Intramolecular Nitroalkene Diels–Alder Reaction Catalyzed by Brønsted Acids

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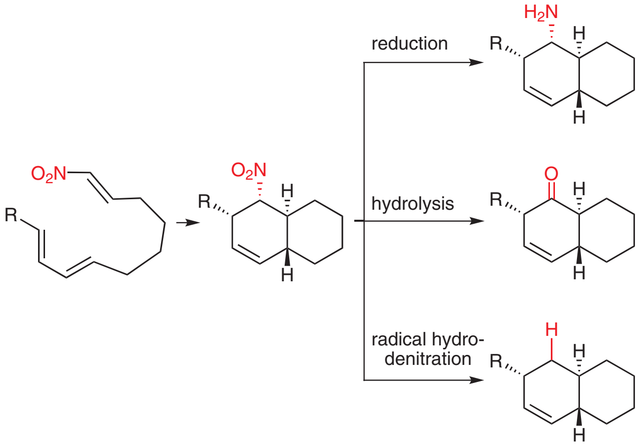
Abstract: Brønsted acid catalysis of intramolecular Diels–Alder cyclizations of (*E*)-1-nitro-1,6,8-nonatrienes and (*E*)-1-nitro-1,7,9-decatrienes was investigated. Catalyzed reactions showed significantly higher *endo* selectivities than the corresponding thermal reactions. To our knowledge, this is the first example of catalysis (substoichiometric amount of catalysts) of the intramolecular nitroalkene Diels–Alder reaction.

Key words: Brønsted acid catalysis, intramolecular Diels–Alder cyclizations, catalysis

The importance of the intramolecular Diels–Alder reaction can hardly be exaggerated. Its many features have been widely discussed (e.g., two new carbon–carbon bonds, two rings and up to four stereocenters can be made in a single step).[1] In particular, its strategic uses have significantly advanced the synthesis of complex natural products. Its nitroalkene variant[2] offers unique advantages due to the synthetic versatility of the nitro group,[3] which allows ready access to bicyclic motifs that are otherwise difficult to obtain (Scheme 1). Therefore, this process is highly complementary to that of carbonyl-based substrates. In this respect, Kurth and co-workers investigated the thermal cyclizations of 1-nitro-1,6,8-nonatrienes for the synthesis of perhydroindenes.[2g] The merits of the intramolecular nitroalkene Diels–Alder reaction were clearly demonstrated by the elegant synthesis of the AB ring system of the zoanthamine alkaloids reported by Williams and co-workers.[2b] It should be mentioned that the intramolecular inverse electron-demand hetero Diels–Alder reaction of nitroalkenes, which provide *nitronate intermediates*, was systematically studied by Denmark and co-workers.[4]

The use of Lewis acid catalysis is a powerful method of increasing the rate and diastereoselectivity of many intramolecular Diels–Alder reactions of carbonyl-based substrates, and thus has had an enormous impact on chemical synthesis.[1c,5,6] Presumably due to the lack of its catalysis method, examples of the nitroalkene variant in the literature are remarkably rare.[2] To this end, Williams and co-workers examined a variety of Lewis acids to catalyze the cyclization of several (*E*)-1-nitro-1,7,9-decatrienes.[2b] Their attempts to enhance the *endo* selectivity through Lewis acid activation proved difficult. Similar problems with Lewis acids were also reported by Guy and co-workers.[2d] These pioneering studies proved that catalysis of the intramolecular nitroalkene Diels–Alder reaction is extremely challenging. In light of our own findings[7] that Brønsted acids periselectively catalyzed the intermolecular nitroalkene Diels–Alder reactions despite the inherent preference of nitroalkenes to undergo the inverse electron-demand hetero Diels–Alder reaction with Lewis acids, we were interested in investigating the effects of Brønsted acids on the intramolecular variant. Herein we report that pyridinium salt **1** (Table 1), NaBArF$_{24}$·2.5H$_2$O {BArF$_{24}$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate}[8] and NaBArF$_{24}$·(H$_2$O)$_x$(PhOH)$_y$[9] are efficient catalysts for the cyclizations of (*E*)-1-nitro-1,6,8-nonatrienes, and (*E*)-1-nitro-1,7,9-decatrienes.



Scheme 1 Intramolecular nitroalkene Diels–Alder reaction

The substrates for the intramolecular Diels–Alder reactions were synthesized readily using well-known methodologies as illustrated in Scheme 2. Negishi coupling of vinyl iodide **2**[10] with either vinylzinc **3a**[11] or **3b**[12] provided dienes **4a** or **4b**, respectively. The removal of TBS group, followed by Swern oxidation afforded aldehydes **6a** and **6b**.[13] A sequence of Henry reaction[14] and the dehydration[15] of the corresponding β-hydroxy nitroalkanes **7a** and **7b** gave (*E*)-1-nitro-1,6,8-nonatrienes **8a** and **8b**. (*E*)-1-Nitro-1,7,9-decatrienes **12a** and **12b** were synthesized analogously from one-carbon elongated aldehydes[16] **10a** and **10b**. It should be mentioned that the dehydration reactions led to exclusive formation of the *E*-olefins (^{1}H NMR analysis of crude products), and these

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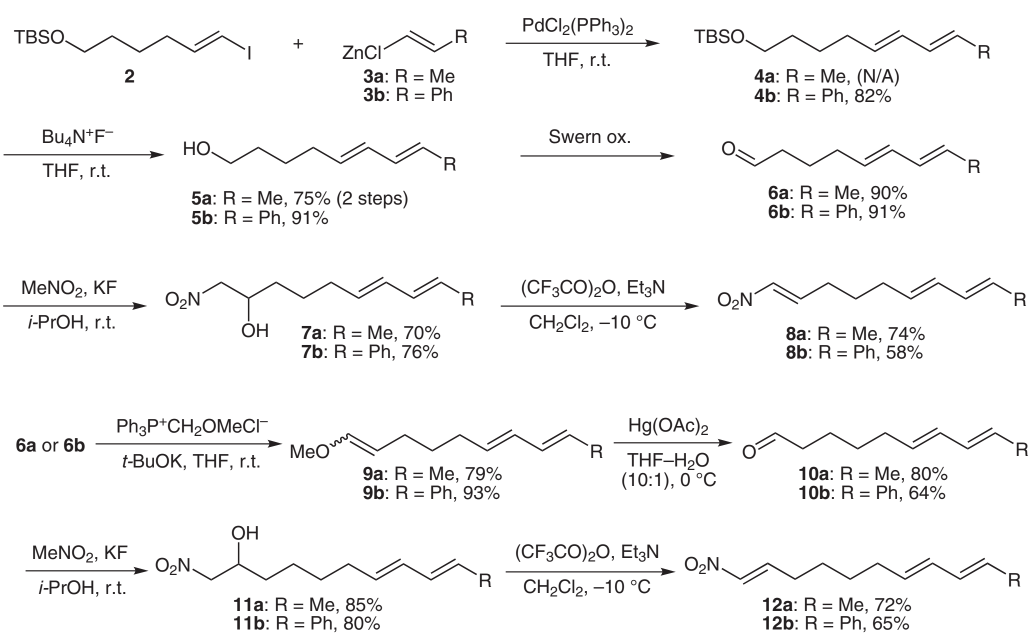
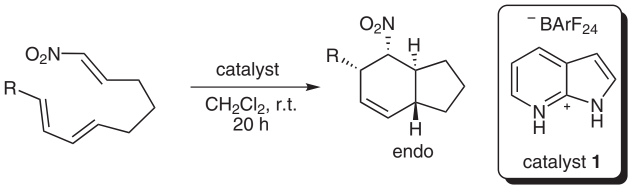


Scheme 2 Synthesis of nona- and decatrienes

Table 1 Intramolecular Diels–Alder Reaction of (*E*)-1-Nitro-1,6,8-nonatrienes



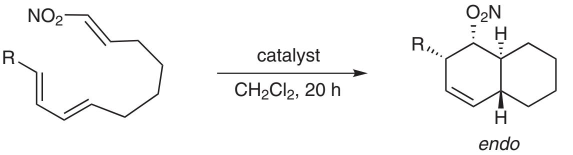
Entry	R	Catalyst (mol%)	Yield (%)	*endo*:*exo*
1	Me	**1** (10)	47	>30:1
2	Me	**1** (20)	91	>30:1
3	Me	$NaBArF_{24}·2.5H_2O$ (10)	87	>30:1
4	Me	$NaBArF_{24}·2.5H_2O$ (20)	85	>30:1
5	Ph	**1** (20)	86	>30:1

nitroalkenes were stable to procedures of flash silica gel chromatography.[2b,17]

We set out to investigate the cyclization of (*E*)-1-nitro-1,6,8-nonatriene **8a** (R = Me) with catalyst **1**, which was found to be optimal in our previous study of intermolecular nitroalkene Diels–Alder reaction.[7] To our delight, it cleanly catalyzed the reaction and provided the product in good yield with excellent *endo* selectivity (Table 1, entry 1) while a 8.1:1 *endo*:*exo* ratio was reported for the corresponding thermal reaction.[2g] The increase in catalyst loading (20 mol%) led to the excellent yield (Table 1, entry 2). Inspired by the Lewis acid assisted Brønsted acids developed by Yamamoto and co-workers,[18] we tested $NaBArF_{24}·2.5H_2O$, and found that it is a competent catalyst for the present reaction. However, unlike a pyridinium salt, increased catalyst loading did not show a beneficial effect on the yield (Table 1, entries 3 and 4). Aromatic substrate **8b** (R = Ph) also underwent the reaction cleanly and afforded the product in high yield with excellent *endo* selectivity (Table 1, entry 5).

(*E*)-1-Nitro-1,7,9-decatrienes were evaluated next (Table 2). Aliphatic substrate **12a** (R = Me) was reported to provide a 2.3:1 *endo*:*exo* ratio of products under thermal conditions.[2b] To our delight, however, the catalyzed reaction provided the product with high *endo* selectivity (Table 2, entry 1). An attempt to increase the selectivity by conducting the reaction at a lower temperature led only to decreased yield (Table 2, entry 2). $NaBArF_{24}·2.5H_2O$ turned out to be less effective in terms of selectivity (Table 2, entries 3 and 4). Interestingly, $NaBArF_{24}·(H_2O)_x(PhOH)_y$ provided better yield and selectivity than $NaBArF_{24}·2.5H_2O$ did (Table 2, entry 5). This may be attributable to the expected higher acidity of the former complex. Aromatic substrate **12b** (R = Ph) also

Table 2 Intramolecular Diels–Alder Reaction of (*E*)-1-Nitro-1,7,9-decatrienes



Entry	R	Catalyst (mol%)	Temp (°C)	Yield (%)	*endo*:*exo*
1	Me	**1** (20)	25	77	14:1
2	Me	**1** (20)	0	44	13:1
3	Me	$NaBArF_{24}·2.5H_2O$ (10)	25	88	8:1
4	Me	$NaBArF_{24}·2.5H_2O$ (10)	0	27	8:1
5	Me	$NaBArF_{24}·(H_2O)_x(PhOH)_y$ (10)	25	93	13:1
6	Ph	**1** (20)	25	71	11:1

underwent the reaction cleanly and afforded the product in good yield, but with slightly decreased *endo* selectivity (Table 2, entry 6).

In summary, we have evaluated the Brønsted acid catalysis of intramolecular Diels–Alder cyclizations of (*E*)-1-nitro-1,6,8-nonatrienes and (*E*)-1-nitro-1,7,9-decatrienes. The present study demonstrated that the Brønsted acid catalysis is an effective strategy for increasing the rate and diastereoselectivity of this class of intramolecular Diels–Alder reactions for which Lewis acid catalysis has proved difficult.

Typical Experimental Procedure for the Brønsted Acid Catalyzed Intramolecular Nitroalkene Diels–Alder Reaction

To a solution of triene **12a** (12 mg, 0.063 mmol) in CH_2Cl_2 (125 μL) cooled to 0 °C was added catalyst **1** (13 mg, 0.013 mmol) in one portion under an atmosphere of dry argon. After stirring for 5 min at 0 °C, the reaction mixture was allowed to warm to 25 °C. After 20 h, the reaction mixture was diluted with CH_2Cl_2, followed by the addition of 50 μL of MeOH–hydrazine monohydrate solution (a 50:50 mixture by volume). The resulting solution was stirred for 5 min, diluted with H_2O, extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The ratio of diastereomers was determined by ^1H NMR analysis of the crude reaction mixture (*endo*:*exo* = 14:1), which was purified by flash chromatography on silica gel (1.5% EtOAc in hexanes) to provide the product (9.4 mg, 77%).

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