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Catalytic Enantioselective Nitroso Diels-Alder Reaction

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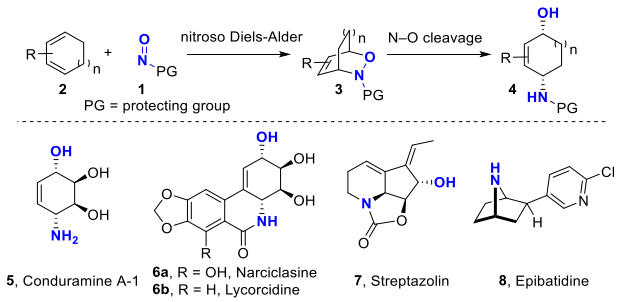
ABSTRACT: The nitroso Diels-Alder (NDA) reaction is an attractive strategy for the synthesis of 3,6-dihydro-1,2-oxazines and 1-amino-4-hydroxy-2-ene derivatives. Herein, we report Cu(I)-DTBM-Segphos catalyzed asymmetric intermolecular NDA reaction of variously substituted cyclic 1,3-dienes using highly reactive nitroso compounds derived from pyrimidine and pyridazine derivatives. In most cases studied, the cycloadducts were obtained in high yields (up to 99%) with very high regio-, diastereo-, and enantioselectivities (up to regioselectivity >99:1, d.r. >99:1, >99% ee). As an application of this methodology, formal syntheses of conduramine A-1 and narciclasine were accomplished.

Introduction

Nitroso compounds **1** are highly fascinating hetero-electrophiles. They are able to selectively transfer either one or both of the hetero-atoms in a variety of asymmetric oxidation reactions.[1] In this context, the nitroso Diels-Alder (NDA)[1a,2] reaction is of high interest to the synthetic communities for its unique ability to transform a simple 1,3-diene **2** into complex 3,6-dihydro-1,2-oxazines **3** in a single step (Scheme 1). The NDA adducts **3** can easily be converted into corresponding 1-amino-4-hydroxy-2-ene derivatives **4** which are important building blocks for the syntheses of several natural products and biologically active molecules; some of them are shown in Scheme 1.[3]

Scheme 1. Nitroso Diels-Alder reaction and its synthetic utility



Given its importance, a huge effort was devoted to the development of catalytic, enantioselective NDA reaction.[4] However, the development of such a process has long been regarded as challenging, due to the high reactivity of the nitroso compounds **1** which undergo a [4+2]-cycloaddition reaction without any activation. The first enantioselective intermolecular NDA reaction was reported by Ukaji and Inomata using a stoichiometric amount of zinc-tartaric acid complex as a chiral promoter.[4k] In 2004, we reported the first example of copper-Segphos-catalyzed enantioselective intermolecular NDA reaction of 6-methyl-2-nitrosopyridine **1a** with cyclic 1,3-dienes.[4b] Although high yields and regioselectivities were obtained, the enantioselectivities were only moderately high and the scope of the dienes was limited. Later, Studer et al. broadened the scope of the NDA reaction of 2-nitrosopyridine **1b** using copper-Walphos-CF3 as a catalyst.[4d-f] This chiral Cu-nitrosopyridine-complexes also undergo other types of cycloaddition reactions.[5] We had also published organocatalytic diastereo- and enantioselective synthesis of nitroso Diels-Alder-type bicycloketones using nitrosobenzenes.[4h,i] While this work was in progress, Masson et al. reported chiral phosphoric acid catalyzed regio-, diastereo-, and enantioselective NDA reactions of 1,3-diene-1-carbamates with nitrosobenzenes.[4j] However, in spite of these advancements, a general and uniformly high enantioselective route for NDA reaction with a very broad substrate scope is highly demanding, especially in view of the high synthetic potential of the NDA-adducts.

The prominent success of nitroso chemistry largely relies on the identification of the proper source of reactive nitroso compounds. Hetero-atom stabilized nitroso compounds are unreactive towards dienes.[3a,6] The acylnitroso compounds[1b,7] are, on the other hand, too reactive for the development of asymmetric intermolecular NDA reaction.[4a,8] We envisage that the reactivities of the 2-nitrosopyridines could be enhanced by inclusion of another hetero-atom and those highly reactive nitroso compounds might undergo NDA reaction with high enantioselectivities with differently substituted 1,3-dienes. Herein, as an extension of our continuous effort to utilize nitroso compounds in asymmetric oxidation reactions,[4b,c,h,i,9] we report an improved Cu-catalyst for highly regio-, diastereo- and enantioselective NDA reaction using highly reactive and readily available nitroso compounds derived from pyrimidine and pyridazine derivatives **1**. As an application of this method, formal syntheses of conduramine-A-1 and narciclasine are described.

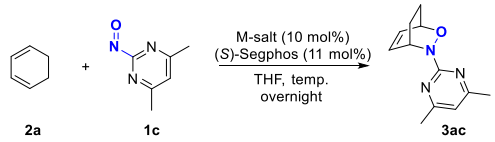
Results and Discussion

Syntheses of nitroso compounds. Highly reactive nitroso pyrimidines (**1c–i**), pyridazines (**1j**,**k**), and triazine

(**1m**) were conveniently prepared in >90% yields in one step by MnO_2 oxidation of the corresponding hydroxyl amines following the modified procedure reported by Moskalenko et al. (see Chart 2 for the structures).[10] All other nitroso compounds **1n–q** were prepared according to the literature procedure.[3e,11]

Reaction optimization. *Effect of temperature and Lewis acid catalysts.* To optimize the reaction conditions, we initially performed the NDA reaction of 4,6-dimethyl-2-nitrosopyrimidine **1c** with 1,3-cyclohexadiene **2a** using $Cu(CH_3CN)_4BF_4$-(*S*)-Segphos as catalyst at various temperatures (Table 1). While the reaction was very sluggish at –78°C, the product **3ac** was obtained with lower enantioselectivities at –40 and –20°C (entries 1–3). However, after addition of a diene at –78°C, if the reaction mixture is placed in a –40°C bath, the enantioselectivity could be improved to 75% ee (entry 4). Finally, if the diene was added at –85°C and then the temperature was gradually increased to –40°C over a period of 2 h, the ee was increased to 78% (entry 5). Variation of metal salts resulted in lower enantioselectivities (entries 6–9).

Table 1. Effect of temperature and metal salts on NDA reaction[a]

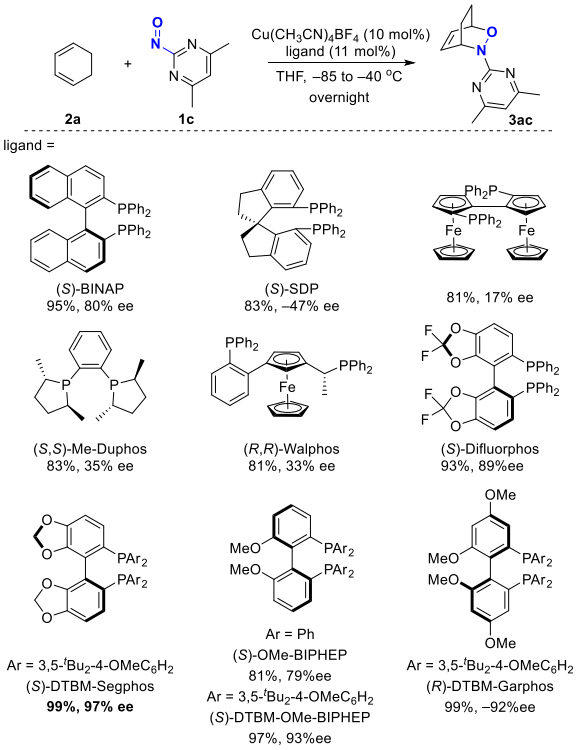


entry	M-salt	temp (°C)	yield (%)[b]	ee (%)[c]
1	$Cu(CH_3CN)_4BF_4$	–78	<20%	nd
2	$Cu(CH_3CN)_4BF_4$	–40	97	64
3	$Cu(CH_3CN)_4BF_4$	–20	97	60
4	$Cu(CH_3CN)_4BF_4$	–78 to –40	99	75
5	$Cu(CH_3CN)_4BF_4$	–85 to –40	99	78
6	AgOTf [d]	–78 to –40	99	5
7	AuCl [e]	–78 to –40	99	3
8	$Ni(OTf)_2$ [e]	–78 to –40	78	0
9	$Pd(OAc)_2$ [e]	–78 to –40	87	0

[a]Reaction conditions: 0.1 mmol of **1c**, 0.12 mmol of **2a** in 1.5 mL of THF. [b]Yields of the isolated products are given. [c]ee was determined by HPLC using a chiral stationary phase. [d]EtCN solvent. [e]CH_2Cl_2 solvent.

Effect of ligands. To further improve the enantioselectivity, various diphosphine ligands with different steric and electronic properties were surveyed, and the results are summarized in Chart 1. The venerable BINAP[12] gave similar enantioselectivity to that of Segphos.[13] The spiro phosphine ligand SDP[14] and ferrocene-based bisphosphine ligands were less efficient. Likewise, a less satisfactory result was obtained using Me-Duphos[15] and Walphos ligands[16]: 35 and 33% ee, respectively. The first significant improvement was observed using a π-acidic Diflourphos ligand (89% ee).[17] Astonishingly, we found that the enantioselectivity was significantly improved to 97% ee using the more electron-rich and sterically bulky DTBM-Segphos as the ligand. However, similarly bulky bisphosphine ligands having a wider dihedral angle DTBM-OMe-BIPHEP[15] and DTBM-Garphos[18] were slightly less effective. Thus, we chose this Cu(I)-DTBM-Segphos catalyst system for development of further reactions.

Chart 1. Effect of ligands on NDA reaction[a]



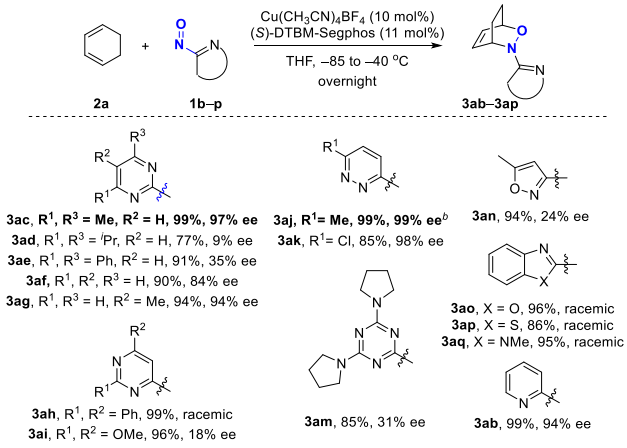
[a]Reaction conditions: 0.1 mmol of **1c**, 0.12 mmol of **2a** in 1.5 mL of THF. Yield of the isolated products are given. ee was determined by HPLC using a chiral stationary phase. A negative ee value indicates the opposite enantiomer of the NDA adduct.

Effect of structure of nitroso compounds. To study the effect of the steric and electronic properties of iminonitroso compounds on enantioselectivities, we have performed their NDA reactions with 1,3-cyclohexadine **2a** using a Cu(I)-DTBM-Segphos catalyst and the results are summarized in Chart 2. Replacement of the methyl groups of **1c** with bulkier isopropyl (→ **1d**) or phenyl groups (→ **1e**) resulted in lower enantioselectivities. A similar results were obtained for the replacement of the methyl groups with hydrogen as the parent 2-nitrosopyrimidine **1f** and 5-methyl-2-nitrosopyrimidines **1g** yielded the NDA-adducts **3af** and **3ag** in 84% and 94% ee, respectively. In contrast to 2-nitrosopyrimidines (**1c–g**), two representative 4-nitrosopyrimidines (**1h**,**i**) underwent NDA reactions with poor enantioselectivities. Interestingly, 3-nitrosopyridazines (**1j**,**k**) were found to be very reactive nitroso-dienophiles and we

were pleased to find 3-methyl-6-nitrosopyridazine **1j** as the best, delivering the NDA-adduct **3aj** in a 99% yield with 99% ee. In this case, the catalyst loading could be lowered to 5 mol% without significant alteration of yield and enantioselectivity (99% and 98%, respectively). However, when the catalyst loading was further decreased to 2 mol%, the enantioselectivity went down to 95%.

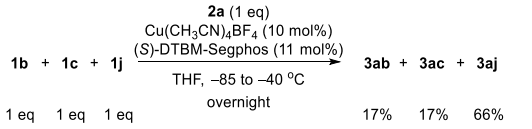
In the triazine series, 2,4-dimethoxy-6-nitroso-1,3,5-triazine **1l** is unstable and the stable 2-nitroso-4,6-di(pyrrolidin-1-yl)-1,3,5-triazine **1m** yielded the NDA adduct **3am** in an 85% yield with 31% ee.[19] At this point, we are also interested in studying other types of heteroaromatic iminonitroso compounds for NDA reaction. 5-Methyl-3-nitrosoisoxazole **1n** introduced by Miller gave 94% of the NDA adduct **3an** with 24% ee under the same conditions.[3e] Disappointingly, 2-nitrosobenzo[d]oxazole **1o**,[11a] 2-nitrosobenzo[d]thiazole **1p**,[11b] and 1-methyl-2-nitroso-1H-benzo[d]imidazole **1q**[11a] delivered racemic products. It is worth mentioning that, under identical conditions, 2-nitrosopyridine **1b** gave 99% of the NDA adduct with 94% ee.

Chart 2. Effect of steric and electronic properties of nitroso compounds on NDA reaction[a]



[a]Reaction conditions: 0.1 mmol of nitroso compound, 0.12 mmol of **2a** in 1.5 mL of THF. Yields of the isolated products are given. ee was determined by HPLC using a chiral stationary phase. [b]99%, 98% ee with 5 mol% catalyst loading and 99%, 95% ee with 2 mol% catalyst loading.

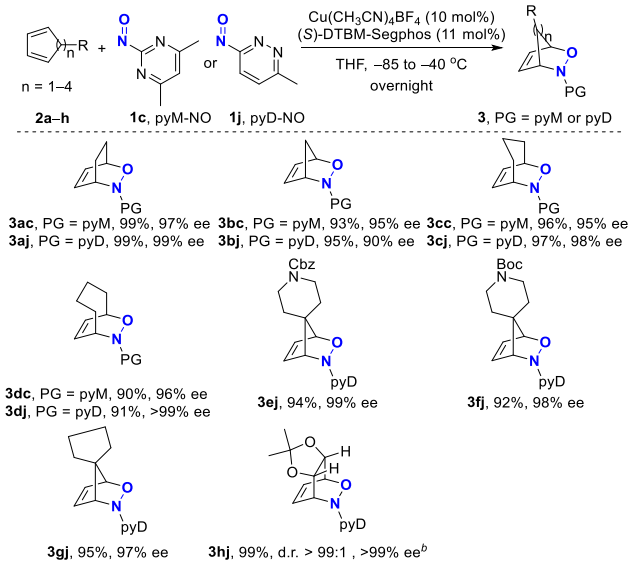
In order to realize the reactivity order between the nitroso compounds **1b**,**c**,**j**, we performed the following competition experiment (Eq. 1). Accordingly, when 1 equivalent 1,3-hexadiene **2a** was reacted with equimolar mixture of **1b**,**c**,**j** (1 equivalent each) in the presence of 10 mol% (with respect to **2a**) of $Cu(CH_3CN)_4BF_4$-DTBM-Segphos in THF, the ratio of the NDA adducts was **3ab**:**3ac**:**3aj** = 17:17:66. This result indicates that, under this condition, **1j** is far more reactive than **1b** and **1c**. A computational study is currently ongoing in order to understand the high reactivities and selectivities obtained for the NDA reactions of the pyridazine derivative **1j**.



Scope of the NDA reaction and its applications. We then performed cycloaddition reactions of a variety of 1,3-dienes with highly reactive iminonitroso compounds **1c** and **1j** (hereafter abbreviated as pyM-NO and pyD-NO, respectively) using the improved catalytic system $Cu(CH_3CN)_4BF_4$-DTBM-Segphos in THF to determine the scope and the limitation of the method. Gratifyingly, all of the reactions went to completion, the cycloadducts were obtained in very high yields, and the enantioselectivities exceed those previously reported.

NDA reactions with symmetrical 1,3-dienes. First symmetrical 1,3-dienes **2a–h** were tested and the results are summarized in Chart 3. Under optimal conditions, cyclopentadiene **2b**, 1,3-cycloheptadiene **2c**, and *cis*,*cis*-1,3-cyclooctadiene **2d** took part NDA reaction with the nitroso compounds **1c**,**j** in very high yields and with very high enantioselectivities. In 2009, Miller et al. introduced *N*-Cbz and *N*-Boc protected aza-spirodienes (**2e**,**f**) for the preparation of racemic spirocyclic carbocyclic nucleoside analogues and spironoraristeromycin using NDA reaction.[3i,j] Surprisingly, when we subjected the aza-spirodienes **2e**,**f** to optimal conditions, the cycloadducts **3ej** and **3fj** were obtained in 94% yield, 99% ee and 92% yield, 98% ee, respectively. A similar result was obtained for the carbocyclic spiro[4.4]nona-1,3-diene **3g**: 95% yield and 97% ee. Using a

Chart 3. Enantioselective NDA reaction with symmetrical dienes 2a–h[a]

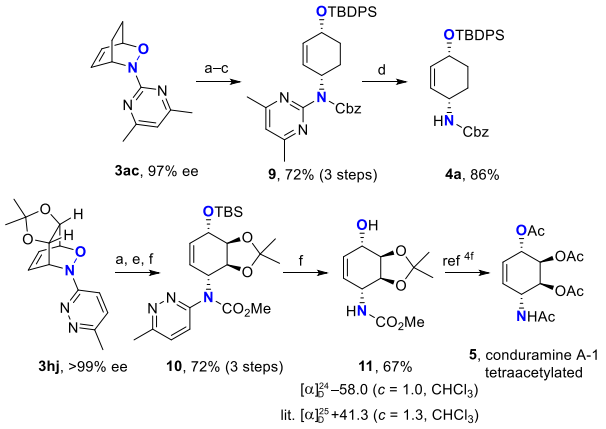


[a]Reaction conditions: 0.1 mmol of nitroso compound **1c**,**j**, 0.12 mmol of 1,3-diene **2a–h** in 1.5 mL of THF. Yields of the isolated product are given. ee was determined by HPLC using a chiral stationary phase. [b]Reaction performed with 5 mol% catalyst loading in 0.2 mmol scale.

5 mol% catalyst, the acetal protected *meso*-cyclohexa-3,5-diene-1,2-diol **2h** reacted with **1j** to yield the NDA product **3hj** in a quantitative yield with perfect diastereo- and enantioselectivities (d.r. >99:1 and >99% ee) for four consecutive stereocenters.[20]

To explain the utility of the highly enantioenriched NDA adducts, we consider their conversion to corresponding 4-aminocyclohex-2-en-1-ol derivatives **4**, which proceeded smoothly, as depicted in Scheme 2. Accordingly, the O,N-protected intermediate **9** was obtained via $Mo(CO)_6$-mediated reductive N–O bond cleavage,[21] and O- and N-protection. The pyrimidyl group was then cleaved by quaternization with MeOTf, followed by hydrolysis with NaOH. Similar treatment of the cycloadduct **3hj** delivered the intermediate **10** from which the pyridazyl group can be removed by first quaternization with 3-iodopropyl triflate, $NaBH_4$ reduction and then second quaternization and hydrolysis with NaOH in one pot. The absolute configuration of the adduct **11** was determined by comparing the optical rotation with previously reported data and, hence, the absolute configuration of the NDA **3hj** can be determined. The absolute configurations of the adducts **3** in Chart 3 were assigned by analogy. Importantly, **11** could easily be transformed to tetracetylated conduramine A-1 **5** in one step.[4f,22]

Scheme 2. Synthesis of protected 4-aminocyclohex-2-en-1-ol 4a and tetracetylated conduramine A-1 5

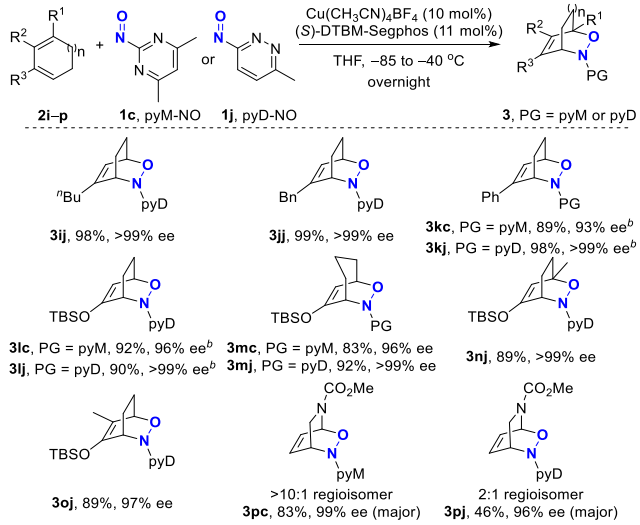


Reagents and conditions: a) $Mo(CO)_6$, $NaBH_4$, CH_3CN-H_2O; b) TBDPS-Cl, imidazole, DMF; c) LiHMDS, CbzCl, THF; d) MeOTf, CH_2Cl_2, then 2 N NaOH, MeOH; e) TBS-Cl, imidazole, DMF; LiHMDS, $ClCO_2Me$, THF; f) $I(CH_2)_3OTf$, CH_2Cl_2, then $NaBH_4$, MeOH, then 2 N NaOH, MeOH.

NDA reactions with unsymmetrical 1,3-dienes. Then unsymmetrical 1,3-dienes **2i–p** were examined (Chart 4). Control of the regioselectivity has long been regarded as a key issue while developing NDA reactions with unsymmetrical 1,3-dienes.[23]

Under optimal conditions, the NDA reactions of 2-butyl and 2-benzyl cyclohexa-1,3-dienes (**2i**,**j**) delivered the cycloadducts **3ij** and **3jj** in very high yields with perfect regio- and enantioselectivities (>99:1 regioselectivity and >99% ee). Likewise, a high regioselectivity (>99:1) was observed for the NDA reaction of 2-phenyl cyclohexa-1,3-diene **2k** using 5 mol% of the catalyst. 2-*tert*-butyldimethylsiloxy-1,3-cyclohexadiene **2l** and 2-*tert*-butyldimethylsiloxy-1,3-cycloheptadiene **2m** similarly underwent NDA reactions with very high regio- and enantioselectivities. We then studied the regioselectivity of the NDA reactions of 2,3- and 2,4-disubstituted 1,3-cyclohexadienes (**2n**,**o**). In these cases also, only one regioisomer could be observed, and the NDA adducts **3nj** and **3oj** were obtained with very high enantioselectivities (>99% and 97% ee, respectively). In all cases, the regiochemical assignments were made based on NMR spectroscopy and comparison with a similar structure in the literature. The high proximal selectivities of these reactions were in accordance with the computational studies for the related Cu(I)-catalyzed NDA reaction of the 2-nitrosopyridines.[23d] Finally, the NDA reaction of *N*-CO_2Me azacyclohexadiene **2p** with **1c**,**j** resulted in the formation of a mixture of regioisomers (10:1 and 2:1, respectively). In both cases, the major isomers **3pc** and **3pj** were formed with very high enantioselectivities (99% and 96% ee, respectively).

Chart 4. Enantioselective NDA reaction with unsymmetrical dienes 2i–p[a]



[a]Reaction conditions: 0.1 mmol of nitroso compound **1c**,**j**, 0.12 mmol of 1,3-diene **2i–p** in 1.5 mL of THF. Yields of the isolated product are given. ee was determined by HPLC using a chiral stationary phase. [b]Reaction performed with a 5 mol% catalyst loading in 0.2 mmol scale.

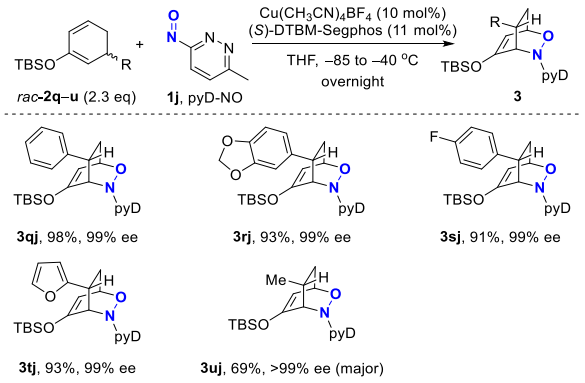
Studer et al. reported a Cu(I)-Walphos-CF_3 catalyzed divergent reaction of the racemic 5-substituted 1,3-cyclohexadienes in which only two products were formed with very high enantioselectivities out of eight possible stereoisomers.[4d] The high regioselectivities obtained for the reaction of 2-substituted 1,3-cyclohexadienes **2i–o** prompted us to study the reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes **2q–u**. We hope, in this case, that the regioselectivity will be governed by the 2-substituents and, hence,

one of the enantiomers of the racemic dienes will react with nitroso compounds faster than the other.

As shown in page S34 of the supporting information, five representative 2,6-disubstituted 1,3-cyclohexadienes **2q–u** were synthesized in good yields over three steps.

The NDA reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes **2q–u** were conducted in THF using 10 mol% of Cu(I)-DTBM-Segphos catalyst and 2.3 equivalent of the dienes (Chart 5). Pleasingly, the NDA reaction proceeded smoothly, and only one regioisomer of the products (**3qj–3tj**) was formed in high yields (91–98% yields) with excellent diastereo- (d.r. >99:1) and enantioselectivities (99% ee). However, for the 6-methyl substituted diene **2u**, the major isomer **3uj** was formed in a 69% yield and >99% ee with a 4:1 mixture with another isomer whose structure has not been determined.

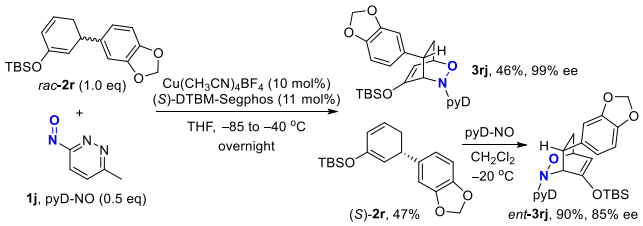
Chart 5. Enantioselective NDA reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes 2q–u [a]



[a]Reaction conditions: 0.1 mmol of nitroso compound **1j**, 0.23 mmol of 1,3-diene **2q–u** in 1.5 mL of THF. Yield of the isolated product is given. ee was determined by HPLC using a chiral stationary phase.

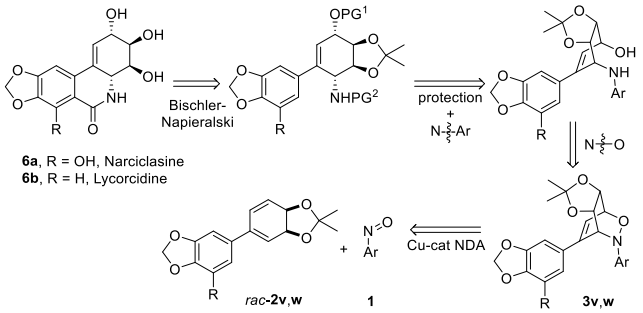
When exactly two equivalents of the diene **2r** were used for the NDA reaction, efficient kinetic resolution of the racemates took place (Scheme 3). The NDA adduct **3rj** was obtained in a 46% yield with 99% ee. Whereas the unreacted diene was recovered in a 47% yield and its enantioselectivity was determined by converting it to the corresponding NDA adduct (*ent*-**3rj**, 90%, 85% ee). This result corresponds to a selectivity factor s >500 for the kinetic resolution of the diene **2r,** which is remarkably high[24] and to best of our knowledge it represents the first example of kinetic resolution in asymmetric nitroso Diels-Alder chemistry.

Scheme 3. Kinetic resolution of racemic diene 2r via enantioselective NDA reaction



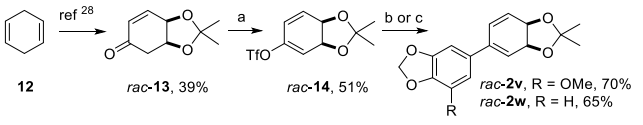
Motivated by the high regio-, diastereo-, and enantioselectivities of the NDA reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes *rac*-**2q–u**, we want to extend it further to more challenging 2-aryl-5,6-dihydroxy-1,3-cyclohexadienes *rac*-**2v**,**w**. Retrosynthetically, the NDA adducts **3v**,**w** could easily be connected to hydroxylated phenanthridones, e.g., narciclasine **6a** and lycoricidine **6b**[25], via N–O bond cleavage and Bischler-Napieralski cyclization[26] (Scheme 4). Narciclasine and its derivatives are an interesting class of biologically active molecules belonging to the *Amaryllidaceae* family of alkaloids. These compounds exhibit unusually high levels of antitumor and antiviral activity[25] and are the subject of great interest in the synthetic community.[27]

Scheme 4. Retrosynthetic analysis of the synthesis of narciclasine and lycoricidine



Syntheses of the dienes **2v**,**w** are shown in Scheme 5. The racemic cyclohexenone derivative **12** was prepared in large scale from 1,4-cyclohexadiene **13** using the procedure reported by Krow.[28] The required dienes *rac*-**2v**,**w** can then be prepared from **13** over two steps with moderate yields.[29]

Scheme 5. Synthesis of the dienes 2v,w

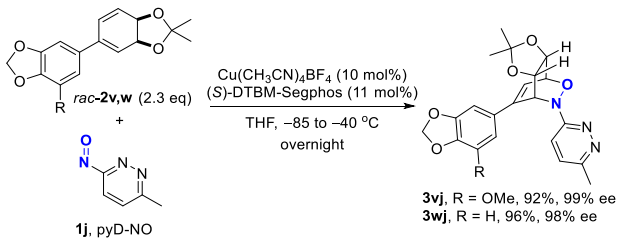


Reagents and conditions: a) LiHMDS, 5-Cl-PyNTf$_2$, THF; b) (7-methoxybenzo[d][1,3]dioxol-5-yl)magnesium bromide, CuI (10 mol%), THF; c) benzo[d][1,3]dioxol-5-ylmagnesium bromide, CuI (10 mol%), THF.

The NDA reaction of the dienes *rac*-**2v**,**w** was similarly performed in THF using 10 mol% of the Cu(I)-DTBM-Segphos complex as catalyst (Scheme 6). The cycloaddition proceeded smoothly and the NDA adducts **3vj** and **3wj**

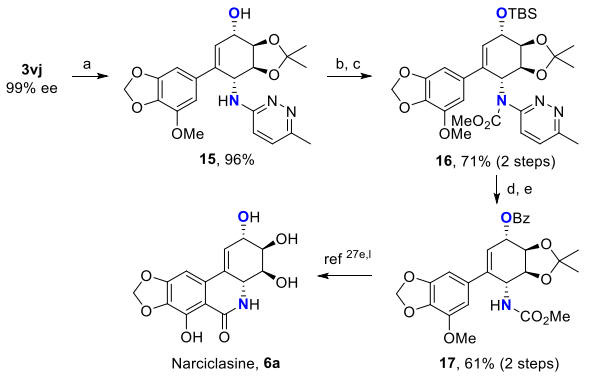
were formed in 92% and 96% yields, respectively with excellent regio-, diastereo- and enantioselectivities (>99:1 regioselectivity, d.r. > 99:1, 99 and 98% ee, respectively).

Scheme 6. Enantioselective NDA reaction of *rac*-2v,w



The N–O bond of the adduct **3vj** was cleaved easily using $Mo(CO)_6/NaBH_4$ in CH_3CN/H_2O to give the intermediate **15** in a 96% yield (Scheme 7).[21] The *O*-protection using TBSOTf, the *O*-silylation took place smoothly within 1 h in CH_2Cl_2. *N*-carbamoylation was performed by the treatment of the corresponding Li-amide with $ClCO_2Me$ in THF to give the intermediate **16** in a 71% yield after 2 steps. Then, the cleavage of the pyridazinyl group under similar conditions described in Scheme 2 and benzoyl protection deliver **17** in a 61% yield (2 steps). The intermediate **17** could be transformed to narciclasine **6a** following the method in the literature.[27e,l]

Scheme 7. Formal synthesis of narciclasine 6a



Reagents and conditions: a) $Mo(CO)_6$, $NaBH_4$, CH_3CN-H_2O; b) TBSOTf, NEt_3, CH_2Cl_2; c) LiHMDS, $ClCO_2Me$, THF; d) $I(CH_2)_3OTf$, CH_2Cl_2, then $NaBH_4$, MeOH, then 2 N NaOH, MeOH; e) BzCl, DMAP, NEt_3, CH_2Cl_2.

Conclusion

In conclusion, we have demonstrated an improved catalyst Cu(I)-DTBM-Segphos for the NDA reaction of variously substituted cyclic 1,3-dienes using highly reactive nitroso compounds derived from pyrimidine and pyridazine derivatives. In most cases studied, the cycloadducts were obtained in high yields and the enantioselectivities exceeded those previously reported. As an application of this methodology, we have shown formal syntheses of conduramine A-1 and narciclasine.

ASSOCIATED CONTENT

Supporting Information. Complete experimental procedures and full compound characterization, including HPLC traces and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors have no competing financial interests to declare.

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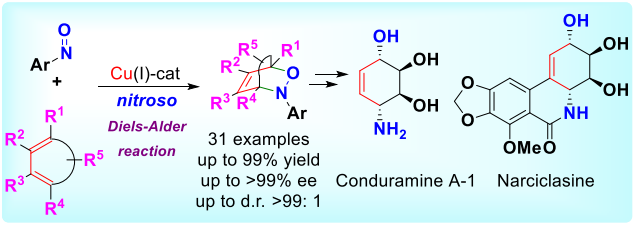
Cu(I)-cat
nitroso
Diels-Alder
reaction
31 examples
up to 99% yield
up to >99% ee
up to d.r. >99: 1
Conduramine A-1
Narciclasine