₂ iPr	95% (100%)	60:40
3	1d	Me	SiMe ₂ tBu	91% (100%)	66:34
4	1e	Me	Si ⁱ Pr ₃	0% (0%)	-
5	1f	tBu	SiEt ₃	53% (54%)	59:41

a. Conversion of **4a**. b. Diastereomeric ratio, determined by ¹H NMR

To evaluate the influence of steric factors on the *trans/cis* selectivity of these cycloaddition reaction, 5-nitroquinoline **4a** was reacted with a series of 1,3-dioxydienes **1b-f** bearing different alkoxy and silyloxy substituents at C-1 and C-3, respectively (Table 2). For dienes **1b-d** (Scheme 2 and entries 1-3), diastereoselectivity slightly increased with the size of the silyloxy group at C-3.¹⁷ The bulky *triisopropylsilyloxy* diene **1e** did not give the reaction, however (entry 4). When the diene bears a *tert*-butyl ether at position 1, a similar *dr* was obtained and this was at the expense of conversion (entry 5).

Conclusions

In conclusion, under high pressure, various common nitroarenes and heteroarenes behave as a classical electron-poor dienophile in Diels-Alder cycloadditions with Danishefsky's diene. Reactions proceed at room temperature without the need for a chemical promoter and give polycyclic adducts with a tetrasubstituted carbon centre in a *cis* ring junction. The ease with which functionalised 3D-structures are accessed from common raw materials is notable. We are currently seeking to improve diastereoselectivity in these reactions and to further exploit the exceptional role of high pressure as a "physical catalysis" in other challenging cycloaddition reactions, with various dienes-electron deficient aromatic combinations.

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