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Improved Dienophilicity of Nitrocycloalkenes: Prospects for the Development of a *trans*-Diels−Alder Paradigm

Woo Han Kim,[†] Jun Hee Lee,[‡] and Samuel J. Danishefsky*[,†,‡]

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10065, and Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027

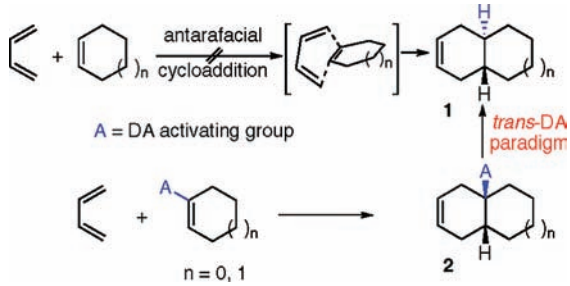
Received July 15, 2009; E-mail: s-danishefsky@ski.mskcc.org

The importance of the Diels−Alder reaction can hardly be exaggerated. Its many features have been widely discussed.[1] The ability to reach *cis*-fused bicyclic systems by a Diels−Alder pathway has been a bulwark of complex target-oriented synthesis.[2] We well recognize that strategy in chemical synthesis is primarily beholden to capabilities arising from advances in methodology. This said, strategy also involves an intrinsic cognitive element. It connects a particular target to the huge database of organic chemistry, seeking to apply its most relevant and salient features to the challenge at hand. Central in this regard has been the logic of retrosynthetic analysis, which prioritizes various bond disconnections in an inverse sequential manner.[3] The attainments resulting from strategic bond retrosynthetic analysis are legion.

Complementary to the powerful thought process of bond disconnections, we have been entertaining a different approach which we term "pattern analysis."[4] Although these approaches have some commonality, pattern analysis emphasizes a holistic view of the target structure, seeking connectivity between its key substructural characteristics (sometimes obvious but sometimes quite subtle) and established or prospectively implementable pathways. For instance, in pattern analysis, the possibility of a Diels−Alder (DA) application is provoked by the recognition of a *cis* junction. By contrast, *trans* junctions tend to teach away[5] from a Diels−Alder universe.

It goes without saying that the scope of pattern analysis would be dramatically expanded if targets containing *trans* junctions could also be encompassed in the general Diels−Alder logic. The simplest scenario would contemplate an antarafacial cycloaddition.[6] Not having any constructive suggestions in this regard, we turned to the next best thing. As outlined in Scheme 1, we envisioned

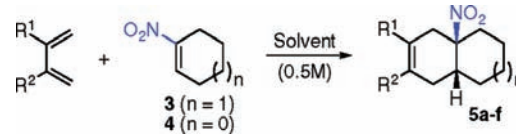
Scheme 1. *Trans*-Diels−Alder Paradigm



equipping an otherwise unreactive dienophile (such as cyclohexene) with a temporary, readily removable activating group (A). Following cycloaddition, a product of the type **2** would be obtained. The resultant *cis*-fused substructure would be diverted to the *trans* series (**1**) through excision of the activating moiety and its controlled replacement. The traceless function (A) would first serve the purpose of activating the dienophile for cycloaddition, thereby affording a *cis* junction. Subsequent chemistry would provide entry to the *trans*-fused series. We selected a nitro group as (A), based on its dienophile activating properties,[7] its known success in controlling DA regioselectivity,[8] and its ability to generate free radical intermediates.[9] We describe herein the use of nitrocycloalkenes as dienophiles, pointing toward an emerging *trans*-Diels−Alder paradigm.

We began by studying the dienophilicity of compound **3**. At the outset, there had been only one evaluation of it as a dienophile in a Diels−Alder reaction.[10] In the event, exploitation of its reactivity in cycloadditions with hydrocarbon dienes (see entries 1−4, Table 1) proved to be a particularly challenging problem. At temperatures below ∼120−130 °C, there was little or no indication of cycloaddition. At temperatures above 140 °C there seemed to be a very serious deterioration of the dienophile, resulting in extremely low yields of cycloadduct. We were, however, able to identify a narrow temperature range in which marginally useful cycloaddition could be achieved. Still, in hydrocarbon solvents such as toluene or on THF, the yields of isolated cycloadducts were quite low, apparently

Table 1. Diels−Alder Reaction of Nitrocycloalkenes



entry	5	*n*	diene	solvent	*T* (°C)	*t* (h)	yield (%)[a]
1	**a**	1	$R^1 = R^2 = CH_3$	toluene[b]	110	12	trace
2	**a**	1	$R^1 = R^2 = CH_3$	toluene[b]	140	36	18
3	**a**	1	$R^1 = R^2 = CH_3$	toluene[b]	150	36	trace
4	**a**	1	$R^1 = R^2 = CH_3$	THF	130 MW[c]	12	17
5	**a**	1	$R^1 = R^2 = CH_3$	CH_3CH_2OH	130 MW[c]	14	36
6	**a**	1	$R^1 = R^2 = CH_3$	CF_3CH_2OH	130	24	70
7	**a**	1	$R^1 = R^2 = CH_3$	CF_3CH_2OH	130 MW[c]	12	78
8	**b**	1	$R^1 = H, R^2 = CH_3$	CF_3CH_2OH	125 MW[c]	14	57[d,e]
9	**c**	1	$R^1 = R^2 = (CH_2)_4$	CF_3CH_2OH	130 MW[c]	10	75
10	**d**	1	$R^1 = R^2 = Ph$	toluene[b,f]	150	48	45
11	**e**	0	$R^1 = R^2 = CH_3$	CF_3CH_2OH	100	12	78
12	**f**	0	$R^1 = H, R^2 = CH_3$	CF_3CH_2OH	110	12	77[g]

[a] Isolated yield. [b] In the presence of 2,6-di-*tert*-butylcresol (5 mol %). [c] MW = microwave. [d] *p*-directed/*m*-directed = 15:1. [e] The reaction in toluene gave a 1:1mixture of regioisomers as a 5% yield. [f] The diene was insoluble in CF_3CH_2OH. [g] *p*-directed/*m*-directed = 11:1.

[†] Sloan-Kettering Institute for Cancer Research.
[‡] Columbia University.

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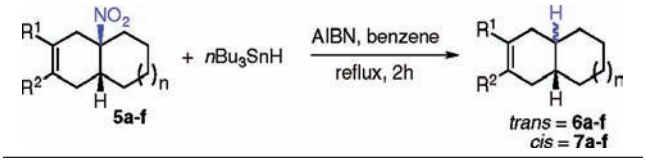
reflecting competition between the innate destruction of **3**, versus its cycloaddition.

During the course of these studies, we did note some improvement of cycloaddition yield in alcoholic solvents[11] (see entry 5, Table 1). Fortunately a more substantial increase in yield was realized when we turned to 2,2,2-trifluoroethanol as solvent, particularly when thermolysis was conducted under microwave conditions (entry 7). We emphasize, however, that the hydroxylic solvent effect, including 2,2,2-trifluoroethanol, apparently does not arise from catalysis (through hydrogen bonding or via other means). Thus, we see no indication that cycloaddition occurs at lower temperatures with 2,2,2-trifluoroethanol. Rather, the differences in yield seem to reflect a more favorable distribution of cycloaddition relative to decomposition. While the basis of this effect remains to be explored, it was very helpful to our program. Reasonable yields of cycloaddition from compound **3** could now be achieved. Happily, the protocol which was worked out for 2,3-dimethyl-1,3-butadiene was extendable to several other dienes (see Table 1). Moreover, we prepared 1-nitrocyclopentene (**4**)[10] and evaluated its dienophilicity with the same dienes. Yields for these reactions are also included in Table 1. Here, we note that the temperatures required for cycloaddition were substantially lower (ca. 100−110 °C) for **4** than for **3**, though, for the moment, the isolated yields tend to be similar. Table 1 summarizes yields for various conditions under which cycloaddition of dienophiles **3** and **4** with various acyclic dienes could be achieved.

Having substantially advanced the practicality of cycloadditions with nitrocycloalkene dienophiles, we next faced the central issue of denitration. We well recognized that if reductive denitration would lead to a *cis* junction, the nitrocycloalkene dienophile would have functioned as an equivalent of otherwise unreactive cyclohexene or cyclopentene.[12] However, if the excision−replacement sequence would afford a *trans* junction, an overall *trans-Diels−Alder type paradigm* would have been demonstrated.

In the event, we began by treating compound **5a** with tri-*n*-butyltin hydride in the presence of AIBN. We noted an 8:1 ratio of *trans*-**6a** to *cis*-**7a**, as established by comparison with authentic reference compounds prepared in multistep sequences.[13] In a similar way, the isoprene adduct **5b** also gave rise to an 8:1 ratio of *trans*-**6b** to *cis*-**7b**. Other examples are shown in Table 2. Thus, while one could hope for an even stronger stereoselectivity, these data encourage application of Diels−Alder logic to the synthesis of *trans* octalins.

Table 2. Radical Denitration



entry	6,7	*n*	diene	yield (%)[a]	6:7[b]
1	**a**	1	$R^1 = R^2 = CH_3$	67	8:1
2	**b**	1	R^1 = H, $R^2 = CH_3$	53	8:1
3	**c**	1	$R^1 = R^2 = (CH_2)_4$	81	12:1[c]
4[d]	**d**	1	$R^1 = R^2$ = Ph	83	7:1
5	**e**	0	$R^1 = R^2 = CH_3$	61	1.3:1
6	**f**	0	R^1 = H, $R^2 = CH_3$	35[d]	1.9:1

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Determined by GC. [d] The compound is volatile.

Perhaps, this selectivity pattern represents a preference for conformer type **A** relative to conformer **B** thereby accounting for the selective formation of *trans* product (Figure 1). However, in the hydrindene series, the ratio of the denitration products, was much closer to unity, presumably reflecting altered *trans*/*cis* preferences.

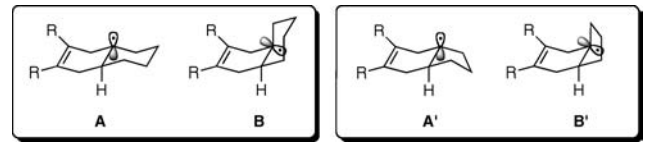
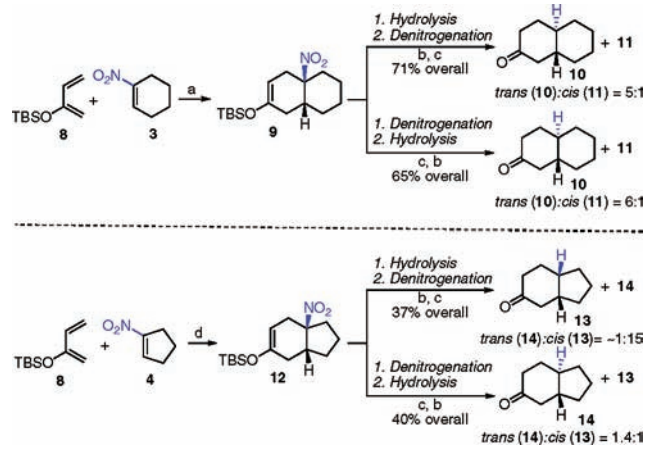


Figure 1. Structures of the tertiary bridge head radical.

In the next step in our exploration, we evaluated the consequences of using a more functionalized diene. In that way, additional exploitable functionality would be delivered to the eventual denitration product. We began by studying the cycloaddition reaction of compound **3** with diene **8**.[14] Fortunately, our conditions described above for cycloaddition with acyclic hydrocarbon dienes work quite well with diene **8.** In 2,2,2-trifluoroethanol at 80 °C, a 61% yield of adduct **9** was obtained.[15] With 1-nitrocyclopentene (**4**), cycloaddition under comparable conditions afforded adduct **12** (Scheme 2).

Scheme 2[a]



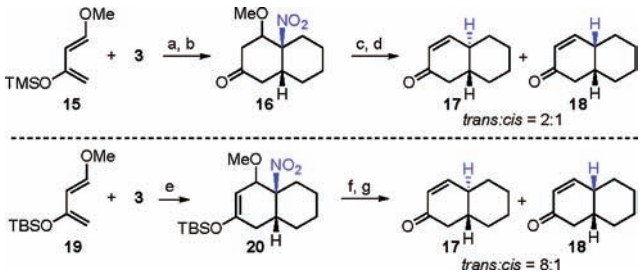
[a] Key: (a) CF_3CH_2OH, 80 °C, MW, 12 h, 61%. (b) HF, CH_3CN, rt, 30 min. (c) nBu$_3$SnH, AIBN, benzene, reflux, 2 h. (d) CF_3CH_2OH, 80 °C, MW, 6 h, 72%.

We then turned to denitration reactions. For each compound, this process was studied in two different sequences. In one arm, the silyl enol ethers were hydrolyzed and the subsequent ketones were denitrated. In this case, a 5:1 ratio of *trans* compound **10** to *cis* compound **11** was obtained. A very similar result pertained when we reversed the order of steps, wherein denitration was carried out at the stage of adduct **9** and followed by hydrolysis of the silyl enol ether, to provide a 6:1 ratio of *trans*-**10**/*cis*-**11**.[16]

We applied the same methodology to adduct **12**, which arose from **4**. Once again, both denitration sequences were pursued. When denitration was conducted at the stage of the silyl enol ether, followed by hydrolysis, a 1.4:1 ratio of *trans*-**14**[17] to *cis*-**13**[18] was obtained. By contrast, when denitration was conducted at the ketone stage (i.e., after hydrolysis), a 15:1 ratio of *cis*-**13** to *trans*-**14** was produced. Thus, once again, in the octalin series a stereoselective route to *trans*-fused ketone **10** has been established. By contrast, in the hydrindane series, a stereoselective route to the *cis* fusion has been realized. Unfortunately, no corresponding protocol now available to us provides a *trans* hydrindanone junction with useful levels of stereoselection (*vide infra*).

Finally, we turned our attention to the cycloaddition reaction of diene **15**[19] with 1-nitrocyclohexene (**3**). As it turned out, this

Scheme 3[a]



[a] Key: (a) xylene, reflux, 36 h. (b) 0.05 M HCl, THF, 2 h, 67% for 2 steps. (c) nBu$_3$SnH, AIBN, benzene, reflux, 2 h, 89%. (d) TFAA, benzene, Dean−Stark, 24 h, 60%. (e) toluene, 130 °C, 36 h, 90%. (f) nBu$_3$SnH, AIBN, benzene, reflux, 2 h. (g) HF, CH_3CN, rt, 10 min, 53% for 2 steps.

reaction could not be conducted in 2,2,2-trifluoroethanol because of rapid conversion of the diene to the corresponding ketone, methoxybutenone. Accordingly, the reaction was conducted in xylene under reflux, as shown in Scheme 3. This treatment gave rise to a mixture of *endo* and *exo* Diels−Alder product, indicated as **16**. Again, we examined the stereochemical outcome of the denitration reaction when conducted at one of the two different stages. Thus, when reduction was conducted at the stage of the ketone **16** (obtained by prior hydrolysis of the silyl enol ether function), a 2:1 ratio of *trans*/*cis* octalones was obtained. In contrast, when the denitration was conducted at the silyl enol ether stage and the denitration product was subjected to acid hydrolysis of the silyl enol ether, an 8:1 ratio of *trans*-**17** to *cis*-**18** was produced.[20] Once again, we see how the chemistry described above points the way to introduction of *trans* ring junctions in Diels−Alder driven constructions.

In summary then, while many provocative possibilities remain to be explored, the chemistry described above already holds promise for application to two types of situations. In the hydrindane series, denitration can be used to generate a *cis* fusion, thereby establishing a Diels−Alder equivalency for the otherwise inert cyclopentene. By contrast in the octalin series, it is possible to take advantage of this chemistry to produce, selectively, *trans* junctions. In that sense, the nitrocyclohexene will have served in a Diels−Alder context as an equivalent of the otherwise unavailable dienophile, *E*-cyclohexene. Studies addressing a menu of follow-up possibilities suggested by these findings are in progress.

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Supporting Information Available: Experimental procedures, copies of spectral data, and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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