Communication

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

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 10 Sep 2015

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

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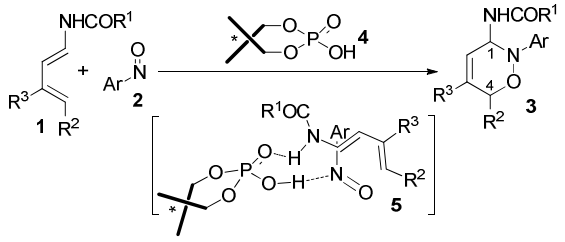
Supporting Information Placeholder

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 not only able to control enantioselectivity but also is able to reverse regioselectivity of the non-catalyzed nitroso-Diels–Alder reaction. Regiochemistry reversal as well as 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, development of asymmetric, catalytic versions of the NDA reaction have been the subject of numerous researches.[1] However, control of the regioselectivity,[3] fast background reaction(s) and the high propensity for dimerization of nitroso compounds[4] under acidic conditions made 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] which 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 a high enantiomeric excess, this method is only effective for 2-nitrosopyridine dienophiles. Afterwards, the same group[8] described two efficient organocatalytic asymmetric NDA reactions of cyclic dienes employing a pyrrolidine-derived tetrazole[8a,9] or BINOL-derived Brønsted acid,[8b] respectively, as chiral catalyst. In spite of these notable achievements, most of efficient enantioselective NDA reactions were 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 nitrosoarene could be activated through double hydrogen bonding to control both regio- and enantioselection (Scheme 1).

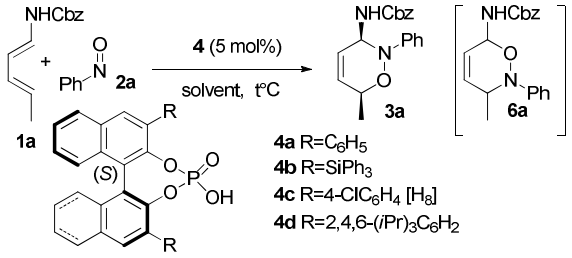
Scheme 1. Bifunctional catalyst for the enantioselective NDA reaction



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 % of chiral phosphoric acid **4** in DCM at -30 °C (Table 1). As shown in Table 1, all 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, enantioselectivity varied widely with the size of the substituents on the 3,3'-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, by simply increasing reaction time from 3 to 16 h, the yield of 3,6-dihydro-1,2-oxazine **3a** (entry 6) was

enhanced to reach 98%. A survey of reaction solvents with 5 mol% of **4d** revealed that toluene was effective to slightly improve enantioselectivity (entry 7). Finally, performing the reaction in toluene at a lower temperature (-50°C) resulted in an improvement of both yield and enantioselectivity (entry 8). It is interesting to note that regioisomer **6a** was not detected under phosphoric acid-catalyzed NDA reaction.

Table 1. Survey of reaction conditions for NDA of 2a.[a]

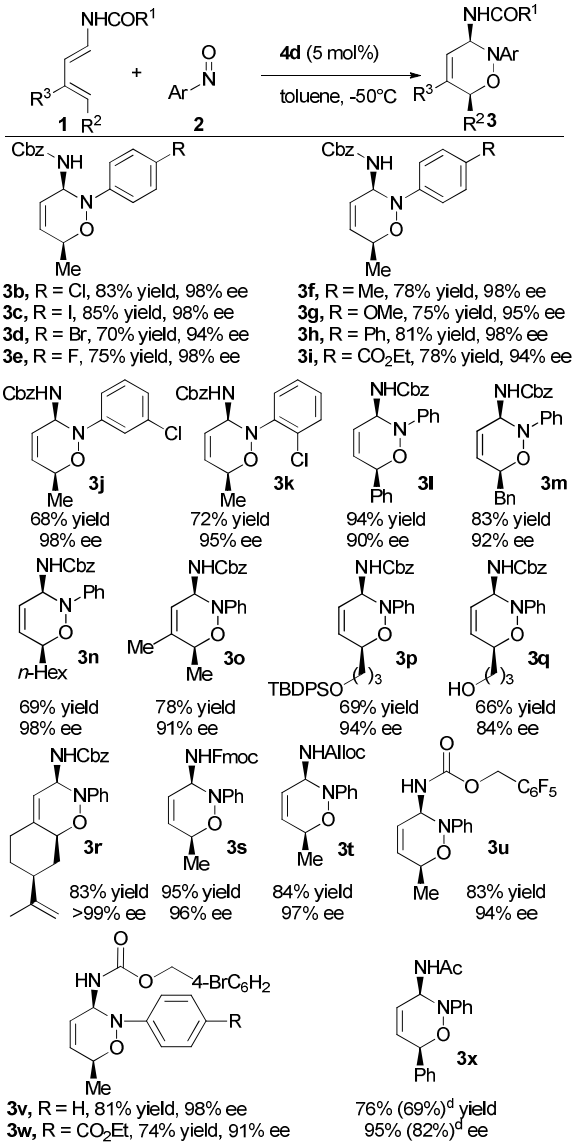


entry	cat	solvent	temp	time (h)	yield (%)[b] (**3a** or **6a**)	*ee* (%)[c,d] (**3a** or **6a**)
1	**4a**	CH_2Cl_2	-30°C	3	60 (**3a**)	20 (**3a**)
2	**4b**	CH_2Cl_2	-30°C	3	80 (**3a**)	65 (**3a**)
3	**4c**	CH_2Cl_2	-30°C	3	47 (**3a**)	17 (**3a**)
4	**4d**	CH_2Cl_2	-30°C	3	98 (**3a**)	90 (**3a**)
5	**4d**	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 product. [c] Determined by HPLC analysis on chiral stationary phases. [d] >95:5 dr. [e] With 1 mol% of **4**.

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-3i** 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 (Table 2). Pleasingly, this asymmetric NDA reaction was found to be successful with various 1,3-diene partners (Table 2). Notably, several carbamate-dienes **1b-d** bearing alkyl (such as benzyl and hexyl) or aryl (such as phenyl) groups at the C-4 position readily participated in the reaction, leading to the obtention of 1,6-dihydro-1,2-oxazines **3l-3n** with yields and enantioselectivities of the same order (Table 2). At the same time, the 3,4-dialkylsubstituted diene **1e** was also a successful substrate of this NDA reaction, providing cycloadduct **3o** with an excellent enantioselectivity (91% ee). The presence of functional groups such as silyl ether (**3p**), alcohol (**3q**) and 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 and perfluoro-Cbz) and amides affording highly substituted 3,6-dihydro-1,2-oxazines **3p-3u** with excellent *ee's* (Table 2). Absolute configuration of chiral centeres in compound **3u** was determined to be 3*S* and 6*S* by single crystal X-ray diffraction analysis (see Supporting information).

Table 2. Substrate scope of 1,3-diene-1-carbamates 1 and nitrosoarenes 2 with 1a.[a-c]

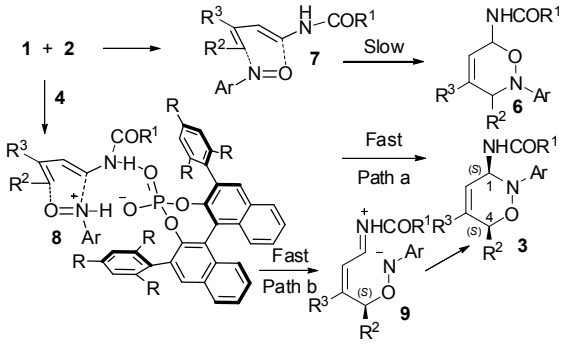


[a] General conditions: **1a** (0.05 mmol), **2** (0.10 mmol) and **4** (0.0025 mmol) in toluene at -50°C. [b] Yields refer to chromatographically pure product. [c] Determined by HPLC analysis on chiral stationary phases. [d] Using catalyst **4e** R = 2,4,6-$(Me)_3$-C_6H_2.

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 (entry 9, Table 1). Moreover, as described in Table 1, only 1 mol% catalyst was required to completely reverse the regioselectivity of the NDA reaction (entry 6, Table 1).[8,15] These findings indicate that the chiral phosphoric acid catalyst is highly active. To confirm this, we performed kinetic studies by measuring the rate of conversion of **1a** with or without

catalyst (see 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 H-bond with nitrogen N 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 favour the isomer **3**.

Scheme 2. Activation models and possible reaction mechanism



To improve our understanding of the mechanism and the regio- and stereochemistry observed experimentally, DFT calculations were performed at the B3LYP/6-31G* level.[16] First, electronic structures of dienophile **2a** and N-acylenamide (R^1=Me, R^2=Ph and R^3=H) **1m** 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 between these two scenarios was consistent with formation of **6** as the major product in the absence of catalyst. Then, 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 4 possible combinations of regio- and stereochemisty, the transition state leading to regio- and stereoisomer **3x** in the presence of (S)-**4e** catalyst had the lowest activation energy (Figure 2). This result was in accordance with **3x** being indeed the major product obtained experimentally. Calculation of the IRC 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; see also Supporting information).

The structure found for this transition state confirmed dual activation of substrates by the catalyst, with the formation of a hydrogen bond 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]

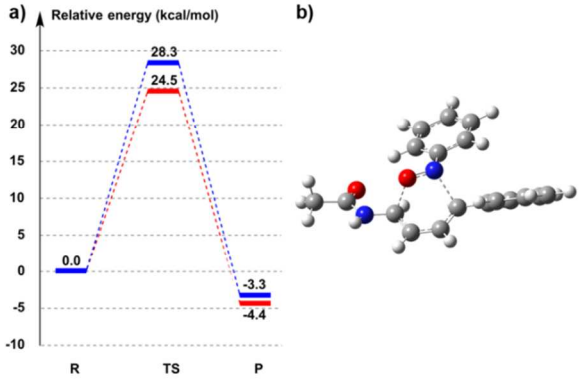


Figure 1. a) Free energy profiles for the spontaneous (uncatalyzed) reactions yielding regioisomers **3x** (blue) and **6x** (red). b) Structure of the transition state for the red pathway, with the lowest energy barrier.

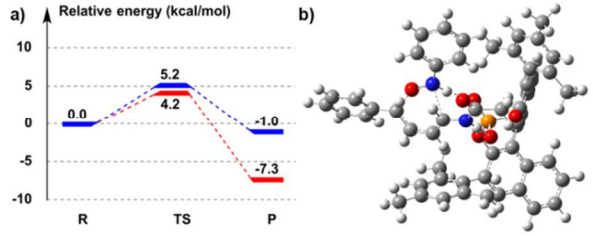
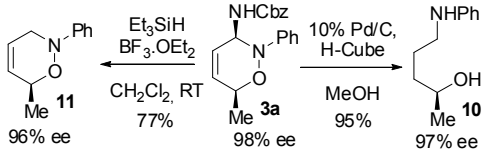


Figure 2. a) Free energy profiles for the (*S*) and (*R*)-**4e**-catalyzed reactions yielding enantiomers **3x** (respectively red and blue). b) Structure of the transition state for the red pathway, with the lowest energy barrier.

To investigate and isolate the influence of this factor, we performed a series of experiments involving non phosphoric, non-chiral acid catalysts with decreasing pKa (see Supporting Information).[10i] The strongest acids (CSA, pTSA) were found responsible of a 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 (such as benzoic acid) yielded almost exclusively isomer **6**. This hypothesis was further studied in the course of a last series of computational transition state searches, where 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 regioselectivity (see Supporting information).

Scheme 3. Synthetic transformation of 3,6-dihydro-1,2-oxazines 3



With optically pure 3,6-dihydro-1,2-oxazines **3** obtained, we next demonstrated the synthetic utility of the NDA products (Scheme 3). Hydrogenation of the 1,2-oxazine product **4a** using an H-Cube apparatus (17) gave valuable 1,4-amino-alcohol **10** in good yield after hydrogenolysis of the double bond, reduction of aminal and N-O bond cleavage. Reduction of **4a** with triethylsilane in the presence of $BF_3.OEt_2$ gave direct access to the corresponding 6-methyl-3,6-dihydro-1,2-oxazine in 77% yield without any loss of enantioselectivity (ee =96%).[18]

In summary, we have developed an efficient enantioselective NDA reaction of nitrosoaryl derivatives with carbamate dienes catalyzed by chiral phosphoric acids. This cycloaddition is applicable to a wide range of nitrosoaryl derivatives and carbamate dienes, 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.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, copies of spectra, crystallographic data, and details of the DFT calculations. This material is available free of charge on the ACS Publication Website http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank ICSN for financial support and doctoral fellowships to J.P.; T.C. thanks MESR for a doctoral fellowship, University of Paris XI. The IT department of Université Paris-Sud as well as ICSN are acknowledged for providing computing resources.

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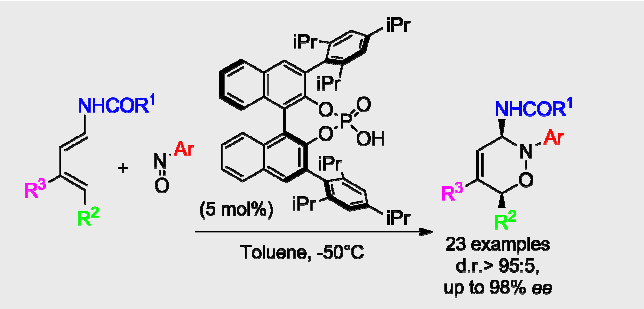
TOC Graphic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+
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iPr
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iPr
(5 mol%)
Toluene, -50°C
NHCOR1
N
Ar
O
R3
R2
23 examples
d.r.> 95:5,
up to 98% ee