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Alder Cyclization

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By

Nicola Camedda, Matteo Lanzi, Franca Bigi, Raimondo Maggi, Giovanni Maestri^{a*}

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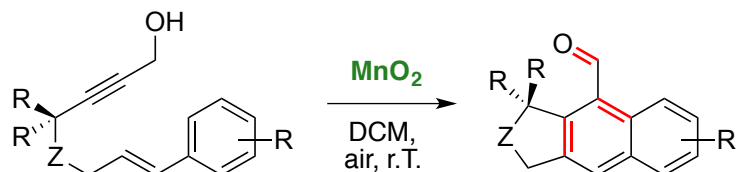
Ambient synthesis of tricyclic naphthalenes via step-wise styryl-yne dearomative Diels-Alder cyclization

Nicola Camedda,^a Matteo Lanzi,^a Franca Bigi,^{a,b} Raimondo Maggi,^a Giovanni Maestri^{a*}

^a Università di Parma, Department of Chemistry, Life Sciences and Environmental Sustainability, Parco Area delle Scienze 17/A, 43124 Parma, Italy

^b IMEM-CNR, Parco Area delle Scienze 37/A, 43124 Parma, Italy

Supporting Information Placeholder



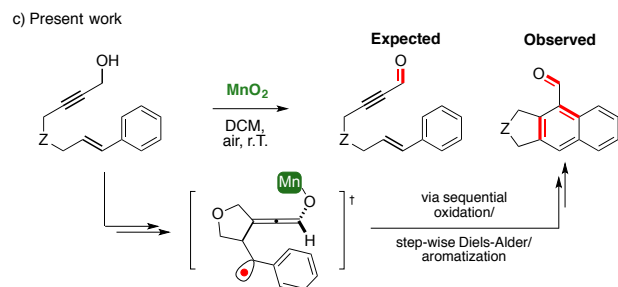
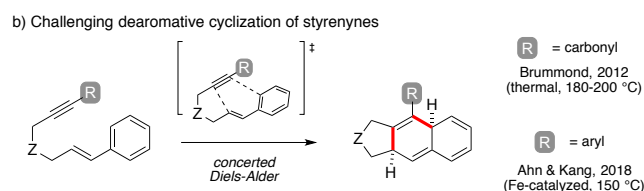
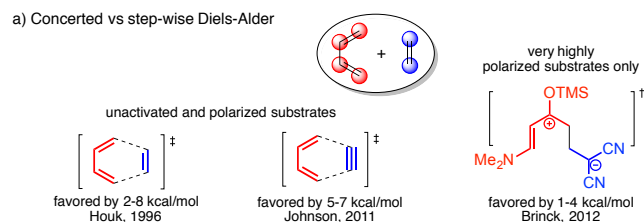
ABSTRACT: a cascade of styrylnols promoted by MnO₂ allows the synthesis of fused tricycles with a naphthalene core. The reaction occurs under ambient conditions, offering a practical synthetic tool thanks to the cheapest and most abundant manganese species. The method affords products through the sequential oxidation of a propargyl alcohol, step-wise Diels-Alder cyclization and final rearomatization. According to DFT, the usually unfavorable step-wise Diels-Alder mechanism is instead a general tool to elicit otherwise challenging dearomative annulation.

The Diels-Alder reaction is among the mostly used transformation in chemistry.¹ Regarding the myriad of elegant uses in elaborate syntheses of natural and bio-active molecules, its value could not be understated. Together with applications, the mechanism of this reaction has been the focus of countless studies (Scheme 1, a) and heated scientific discussions.²

Reactions in which vinylarenes are 4- π partner remain however limited, especially for intermolecular approaches.³ This is due to the intrinsic challenges connected with the energetic toll of a dearomative cyclization. Intramolecular reactions perform slightly better, especially when the dienophile is a polarized alkyne (Scheme 1, b). Brummond extensively worked on the fluorescent properties of tricyclic naphthalenes that were prepared from styryl-yneones.⁴ The reaction was very general but it required a strong thermal activation, usually in the 180-200 °C range. The use of Fe(II)/Fe(III) catalysts could allow to perform the cyclization at 150 °C under microwave conditions.⁵ Very recently, Zhang reported an unexpected outcome from the preparation of imido-tethered 1,6-enynes.⁶ A cinnamoyl chloride and a propiolamide, in the presence of sodium hydride, afforded the rearomatized styryl-yne Diels-Alder cycloadduct operating at room temperature under air. A rationale for the easiness of this putative dearomative cyclization is however still unclear.

We report herein a method that uses readily accessible styrylnols and provides tricyclic naphthalenes in good yields (Scheme 1, c). The reaction is promoted by manganese dioxide, which is the cheapest⁷ and most abundant form of this first-row transition metal.⁸ Albeit extensively used in synthesis across several decades,⁹ we are unaware of reports in which MnO₂ unleashed a polycyclization cascade.

SCHEME 1. Strategies for dearomative Diels-Alder.



Moreover, the key annulation of the sequence is likely a step-wise Diels-Alder reaction, whose energetic profile is surprisingly easier than that of an uncatalyzed concerted process. A similar mechanism is original within the context of dearomative Diels-Alder reactions,¹⁰ which are invariably proposed to be concerted cycloadditions.²⁻⁶ According to DFT, step-wise catalytic cyclizations of styryl-yne are however quite general and we thus anticipate vast applications of this concept in the future.

We serendipitously discovered this reaction while treating propargylic alcohol **1a** with MnO₂,⁹ as part of our interest in the development of atom-economical cascades.¹¹ The reaction gave tricycle **2a**, in which a new aromatic ring has been assembled through the formal functionalization of an aromatic C-H bond (Table 1), together with traces of the expected linear aldehyde.

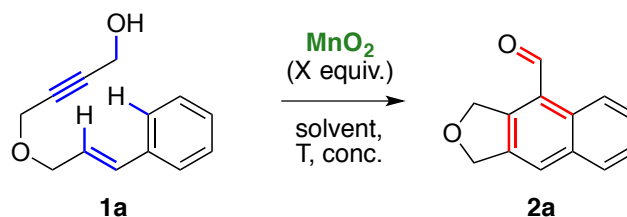


TABLE 1. Optimization of reaction conditions.

Entry ^a	Solvent	T (°C)	MnO ₂ equiv.	Conc. of 1a (M)	Yield of 2a (%) ^b
1	DCE	25	4	0.12	20
2	DCE	50	10	0.12	28
3	DCE	50	40	0.12	45
4	Toluene	50	40	0.12	29
5	MTBE	50	40	0.12	15
6	CHCl ₃	50	40	0.12	44
7	CH ₂ Cl ₂	40	40	0.12	38
8	CH ₂ Cl ₂	25	40	0.12	35
9	CH ₂ Cl ₂	25	40	0.025	51
10	CH ₂ Cl ₂	25	40	0.0125	58
11	CH ₂ Cl ₂	25	40	0.0083	63

^a: 0.25 mmol of **1a**, X equiv. of MnO₂, stirred under air overnight; ^b: isolated yield.

In a preliminary experiment, 0.25 mmol of **1a** were mixed overnight with 4 equiv. of MnO₂ in dichloroethane (DCE) at room temperature (entry 1). The conversion of **1a** was not complete and cinnamaldehyde was the main byproduct. Naphthalene **2a** was isolated in 20% yield. A higher loading of the oxide and warming to 50 °C led to a modest improvement (28%, entry 2). Further increase of the amount of MnO₂ to 40 equiv. pushed the yield to 45% (entry 3). Halogen-free solvents proved detrimental (entries 4-5). On the contrary, alternatives to DCE gave comparable results (entries 6-7). We picked dichloromethane (DCM) as the cheapest and eco-friendliest of the halogenated series, and found that the reaction could be performed at room temperature (entry 8). The substrate was consumed and cinnamaldehyde remained the most abundant byproduct (23%). Lowering the concentration of **1a** proved crucial to reduce this side-reaction (entries 9-10). The best result was obtained by further dilution (entry 11, 63%). We tested the use of 20 equiv. of manganese but the yield of **2a** decreased to 53%. We attempted to recover MnO₂ at the end of the reaction and reuse it without further treatments. We retrieved 91% of the initial mass of the oxide but its further exposure to **1a** gave **2a** in 34% yield and uncomplete conversion (45%). The use of dry solvents and/or an inert atmosphere had no impact on the sequence.

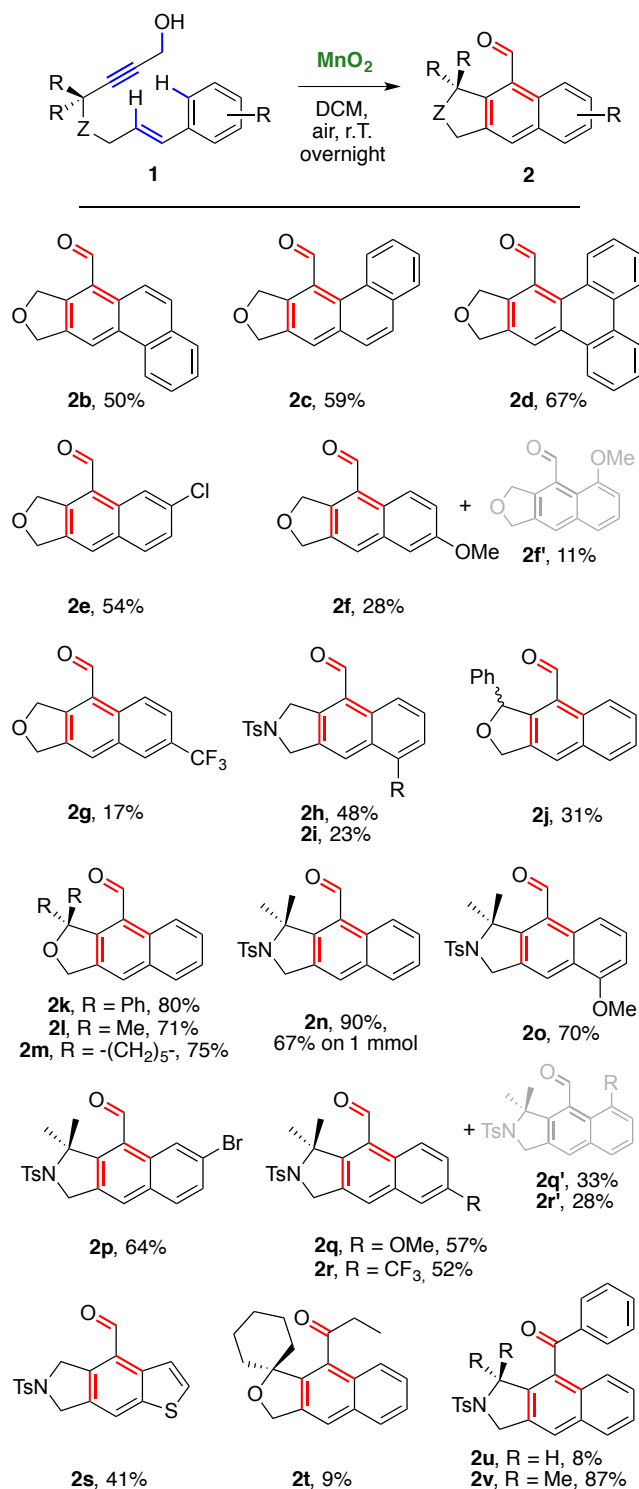


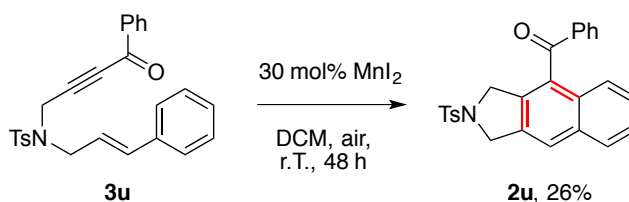
FIGURE 1. Scope of the method, isolated yields, conditions as Table 1, entry 11.

We then assessed the generality of the method by preparing a library of styrylnols (Figure 1), which can be synthesized from 1,6-enynes. The phenyl group of **1a** could be replaced by an extended aromatic, such as the 1- or 2-naphthyl group, and the reaction afforded the corresponding fused tetracycles with comparable efficiency (**2b-c**, 50-59%). It is worth noting that a single regioisomer of **2c** was retrieved. This indicates that the functionalization of the aromatic C-H group occurred selectively at the 1- position of the naphthyl group, leaving the 3- position untouched despite its lower steric hindrance. Further extension of the π -network was achieved preparing **1d** that had a phenanthrene arm. The fused pentacycle **2d** was recovered in 67% yield. The presence of a chlorine atom on the aryl ring was tolerated (**2e**, 54%). Two isomers of the product were observed using **1f** that had a *meta*-methoxy substituent. The reaction afforded **2f** and **2f'** in 28% and 11% yield, respectively. The trifluoromethyl derivative **1g** gave a single product, albeit in low yield (17%). A protected nitrogen atom in the tether did not hinder the reaction (**2h**, 48% yield). Substitution at the *ortho*-position

of the aryl group led to a diminished amount of **2i**, (23%). The presence of one group at the propargylic position proved detrimental (**2j**, 31%). However, di-substitution at this position greatly enhanced the yield of **2**. Indeed, substrate **1k** that had two phenyl groups alpha to its triple bond led to the formation of tricycle **2k** in 80% yield. This effect was observed with **1l** and spirocyclic derivative **1m**, which gave products **2l-m** in 71% and 75% yield, respectively. The trend was maintained using **1n**, which afforded **2n** in 90% yield. This reaction could be scaled to 1 mmol, albeit with a diminished yield (67%). The positive effect exerted by di-substitution at the propargylic position allowed one to react substrates with *ortho*-substituted aromatics without a significant erosion of the yield (**2o**, 70%). The bromine substituent of **1p** was tolerated and the reaction afforded **2p** in 64% yield. Halogenated tricycles (**2e**, **2p**) could smoothly undergo Buchwald-Hartwig coupling with a secondary amine to provide the corresponding fluorescent probes.^{4a} Substrates with a *meta*-substituent, regardless of its electronic effect (**1q-r**), gave a mixture of two isomers. The functionalization of the phenyl group of the reagent occurred preferentially at the least sterically hindered position in both cases, and the two products were retrieved in excellent combined yields (90% and 80% for **q** and **r**, respectively). These results indicated that the electronic effect of the substituent on the aromatic ring had a limited impact on the outcome of the cascade. The cyclization seems thus unlikely to occur through an ionic mechanism. The aromatic ring of the reagent could be a 2-thiophene group, and product **2s** was recovered in a synthetically useful yield (41%). Finally, we tested substrates with a secondary alcohol. The presence of an alkyl group on **1t** proved detrimental, leading to 9% yield of **2t**. The linear ketone derived from the oxidation of the substrate was the main product in this case. Reagent **1u**, which had a benzyl alcohol arm, gave the corresponding linear ketone as main product (51%) and **2u** was isolated in a low yield (8%). However, **1v** that had a *gem*-dimethyl substituent, reacted smoothly, allowing us to obtain product **2v** in 87% yield. This striking difference further highlighted the strong Thorpe-Ingold effect that is at work in present cyclization. Moreover, disubstitution at the propargylic position inhibited the formation of the cinnamaldehyde derivative that is the main byproduct of the reaction. It can be envisaged that it formed upon the homolytic cleavage of a propargylic C-H bond, which could be caused by a manganese species.⁹ The resulting C-centered radical would undergo β -fragmentation to give a stabilized (aryl)allyl radical, which eventually leads to cinnamaldehyde under aerobic conditions. This hypothesis is consistent with the low yield of **2j**, which has a propargylic C-H bond that is prone to undergo homolysis.

The following working hypothesis could be a rationale for the formation of **2** that accounts for the lack of clear electronic effects (**2q-r**) and the formation of **2c** as a single regioisomer. Substrate **1** would undergo oxidation by means of MnO₂, generating an aldehyde.⁹ This was confirmed by its transient observation during the early stages of the reaction. Then, the ynal would undergo a Diels-Alder-like cyclization, possibly involving a manganese species via carbonyl coordination. The resulting dihydronaphthalene would eventually give **2** by means of a second equivalent of MnO₂.¹² Alternatively, an uncatalyzed *syn*-elimination of H₂^{4c} or an oxidative dehydrogenation in the presence of air could take place.

In order to support a similar scenario, we prepared ynone **3u** (Scheme 2), which showed almost no competence to evolve into **2u** (Figure 1).



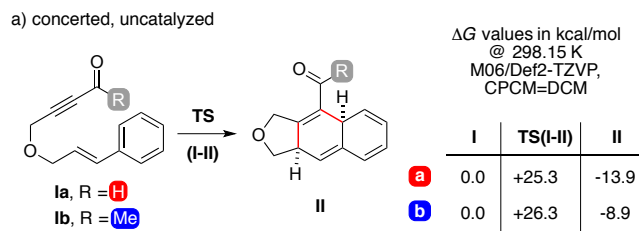
SCHEME 2. Attempted cyclization of styryl ynone **3u**.

We treated **3u** with 1.5 equiv. of MnO₂, Mn(OAc)₃ and MnI₂ as representative sources of the metal in the IV, III and II oxidation state. Low conversion (10%) and traces of **2u** were observed in the first case (4%). The Mn(III) derivative gave 7% of **3u** (85% of recovered **3u**). The best result was found employing MnI₂, which afforded **2u** in 27% and 26% yield using 1.5 and 0.3 equiv., respectively (see SI for details). These results suggested that a Mn(II) species could catalyze the key cyclization of the cascade. It could be thus imagined that the oxidation of **1**⁹ formed *in-situ* both the substrate and the metal species involved in the subsequent annulation.

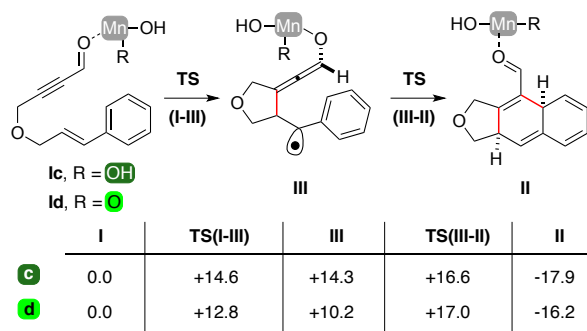
This Diels-Alder should involve a single transition state (TS) according to the literature.¹⁻⁶ This pathway should have a lower energetic cost compared to a step-wise, two TSs manifold (Scheme 1). The latter is a feature of a few processes only,¹³ which use strongly polarized reagents and involve a zwitterionic or biradical intermediate.

Present cyclization was studied by DFT to gain insight on its mechanism. Exchange/correlation functionals with varying degrees of Hartree-Fock contamination (M06, M06-2X and M06-L) were employed, together with both double- and triple- ζ basis sets (Def2-SVP and Def2-TZVP, respectively), to reduce the odds of modeling artefacts.^{11a-b} Overall, all of these different models gave comparable results (details in SI).

The cyclization of **1a** could occur through a single TS (Figure 2). The distance between the alkyne and alkene carbons was much shorter compared to the alkyne-aryl one in the TS. This indicated a considerably asynchronous character, which was due to the tether between the two π -systems and to the polarizing acyl group. The TS had a very costly barrier (between +23 and +27 kcal/mol in ΔG for **1a** among the various functionals and basis sets tested). Analogous results were observed using ketone **1b**, the corresponding barriers being 1-2 kcal/mol higher in ΔG . The energetic cost connected with the loss of aromaticity was at the root of these high-energy TSs, suggesting that a strong thermal activation would be required by these processes. This evenly correlated with experiments,⁴ in which the uncatalyzed cyclization occurred at 180-200 °C.

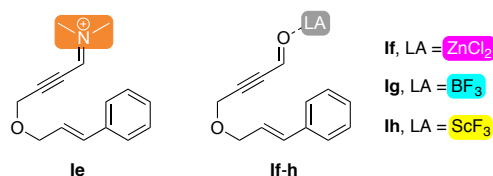


b) step-wise, ${}^6\text{Mn}(\text{OH})_2$ - and ${}^5\text{MnOOH}$ -catalyzed



c) step-wise, iminium & diamagnetic Lewis-acid catalysis

	I	TS(I-III)	III	TS(III-II)	II
e	0.0	+9.8	+7.5	+16.6	-10.3
f	0.0	+12.2	+8.4	+16.2	-18.5
g	0.0	+8.7	+3.0	+11.8	-20.8
h	0.0	+10.2	+6.7	+14.9	-18.7



d) representative key features of intermediates III

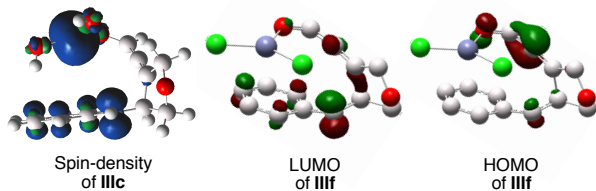


FIGURE 2. Concerted vs step-wise dearomative cyclizations.

The energy profile changed in the presence of ${}^6\text{Mn}(\text{OH})_2$,¹³ which is the coproduct of the oxidation of **1**.⁹ We did not find a stable TS for a concerted process while the step-wise one became highly competitive. Its two barriers were well below the 20 kcal/mol threshold among all tested models. In particular, barriers calculated at the M06/Def2-TZVP level using DCM as implicit solvent gave values of +14.6 and +1.4 kcal/mol in ΔG for **TS(I-III)** and **TS(III-II)**, respectively. This could fit with reactions that occur at room temperature. Intermediate **IIIc** has an allenol character, its two key C-C distances being 1.30 and 1.31 Å. Partial oxidation of the high-spin Mn nucleus occurred in **IIIc**. In parallel, the spin density on the metal decreased and a consistent benzyl radical character emerged. Very similar results were observed modeling the reaction with ${}^5\text{MnOOH}$ as model Mn(III) derivative (**d**).¹³ Present arene-yne cyclization seemed a rare event in which the most favorable Diels-Alder mechanism was the step-wise one.^{1-6,10,14} We wondered whether this process might have been a general feature of catalytic dearomative Diels-Alder cyclizations.

The hypothesis was tested on the reaction of iminium cation **Ie**.¹⁵ The two-step route provided low barriers, which were +9.8 and +9.1 kcal/mol in ΔG respectively, for this model activated substrate. Intermediate **IIIe** was similar to **IIIc**, presenting an allenamide unit and a cationic benzyl arm. The nucleophilic sp carbon of the former smoothly reacted with the electron-impoorished ring of the latter in the second TS. We further proved the concept using ZnCl_2 .¹⁶ This model diamagnetic Lewis acid showed low barriers for the

two-TSs manifold. These were +12.2 kcal/mol and +7.8 kcal/mol in ΔG . Zwitterionic intermediate **III**f had a benzyl cation arm and an allenolate one with a partial vinyl anion character (C-C distances were 1.30 and 1.35 Å). We used the same approach with BF_3 and ScF_3 , which are proxies of redox-neutral main-group and early transition-metal Lewis acids, respectively (**g-h**). Both BF_3 and ScF_3 closely paralleled the energetic pattern shown by ZnCl_2 (barriers between +8.2 and +10.9 kcal/mol). Overall, six very different catalytic reactions (**c-h**) invariably provided barriers for a two-TSs dearomative Diels-Alder that were 10-to-15 kcal/mol lower than those of the concerted, uncatalyzed cyclization (**a-b**).

Taken together, these results strongly suggest that a catalytic process can reduce the energetic burden of a dearomative Diels-Alder reaction by spreading it through two steps. Upon substrate activation, the first barrier allows to form a new C-C bond. This energetic gain is offset by the localization of significant spin density (or Coulomb charge) to a benzyl arm. Then, the relative instability of this intermediate paves the way to a second low barrier. The combination of these two points allows to offset the energetic toll of dearomatization. We hope that these findings will become a blueprint to elicit otherwise challenging cyclization under mild conditions in the future.

We reported that MnO_2 promotes an unexpected cascade of styrylnols. The method is a practical synthetic tool that occurs under ambient conditions and uses the most abundant form of a cheap first-row element. The reaction involves the sequential substrate oxidation, cyclization and aromatization to afford a variety of decorated naphthalenes. The annulation likely occurs through a catalytic step-wise Diels-Alder mechanism, whose energetic convenience might lead to ample developments for dearomative transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, synthesis of reagents, characterization of products, modeling data, copies of NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

* giovanni.maestri@unipr.it

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