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Regio-, Diastereo-, and Enantioselective Nitroso-Diels–Alder Reaction of 1,3-Diene-1-carbamates Catalyzed by Chiral Phosphoric Acids

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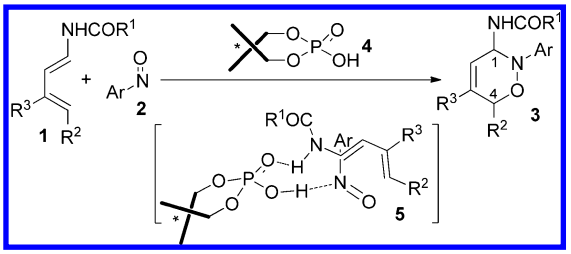
Supporting Information

ABSTRACT: Chiral phosphoric acid-catalyzed asymmetric nitroso-Diels–Alder reaction of nitrosoarenes with carbamate-dienes afforded *cis*-3,6-disubstituted dihydro-1,2-oxazines in high yields with excellent regio-, diastereo-, and enantioselectivities. Interestingly, we observed that the catalyst is able not only to control the enantioselectivity but also to reverse the regioselectivity of the noncatalyzed nitroso-Diels–Alder reaction. The regiochemistry reversal and asynchronous concerted mechanism were confirmed by DFT calculations.

The nitroso-Diels–Alder (NDA)[1] reaction has attracted considerable attention among synthetic chemists because of the utility of the resulting 3,6-dihydro-1,2-oxazines for the synthesis of natural products and biologically active molecules.[1,2] Therefore, the development of asymmetric, catalytic versions of the NDA reaction has been the subject of numerous studies.[1] However, control of the regioselectivity,[3] fast background reaction(s), and the high propensity for dimerization of nitroso compounds[4] under acidic conditions have made the development of a catalytic enantioselective intermolecular process challenging.[1,5] The first intermolecular enantioselective NDA reaction was reported by Ukaji and Inomata using a stoichiometric amount of a Zn(II) tartaric acid ester complex.[6] A major breakthrough came from Yamamoto's group,[7] who reported that a copper complex could catalyze the intermolecular asymmetric NDA reaction of 2-nitrosopyridines with cyclic and acyclic dienes. Although cycloadducts were generally isolated with high enantiomeric excess, this method is effective only for 2-nitrosopyridine dienophiles. Afterward, the same group[8] described two efficient organocatalytic asymmetric NDA reactions of cyclic dienes employing a pyrrolidine-derived tetrazole[8a,9] or a BINOL-derived Brønsted acid[8b] as chiral catalysts. In spite of these notable achievements, most of the efficient enantioselective NDA reactions are mainly restricted to specific nitroso dienophiles or cyclic dienes.

In light of the recent development of chiral phosphoric acid-catalyzed asymmetric transformations[10] of secondary enamides[11] that have been disclosed by us[12] and others,[13] we reasoned that 1,3-diene-1-carbamates bearing an NH directing group would be ideal partners for implementing an enantioselective catalytic NDA reaction. Indeed, the dienecarbamate as well as the nitrosoarene could be activated through double hydrogen bonding to control both the regio- and enantioselection (Scheme 1).

Scheme 1. Bifunctional Catalyst for the Enantioselective NDA Reaction



To validate our hypothesis, we examined the reaction of benzyl (penta-1,3-dien-1-yl)carbamate (**1a**) with commercially available nitrosobenzene (**2a**) in the presence of 5 mol % chiral phosphoric acid **4** in CH_2Cl_2 at −30 °C. As shown in Table 1, all of the catalysts tested were capable of catalyzing the reaction with complete O-regioselectivity[3,8b,13f] and excellent diastereoselectivity in favor of the cis diastereomer. However, the enantioselectivity varied widely with the size of the substituents at the 3- and 3′-positions of **4** (entries 1−4).[10] We found that the bulkier (*S*)-3,3′-bis(2,4,6-triisopropylphenyl)-BINOL (TRIP) phosphoric acid **4d** provided cycloadduct **3a** in a much higher yield and enantiomeric excess (entry 4). When the catalyst loading was reduced to 1 mol %, the enantioselectivity was maintained at almost the same level, although the yield decreased to 33% (entry 5). However, simply increasing the reaction time from 3 to 16 h enhanced the yield of 3,6-dihydro-1,2-oxazine **3a** to 98% (entry 6). A survey of reaction solvents with 5 mol % **4d** revealed that toluene was effective to slightly improve the enantioselectivity (entry 7). Finally, performing the reaction in toluene at a lower temperature (−50 °C) improved both the yield and enantioselectivity (entry 8). It is

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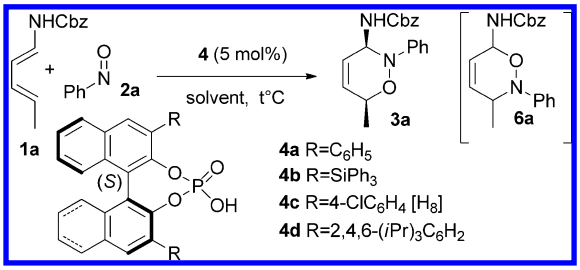
Table 1. Survey of Reaction Conditions for NDA of 2a[a]



entry	cat	solvent	temp	time (h)	yield (%)[b]	ee (%)[c,d]
1	**4a**	CH_2Cl_2	−30 °C	3	60 (**3a**)	20 (**3a**)
2	**4b**	CH_2Cl_2	−30 °C	3	80 (**3a**)	65 (**3a**)
3	**4c**	CH_2Cl_2	−30 °C	3	47 (**3a**)	17 (**3a**)
4	**4d**	CH_2Cl_2	−30 °C	3	98 (**3a**)	90 (**3a**)
5	**4d**	CH_2Cl_2	−30 °C	3	33 (**3a**)	87 (**3a**)[e]
6	**4d**	CH_2Cl_2	−30 °C	16	98 (**3a**)	88 (**3a**)
7	**4d**	toluene	−30 °C	16	73 (**3a**)	93 (**3a**)
8	**4d**	toluene	−50 °C	16	80 (**3a**)	98 (**3a**)
9		toluene	rt	3	80 (**6a**)[d]	

[a]General conditions: **1a** (0.05 mmol), **2a** (0.10 mmol), and **4** (0.0025 mmol). [b]Yields refer to chromatographically pure products. [c]Determined by HPLC analysis on chiral stationary phases. [d]>95:5 dr. [e]With 1 mol % **4**.

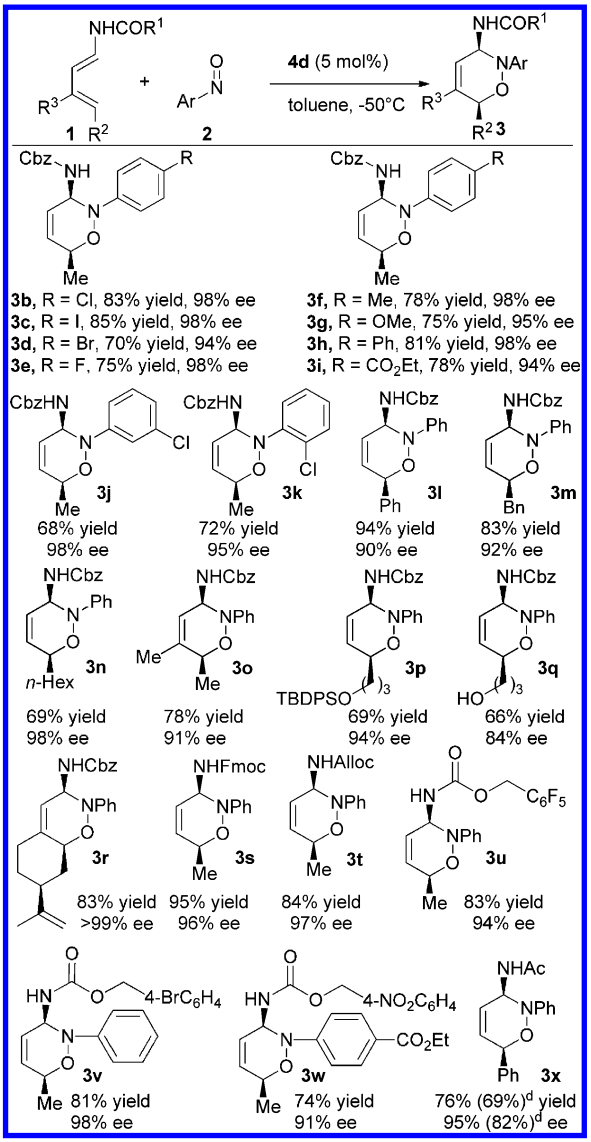
interesting to note that regioisomer **6a** was not detected in the phosphoric acid-catalyzed NDA reaction.

The scope of this Brønsted acid-catalyzed NDA reaction was next investigated using our optimized conditions. As shown in Table 2, various nitrosoarenes bearing electron-donating and -withdrawing groups at the para position[14] could be successfully employed to afford 3,6-dihydro-1,2-oxazines **3b−i** in good yields with complete regioselectivity and excellent diastereo- and enantioselectivities. In addition, both ortho- and meta-substituted nitrosoarenes efficiently provided the corresponding cycloadducts **3j** and **3k** with excellent enantioselectivities. Pleasingly, this asymmetric NDA reaction was found to be successful with various 1,3-diene partners. Notably, dienecarbamates **1b−d** bearing alkyl (e.g., benzyl, hexyl) or aryl (e.g., phenyl) groups at C-4 readily participated in the reaction, affording 1,6-dihydro-1,2-oxazines **3l−n** in yields and enantioselectivities on the same order. At the same time, the 3,4-dialkyl-substituted diene **1e** was also a successful substrate for this NDA reaction, providing cycloadduct **3o** with an excellent enantioselectivity (91% ee). The presence of functional groups such as silyl ether (**3p**), alcohol (**3q**), or double bond (**3r**) is well-tolerated in the NDA reaction as well. To our delight, the enantiomerically pure dienecarbamate **1h** having one endocyclic double bond afforded **3r** as a single diastereomer. Finally, the catalytic system also proved to be efficient for various carbamates (Alloc, Fmoc, *p*-Br-Cbz, *p*-NO_2-Cbz, and perfluoro-Cbz) and amides, affording highly substituted 3,6-dihydro-1,2-oxazines **3s−x** with excellent ee values. The absolute configurations of the chiral centers in compound **3w** were determined to be 3*S* and 6*S* by single-crystal X-ray diffraction analysis (see the Supporting Information).

The following control experiments were carried out in order to gain some mechanistic insight. When the reaction of 1,3-diene **1a** and nitrosobenzene **2a** was conducted in the absence of catalyst, the other regioisomer **6a** was exclusively obtained in 80% yield (Table 1, entry 9). Moreover, as described in Table 1, only 1 mol % catalyst was required to completely reverse the regioselectivity of the NDA reaction (Table 1, entry 6).[8,15] These findings indicate that the chiral phosphoric acid catalyst is highly active. To confirm this, we performed kinetic studies by measuring the rates of conversion of **1a** with and without catalyst (see the Supporting Information). As expected, we found that the phosphoric acid-catalyzed reaction was much faster than the uncatalyzed one. To probe the origin of the regioselectivity reversal,[2b,3,5a,15] two different transition state models, **7** and **8**, were proposed (Scheme 2). The high azaphilicity of phosphoric acid catalysts[9] could result in the preferential formation of a hydrogen bond with the nitrogen of nitroso **2**, thus favoring the regioisomer **3**. In this assembly **8**, the phosphoric acid would form hydrogen bonds with 1,3-diene **1** and the nitrogen atom of **2** to favor **3**.

To improve our understanding of the mechanism and the regio- and stereochemistry observed experimentally, density

Table 2. Substrate Scope of 1,3-Diene-1-carbamates 1 and Nitrosoarenes 2[a−c]



[a]General conditions: **1a** (0.05 mmol), **2** (0.10 mmol), and **4** (0.0025 mmol) in toluene at −50 °C. [b]Yields refer to chromatographically pure products. [c]Determined by HPLC analysis on chiral stationary phases. [d]Using catalyst **4e** (R = 2,4,6-$(Me)_3$-C_6H_2).

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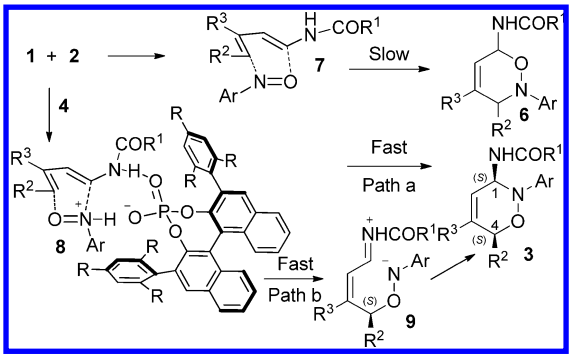
Scheme 2. Activation Models and Possible Reaction Mechanism



functional theory (DFT) calculations were performed at the B3LYP/6-31G* level.[16] First, electronic structures of dienophile **2a** and *N*-acylenamide **1m** (R^1 = Me, R^2 = Ph, R^3 = H) were calculated and opposed to each other in order to locate transition states leading to regioisomers **3x** and **6x** on the potential energy surface (Figure 1). The free energy difference

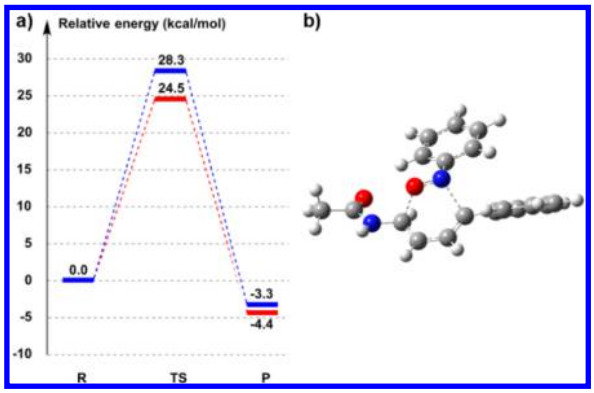


Figure 1. (a) Free energy profiles for the spontaneous (uncatalyzed) reactions yielding regioisomers **3x** (blue) and **6x** (red). (b) Structure of the transition state for the red pathway, which has the lower energy barrier.

between these two scenarios was consistent with the formation of **6** as the major product in the absence of catalyst. Next, the equivalent transition states were studied again, this time in the presence of each enantiomer of phosphoric acid catalyst **4e** (Figure 2), in order to explain both the regioselectivity inversion and the stereochemical outcome of the reaction. Among the four possible combinations of regio- and stereochemistry, the transition state leading to regio- and stereo-

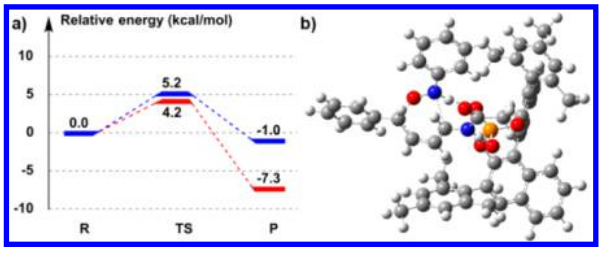


Figure 2. (a) Free energy profiles for the (*S*)- and (*R*)-**4e**-catalyzed reactions yielding enantiomers of **3x** (red and blue, respectively). (b) Structure of the transition state for the red pathway, which has the lower energy barrier.

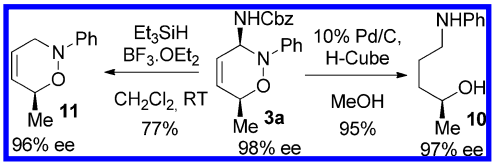
isomer **3x** in the presence of (*S*)-**4e** had the lowest activation energy (Figure 2). This result was in accordance with **3x** being the major product obtained experimentally. Calculation of the intrinsic reaction coordinate of this theoretically most-favored pathway revealed an asynchronous concerted mechanism (path a in Scheme 2)[2b,5a,17] with a concomitant boat-to-half-chair conformational change of the dihydrooxazine ring, to the detriment of an alternative stepwise[7] vinylogous *O*-nitroso aldol reaction followed by intramolecular aminalization (path b in Scheme 2; also see the Supporting Information).

The structure found for this transition state confirmed the dual activation of the substrates by the catalyst, with the formation of a hydrogen-bonding network. Moreover, on this preferred pathway we observed a total proton transfer from phosphoric acid to the (basic) nitrogen belonging to the nitroso derivative. This finding led us to wonder whether the sole protonation of the nitroso partner sufficed to control the regioselectivity of the reaction.[5a,15b]

To investigate and isolate the influence of this factor, we performed a series of experiments involving non-phosphoric, nonchiral acid catalysts with decreasing pK_a (see the Supporting Information).[10i] The strongest acids (CSA, pTSA) were found to result in total regiochemistry inversion in favor of derivative **3**,[8b,13f] to the credit of our speculation, whereas reactions conducted in the presence of weaker acids (e.g., benzoic acid) yielded almost exclusively isomer **6**. This hypothesis was further studied in the course of a last series of computational transition state searches in which the nitrogen atom of the nitroso derivative was protonated in the absence of any counteranion. The energy barriers found were in agreement with the role supposedly played by the proton in the regioselectivity (see the Supporting Information).

Having obtained optically pure 3,6-dihydro-1,2-oxazines **3**, we next demonstrated their synthetic utility (Scheme 3).

Scheme 3. Synthetic Transformation of 3,6-Dihydro-1,2-oxazines 3



Hydrogenation of 1,2-oxazine product **3a** using an H-Cube apparatus[17] gave valuable 1,4-amino alcohol **10** in good yield after hydrogenolysis of the double bond, reduction of the aminal, and N−O bond cleavage. Reduction of **3a** with triethylsilane in the presence of BF_3·OEt_2 gave direct access to the corresponding 6-methyl-3,6-dihydro-1,2-oxazine **11** in 77% yield without any loss of enantioselectivity (96% ee).[18]

In summary, we have developed an efficient enantioselective NDA reaction of nitrosoaryl derivatives with dienecarbamates catalyzed by chiral phosphoric acids. This cycloaddition is applicable to a wide range of nitrosoaryl derivatives and dienecarbamates, providing a highly diastereo- and enantioselective route to (3*S*,6*S*)-dihydro-1,2-oxazines **3**. Early mechanistic studies seem to indicate that the present NDA reaction proceeds via a highly asynchronous concerted mechanism.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08515.

Experimental procedures, characterization data, copies of spectra, and details of the DFT calculations (PDF)
Crystallographic data for **3w** (CIF)

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Notes

The authors declare no competing financial interest.

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