



Nitrosocarbonyl hetero-Diels–Alder cycloaddition with 2-substituted 1,3-butadienes



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ABSTRACT

A study of the reactivity of 2-substituted 1,3-butadienes with nitrosocarbonyl compounds in the 4+2 cycloaddition has been carried out showing that the regioselectivity involves a delicate balance of steric and electronic effects. 2-Aryl 1,3-butadienes favor the distal isomer with the magnitude of preference ranging from 4:1 to 15:1 depending on the nature of the nitrosocarbonyl group. However, when bulky 2-substituted dienes are used the proximal isomer is formed preferentially. The results obtained, together with previous theoretical calculations and experimental data, provide further data to aid in synthetic planning.

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1. Introduction

Transformations that simultaneously construct carbon–nitrogen and carbon–oxygen bonds are essential for streamlining the synthesis of natural products and pharmaceutically relevant agents.¹ In this regard, hetero-Diels–Alder reactions between nitroso compounds and dienes have played an important role in organic chemistry since their discovery in 1947.² The oxazine scaffold, which results from the [4+2] cycloaddition, serves as a strategic intermediate for the synthesis of a wide-range of natural products.³ For example, cleavage of the N–O oxazine bond results in a skeleton with a 1,4-relationship between the alcohol and amine substituents, which are valuable for further elaboration.^{1,3,4} However, like many heterocycloadditions, the use of unsymmetrical dienes, such as 2-substituted 1,3-butadiene, necessitates regiocontrol for this transformation to be truly synthetically useful because the nitroso [4+2]-cycloaddition can provide two regioisomers. Fig. 1 shows the regiochemical outcome for 2-substituted dienes. When the 2-substituent is close to the oxygen heteroatom of the oxazine adduct it is referred to as the proximal isomer and when the 2-substituent is close to the nitrogen heteroatom of the oxazine adduct it is referred to as the distal isomer.

Several groups have independently reported on the regiocontrol of the nitroso-Diels–Alder (NDA) reaction using both computational and experimental studies.⁵ As can be seen by Scheme 1 the regioselectivity for 2-substituted dienes can depend on a combination of both steric and electronic effects on both the nitroso and the diene partners. Using FMO and DFT calculations, as well as experimental data accumulated from the literature, Houk and co-workers proposed a general rationale for regiochemical preference for various monosubstituted dienes, including 2-substituted dienes, and nitroso sources (Scheme 1a).^{6a,5d,6b} They showed that the principle interaction is between the HOMO(diene) and LUMO(nitroso heterodienophile) and that there is a strong preference for an endo transition state. In general, for 2-substituted dienes the HOMO should have its largest coefficient at the C1-position and hence, the distal isomer is typically expected (Scheme 1b). However, as seen by Scheme 1c using an electron-rich diene in combination with an electron-poor aryl nitroso compound favors the proximal isomer.^{5b} Furthermore, Whitting and co-workers recently reported that the magnitude of preference for the proximal vs. distal isomer can also depend on the nature of the nitroso group.^{5h} For example, the reaction of nitrosoformate (Scheme 1d) and nitrosoformamide (Scheme 1e), generated in situ through a copper-catalyzed aerobic oxidation, with 2-methyl-1,3-butadiene gave distal and proximal isomers with a preference for the distal form that varied from ~1.7:1 to ~4.6:1 depending on the nature of the nitroso compound. Finally, Boger and co-workers showed that

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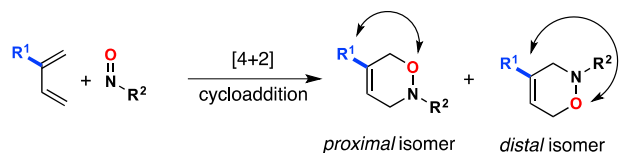


Fig. 1. Regioselectivity of nitroso-Diels–Alder reactions with 2-substituted dienes.

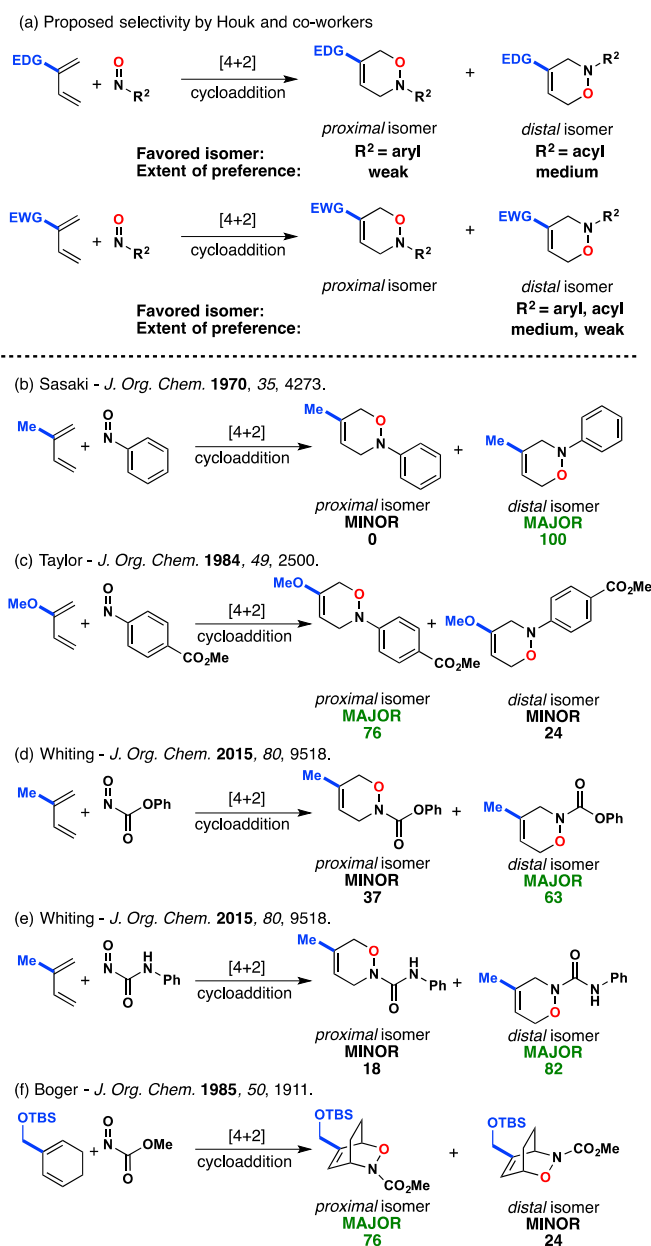
steric effects are also important in governing regioselectivity (Scheme 1f).^{5c} Because there is a significant unfavorable interaction between the nitrogen lone pair with the π electrons of the electron-rich diene, the endo transition state is favored.^{5d} This exo lone pair effect causes the diene to be in close proximity to the nitrogen substituent and if the steric interaction is large the proximal isomer can be favored. It is clear that the regiochemical preference for the

NDA reaction can vary from substrate to substrate and more studies are necessary to help facilitate predictability, specifically for the nitrosocarbonyl Diels–Alder reaction. In the present article, we wish to report our studies with a range of both nitrosocarbonyl compounds and 2-substituted dienes.

2. Results and discussion

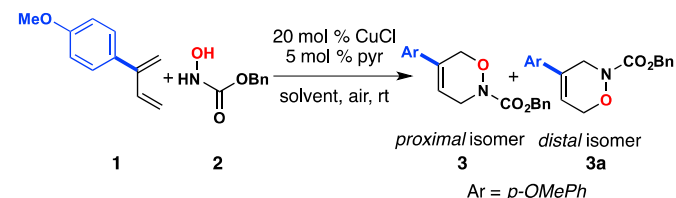
We chose to study 2-aryl-1,3-butadienes initially as they avoid the potentially competing nitrosocarbonyl ene reaction due to their lack of allylic protons.⁷ To generate the nitrosocarbonyl compound in situ we employed our previously developed copper-catalyzed aerobic oxidation conditions (20 mol% CuCl, 5 mol% pyridine).^{8a,7f,8b-d} Initially a solvent and ligand screen were conducted using 2-aryl-1,3-butadiene **1** and *N*-hydroxycarbamate **2** (Table 1) and in all cases we observed a preference for the distal isomer. The regioselectivity was determined with the aid of HSQC and ¹⁵N HMBC. The reaction solvent and ligand for copper showed a modest influence on the overall yield of the NDA reaction, but had little effect on the observed regioselectivity. This is consistent with previous results and supports a transition state with little polar character.^{5c,5d}

We next evaluated the electronic effects of the 2-substituent of the 1,3-butadiene on regioselectivity using *N*-hydroxycarbamate **2** as the nitroso precursor (Table 2, only major regioisomer shown). Based on Houk's model one would predict that the distal isomer would be preferred as the group at the 2-position increases in electron density because the interaction between the HOMO(-diene) and LUMO(nitroso heterodienophile) is maximized.^{5d} This trend was observed in our experimental results. Electron donating aryl groups give the highest preference for the distal regioisomer with selectivities up to 15:1, while electron withdrawing aryl groups show a lower preference for the distal regioisomer with selectivities dropping to 4:1. Interestingly, the *o*-methoxy aryl group (**11**) resulted in a modest 4:1 selectivity despite being electronically similar to the *p*-methoxy aryl group (**7**). Presumably, the reduced selectivity results from allylic strain that causes the aryl ring to rotate out of conjugation with the diene in the reactive *s*-cis conformation thus reducing electron density on the alkene and minimizing the electronic preference for the distal isomer. Consistent with the literature, 2-methyl-1,3-butadiene gave only a slight preference for the distal isomer (2:1, distal:proximal) and nitrosocarbonyl ene adduct was also observed in 38% yield.^{5h} However, in the case of a bulky 2-substituent the proximal



Scheme 1. Literature examples of regiochemical studies for the nitroso-Diels–Alder reaction with 2-substituted dienes.

Table 1
Optimization screen for NDA reaction.



Entry	Solvent	Ligand	% Yield	Proximal:Distal
1	Toluene	Pyridine	61	1:14
2	MeOH	Pyridine	61	1:15
3	2-Me THF	pyridine	71	1:15
4	THF	Pyridine	85	1:15
5	THF	Ethyl oxazoline	78	1:15
6	THF	Ethyl nicotinate	58	1:14
7	THF	Bipyridyl	60	1:15

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