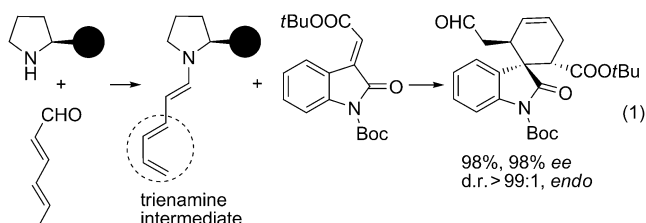## Diels–Alder Reaction

exo-Selective Asymmetric Diels–Alder Reaction of 2,4-Dienals and Nitroalkenes by Trienamine Catalysis**

Zhi-Jun Jia, Quan Zhou, Qing-Qing Zhou, Peng-Qiao Chen, and Ying-Chun Chen*

The asymmetric Diels–Alder reaction continues to generate research interest in organic chemistry because it provides one of the most powerful protocols to prepare six-membered carbo- or heterocycles with multiple chiral centers. The asymmetric Diels–Alder reaction is dominated by the activation of the LUMO of electron-poor dienophiles with chiral metal complexes[1] or organic molecules.[2] However, over the past decade, an alternative strategy has emerged in which the asymmetric Diels–Alder reaction can be promoted and controlled by raising the energy of the HOMO of the dienophile (inverse electron demand) or the diene (normal electron demand) through enamine[3] or dienamine catalysis.[4,5] Very recently, our research group and Jørgensen and co-workers[6] further expanded the synthetic potential of such an activation mode. It was discovered that a trienamine intermediate, which was generated in situ from 2,4-hexadienal and a chiral secondary amine, could serve as a diene in a normal-electron-demand Diels–Alder reaction with electron-deficient dienophiles, such as 3-olefinic oxindoles. The reaction exhibited exclusive regioselectivity and afforded the *endo* products in excellent *ee* and d.r. values [Eq. (1), Boc = *tert*-butyloxycarbonyl].[6]

Unfortunately, we subsequently found that the reaction is limited to highly activated dienophiles, such as alkylidene-cyanoacetates. Although nitroalkenes typically demonstrate good dienophilicity in numerous Diels–Alder reactions,[7] the cycloaddition of 2,4-hexadienal and β-nitrostyrene did not proceed even at higher temperature (80 °C).[8] Although nitro-containing materials have great synthetic versatility in organic chemistry, there is still scarce precedence for catalytic stereoselective Diels–Alder reactions of nitroalkenes[9,10] in comparison with the wealth of asymmetric Michael addition reactions.[11] As a result, the development of such an asymmetric Diels–Alder reaction would be highly desirable. We envisioned that the electron-donating effect of appropriate alkyl substituents could further raise the HOMO level of the trienamine intermediate (Scheme 1),[12] such that the reaction barriers of the desired cycloaddition might be overcome.
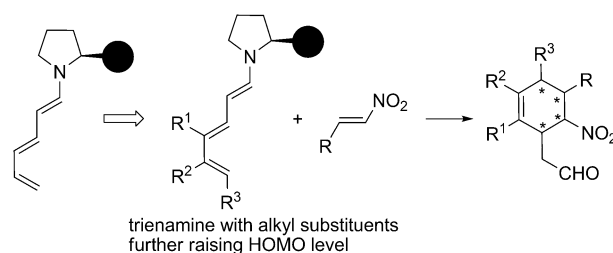
Scheme 1. Diels–Alder reaction of nitroalkenes with 2,4-dienals by the strategy of raising the HOMO energy.
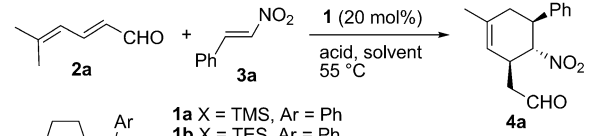

98%, 98% *ee*
d.r. > 99:1, *endo* (1)

Based on the above-mentioned considerations, 5-methyl-2,4-hexadienal (**2a**) was prepared and tested in the possible reaction with β-nitrostyrene **3a** catalyzed by the chiral secondary amine **1a** and *o*-fluorobenzoic acid in CHCl₃ at ambient temperature.[13] Gratifyingly, the desired Diels–Alder reaction occurred, which verified the beneficial effect of the 5-methyl group in raising the HOMO energy of the trienamine intermediate.[14] After 72 h, cycloadduct **4a** was isolated in moderate yield as an inseparable mixture of diastereomers, but with high diastereo- and enantioselectivity (Table 1, entry 1). Moreover, the reaction could be greatly accelerated at higher temperatures, providing **4a** in higher yield and with maintained stereocontrol (Table 1, entry 2). Much poorer results were achieved when other solvents were used (Table 1, entries 3–5). In addition, slightly lower yields were obtained when either benzoic acid or *p*-methoxybenzoic acid were applied (Table 1, entries 6 and 7). Subsequently, a few chiral secondary amines were explored. The results could not be improved when the bulkier catalysts **1b** and **1c** were

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Table 1: Screening studies of the Diels–Alder reaction of 5-methyl-2,4-hexadienal **2a** and β-nitrostyrene **3a**[a]

| Entry	1	Solvent	Acid	t [h]	Yield [%][b]	d.r.[c]	ee [%][d]
1[e]	1a	CHCl₃	OFBA	72	59	93:7	93
2	1a	CHCl₃	OFBA	2	87	90:10	93
3	1a	MeCN	OFBA	96	43	84:16	86
4	1a	toluene	OFBA	96	55	95:5	87
5	1a	dioxane	OFBA	96	75	95:5	91
6	1a	CHCl₃	BA	6	79	91:9	92
7	1a	CHCl₃	PMBA	6	71	90:10	93
8	1b	CHCl₃	OFBA	3	87	89:11	93
9	1c	CHCl₃	OFBA	3	75	91:9	89
10	1d	CHCl₃	OFBA	96	31	>95:5	75
11[f]	1a	CHCl₃	OFBA	17	85	85:15	86

[a] Unless noted otherwise, reactions were performed with **2a** (0.2 mmol), **3a** (0.1 mmol), **1** (0.02 mmol), and acid (0.02 mmol) in solvent (0.5 mL) at 55 °C. [b] Yield of isolated inseparable diastereomers. [c] Determined by ¹H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase after conversion of the product into the alcohol, for the major diastereomer. [e] At RT. [f] At 1.0 mmol scale. BA = benzoic acid, OFBA = *o*-fluorobenzoic acid, PMBA = *p*-methoxybenzoic acid, TMS = trimethylsilyl, TES = triethylsilyl.

applied (Table 1, entries 8 and 9). Although the reaction that was catalyzed by amine **1d** bearing electron-withdrawing aryl groups resulted in an excellent diastereomeric ratio, the conversion was quite low and the enantioselectivity was also dramatically decreased (Table 1, entry 10). Finally, we tested the cycloaddition reaction on a larger scale under the optimized conditions; slightly lower stereoselectivity with high yield was attained (Table 1, entry 11).

Next, an array of diversely substituted 2,4-dienals and nitroalkenes were explored for this new asymmetric Diels–Alder reaction (Scheme 2). At first, a number of nitroalkenes bearing aryl or heteroaryl groups were reacted with 5-methyl-2,4-hexadienal (**2a**). The substitution patterns were well tolerated, and in general products **4a–4j** were obtained with good yields and in high diastereo- and enantioselectivities. We also paid much attention to the substrate scope of and limitations on the 2,4-dienals. 4-Alkyl-substituted 2,4-hexadienals and 2,4-heptadienals could be utilized, affording cyclohexenes **4k–4n** with good stereocontrol. Interestingly, 2,4-dienals with a 4-phenyl group exhibited even higher reactivity,[12] and excellent yield and stereoselectivity were attained for products **4o** and **4p**. Moreover, the combinations with nitroalkenes carrying linear or branched alkyl groups were also compatible and provided products **4q** and **4r** with high d.r. and *ee* values. Importantly, bicyclic compounds **4s** and **4t**, whose skeletons are common motifs in natural products, could be efficiently constructed, although polyhydronaphthalene **4s** was only isolated in modest yield because of incomplete conversion. In addition, we tested some tri- and
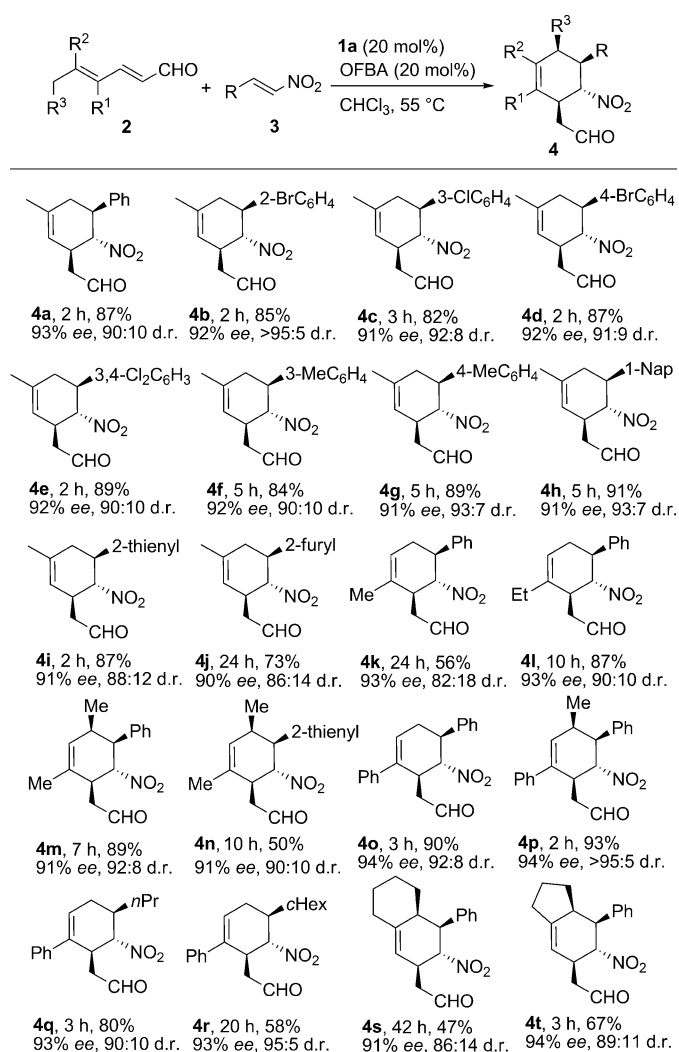
Scheme 2. Substrate scope of the Diels–Alder reaction. Reactions leading to **4a–4p** were performed with **2** (0.2 mmol), **3** (0.1 mmol), catalyst **1a**, and OFBA (20 mol%) in CHCl₃ (0.5 mL) at 55 °C; in reactions leading to **4q–4t**, **2** (0.1 mmol) and **3** (0.2 mmol) were used. The yields are those of isolated inseparable diastereomers. The d.r. values were determined by ¹H NMR analysis. The *ee* values (major diastereomer) were determined by HPLC analysis on a chiral stationary phase after conversion of the product into the corresponding alcohol. The absolute configuration of **4n** was determined by X-ray analysis after conversion into the 2,4-dinitrobenzenehydrazone (see the Supporting Information).[16] The other products were assigned by analogy. *c*Hex = cyclohexyl, Nap = naphthyl.

tetrasubstituted nitroalkenes, but the results were not satisfying (see the Supporting Information).[15]

The multifunctionality of the Diels–Alder adducts enables further transformations to access chiral compounds with higher degrees of molecular complexity. As outlined in Scheme 3, the alcohol generated from Diels–Alder adduct **4a** was readily converted to tetrahydrofuran derivative **5** as an isolable single diastereomer by an iodoetherization process. Moreover, the domino Michael addition/aldol reaction of **4a** and acrolein proceeded smoothly by tetramethylguanidine catalysis, affording the fused bicyclic product **6** bearing a quaternary chiral center.[17,18]
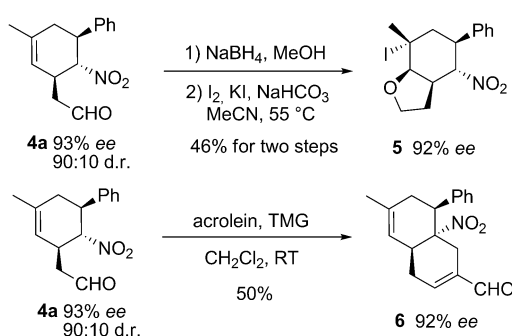
Scheme 3. Synthetic transformations of Diels–Alder adduct **4a**. TMG = tetramethylguanidine.

To study the selectivity of the reaction, we obtained the X-ray structure of enantiopure **4n** after conversion to its 2,4-dinitrobenzenehydrazone derivative.[16] Surprisingly, the product displays an *exo* configuration in contrast to the previous *endo*-favored stereoselectivity of 3-olefinic oxindoles.[6] Although an *exo*-selective Diels–Alder reaction[19] of nitroalkenes with Danishefsky's diene was reported to be based on electrostatic repulsion between the nitro group and the silyloxy group of the diene,[20] the O-trimethylsilyl (OTMS) ether moiety of catalyst **1a** would not account for the *exo* selectivity in a similar way in the present study. As shown in Scheme 4, catalysts **1e** and **1f** delivered the same
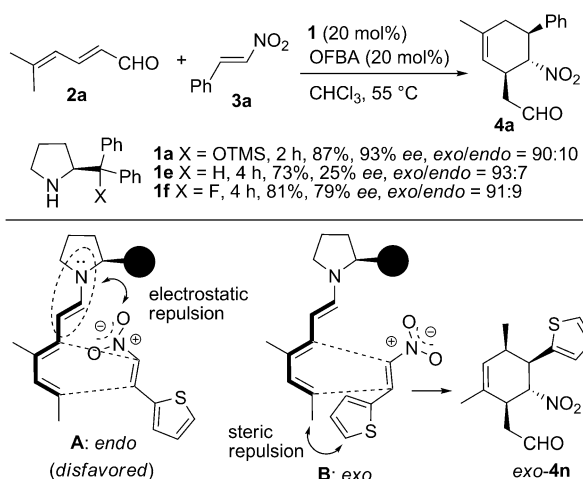
Scheme 4. Rationalization for the *exo*-selective Diels–Alder reaction.

exo/endo ratios as that obtained with OTMS ether **1a** in the Diels–Alder reaction of 2,4-dienal **2a** and β-nitrostyrene **3a**, though the enantioselectivity was decreased. This is in accordance with the calculated trienamine model which indicates that the bulky OTMS group is helpful for the face selectivity in the Diels–Alder reaction.[6] Based on these results, we propose that the inherent secondary-orbital effect and the steric repulsion (Scheme 4, mode **B**) of the Diels–Alder reaction might be overcome by the electrostatic repulsion between the negative charge of the nitro group and the π electrons of the electron-rich enamine motif (Scheme 4, mode **A**), thus favoring the formation of the

observed product *exo*-**4n**.[21] Nevertheless, more studies are still required to elucidate this *exo*-selective Diels–Alder reaction.

In conclusion, we have presented the first asymmetric Diels–Alder reaction of 2,4-dienals and nitroalkenes by a newly developed trienamine catalysis. The strategy of raising the HOMO energy through the introduction of appropriate substituents in the skeleton of 2,4-dienals proved to be successful since unsubstituted 2,4-hexadienal and 2,4-heptadienal were inactive under the same catalytic conditions. Many diversely substituted 2,4-dienals and nitroalkenes have been explored, generally giving densely substituted chiral cyclohexene derivatives in high diastereo- and enantioselectivities. Moreover, an unexpected *exo* selectivity was observed in this Diels–Alder reaction, and a plausible mechanism based on electrostatic repulsion between the nitro group of the dienophile and the π electrons of the enamine motif was proposed. We also believe that the strategy of raising the HOMO energy for trienamine catalysis could be applicable to more cycloadditions or other types of reactions of 2,4-dienals. These studies are currently under way in our laboratory and the results will be reported in due course.

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