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Catalytic Enantioselective Nitroso Diels–Alder Reaction

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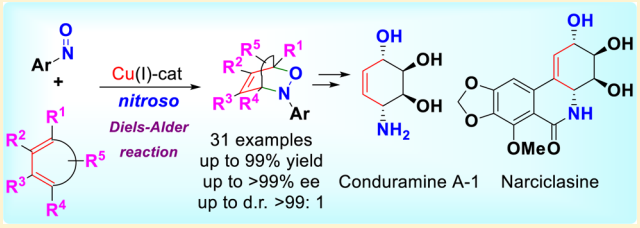
Supporting Information

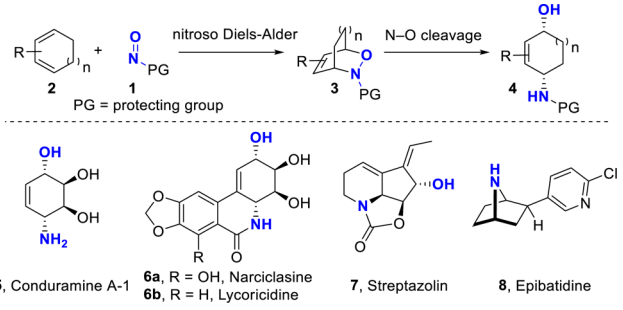
ABSTRACT: The nitroso Diels–Alder (NDA) reaction is an attractive strategy for the synthesis of 3,6-dihydro-1,2-oxazines and 1-amino-4-hydroxy-2-ene derivatives. Herein we report the Cu(I)–DTBM-Segphos catalyzed asymmetric intermolecular NDA reaction of variously substituted cyclic 1,3-dienes using highly reactive nitroso compounds derived from pyrimidine and pyridazine derivatives. In most of the 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, and >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 heteroelectrophiles. They are able to selectively transfer either one or both of the heteroatoms 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 the 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



Because of its importance, a huge effort was devoted to the development of the catalytic, enantioselective NDA reaction.[4] However, the development of such a process has long been regarded as challenging because of the high reactivity of 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 a copper–Segphos-catalyzed enantioselective intermolecular NDA reaction, involving 6-methyl-2-nitrosopyridine (**1a**) and 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 and co-workers broadened the scope of the NDA reaction of 2-nitrosopyridine (**1b**) using copper–Walphos-CF_3 as a catalyst.[4d–f] This chiral Cu–nitrosopyridine complex also undergoes other types of cycloaddition reactions.[5] We had also published an organocatalytic diastereo- and enantioselective synthesis of NDA-type bicycloketones using nitrosobenzenes.[4h,i] While this work was in progress, Masson and co-workers 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 highly enantioselective route for the 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. Heteroatom-stabilized nitroso compounds are unreactive toward dienes.[3a,6] On the other hand, acylnitroso compounds[1b,7] are too reactive for the development of an asymmetric intermolecular NDA reaction.[4a,8] We envisaged that the reactivities of 2-nitrosopyridines could be enhanced by the inclusion of another heteroatom and that those highly reactive nitroso compounds might undergo the NDA reaction with differently substituted 1,3-dienes with high enantioselectivities. 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 a highly

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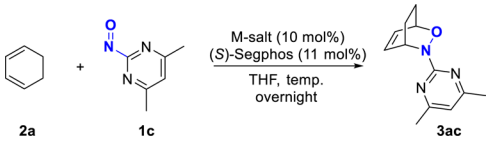
regio-, diastereo-, and enantioselective NDA reaction using highly reactive and readily available nitroso compounds derived from pyrimidine and pyridazine derivatives **1**. As an application of this method, formal syntheses of conduramine-A-1 and narciclasine are described.

RESULTS AND DISCUSSION

Syntheses of Nitroso Compounds. Highly reactive nitroso pyrimidines (**1c–i**), pyridazines (**1j** and **1k**), and triazine (**1m**) were conveniently prepared in >90% yield in one step by MnO_2 oxidation of the corresponding hydroxylamines following the modified procedure reported by Moskalenko et al.[10] (see Chart 2 for the structures). The other nitroso compounds **1n–q** were prepared according to literature procedures.[3e,11]

Reaction Optimization. *Effect of Temperature and the Lewis Acid Catalyst.* 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 the catalyst at various temperatures (Table 1). While the reaction was very sluggish

Table 1. Effect of Temperature and the Metal Salt on the NDA Reaction[a]



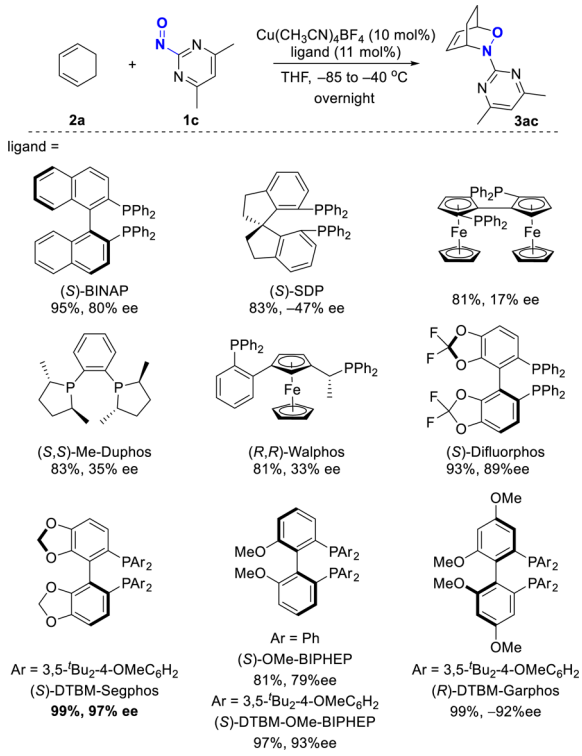
entry	M-salt	temp (°C)	yield (%)[b]	ee (%)[c]
1	$Cu(CH_3CN)_4BF_4$	−78	<20	nd
2	$Cu(CH_3CN)_4BF_4$	−40	97	64
3	$Cu(CH_3CN)_4BF_4$	−20	97	60
4	$Cu(CH_3CN)_4BF_4$	−78 to −40	99	75
5	$Cu(CH_3CN)_4BF_4$	−85 to −40	99	78
6	AgOTf[d]	−78 to −40	99	5
7	AuCl[e]	−78 to −40	99	3
8	$Ni(OTf)_2$[e]	−78 to −40	78	0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

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

at −78 °C, the product **3ac** was obtained with lower enantioselectivities at −40 and −20 °C (entries 1–3). However, when the reaction mixture was placed in a −40 °C bath after addition of the diene at −78 °C, the enantioselectivity improved to 75% ee (entry 4). Finally, when the diene was added at −85 °C and then the temperature was gradually increased to −40 °C over a period of 2 h, the enantioselectivity increased to 78% ee (entry 5). Variation of the metal salt resulted in lower enantioselectivities (entries 6–9).

Effect of the Ligand. 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 enantioselectivity similar to that with Segphos.[13] The spiro phosphine ligand SDP[14] and a ferrocene-based bisphosphine ligand were less efficient. Likewise, less satisfactory results were obtained using the ligands Me-Duphos[15] and Walphos[16] (35 and 33% ee, respectively). The first significant improvement was observed using a π-acidic Difluorphos ligand (89% ee).[17]

Chart 1. Effect of the Ligand on the NDA Reaction[a]



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

Astonishingly, we found that the enantioselectivity was significantly improved to 97% ee using the more electron-rich and sterically bulky ligand DTBM-Segphos. 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 the development of further reactions.

Effect of the Structure of the Nitroso Compound. To study the effect of the steric and electronic properties of the iminonitroso compound on the enantioselectivity, we performed the NDA reaction of various nitroso compounds with 1,3-cyclohexadiene **2a** using the 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. Similar results were obtained for the replacement of the methyl groups with hydrogen, as the parent 2-nitrosopyrimidine (**1f**) and 5-methyl-2-nitrosopyrimidine (**1g**) yielded the NDA adducts **3af** and **3ag** with 84% and 94% ee, respectively. In contrast to 2-nitrosopyrimidines (**1c–g**), two representative 4-nitrosopyrimidines (**1h** and **1i**) underwent NDA reactions with poor enantioselectivities. Interestingly, 3-nitrosopyridazines (**1j** and **1k**) proved to be very reactive nitroso dienophiles, and we were pleased to find 3-methyl-6-nitrosopyridazine (**1j**) to be the best, delivering the NDA adduct **3aj** in 99% yield with 99% ee. In this case, the catalyst loading could be lowered to 5 mol % without significantly altering the yield (99%) and enantioselectivity (98% ee). However, when the catalyst loading was further decreased to 2 mol %, the enantioselectivity decreased to 95%.

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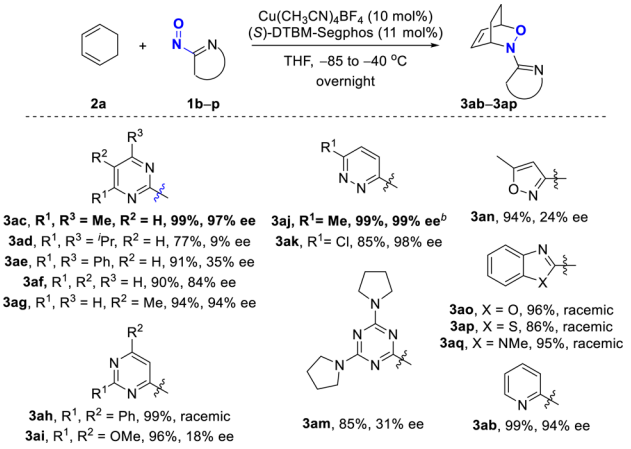
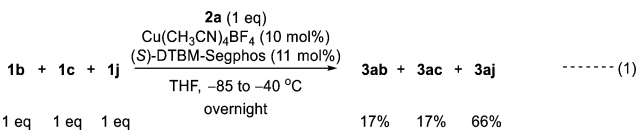
Chart 2. Effect of the Steric and Electronic Properties of the Nitroso Compound on the NDA Reaction[a]



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

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

In order to determine the order of the reactivities of the nitroso compounds **1b**, **1c**, and **1j**, we performed the competition experiment depicted in eq 1. When 1 equiv of

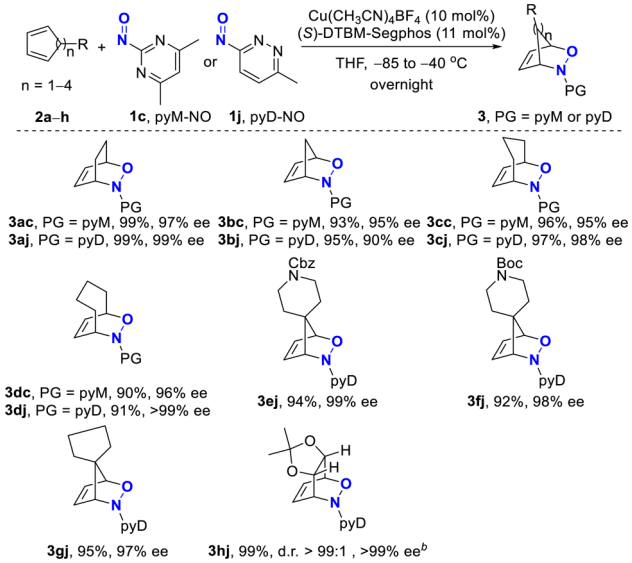


2a was reacted with an equimolar mixture of **1b**, **1c**, and **1j** (1 equiv each) in the presence of 10 mol % (with respect to **2a**) $Cu(CH_3CN)_4BF_4$/DTBM-Segphos in tetrahydrofuran (THF), the ratio of the NDA adducts was **3ab**:**3ac**:**3aj** = 17:17:66. This result indicates that **1j** is far more reactive than **1b** and **1c** under these conditions. A computational study is currently ongoing in order to understand the high reactivities and selectivities obtained for the NDA reactions of 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 denoted 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 limitations of the method. Gratifyingly, all of the reactions went to completion, the cycloadducts were obtained in very high yields, and the enantioselectivities exceeded 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 in the NDA reaction with nitroso compounds **1c** and **1j** in very high yields with very high enantioselectivities. In 2009, Miller and co-workers introduced *N*-Cbz- and *N*-Boc-protected aza-spirodienes (**2e** and **2f**, respectively) for the preparation of racemic spirocyclic carbocyclic nucleoside analogues and spironoraristeromycin using the NDA reaction.[3i,j] Surprisingly, when we subjected aza-spirodienes **2e** and **2f** to the optimal conditions, the cycloadducts **3ej** and **3fj** were obtained in 94% yield with 99% ee and 92% yield with 98% ee, respectively. Similar results were obtained for carbocyclic spiro[4.4]nona-1,3-diene (**3g**) (95% yield with 97% ee). With 5 mol % catalyst, acetal-protected *meso*-cyclohexa-3,5-diene-1,2-diol (**2h**) reacted with **1j** to yield the NDA product **3hj** in quantitative yield with perfect diastereo- and enantioselectivity (d.r. > 99:1 and >99% ee) for four consecutive stereocenters.[20]

Chart 3. Enantioselective NDA Reaction with Symmetrical Dienes 2a–h[a]



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

To demonstrate the utility of the highly enantioenriched NDA adducts, we considered their conversion to the 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 to give **4a**. Similar treatment of the cycloadduct **3hj** delivered intermediate **10**, from which the pyridazyl group could be removed by quaternization with 3-iodopropyl triflate, $NaBH_4$ reduction, and then a second quaternization and hydrolysis with NaOH in one pot. The absolute configuration of adduct **11** was determined by comparing its optical rotation

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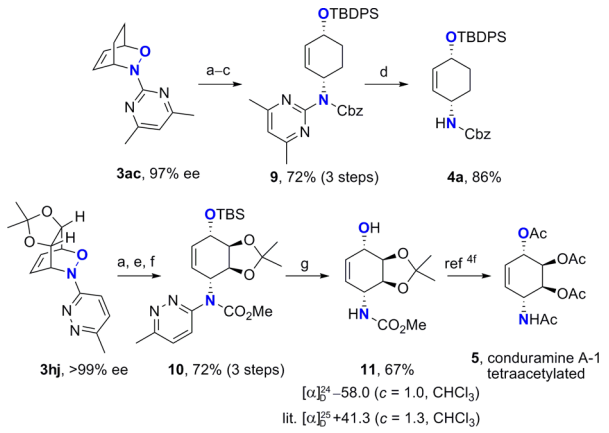
Scheme 2. Synthesis of Protected 4-Aminocyclohex-2-en-1-ol (4a) and Tetracetylated Conduramine A-1 (5)[a]



[a]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; (f) LiHMDS, $ClCO_2Me$, THF; (g) $I(CH_2)_3OTf$, CH_2Cl_2, then $NaBH_4$, MeOH, then 2 N NaOH, MeOH.

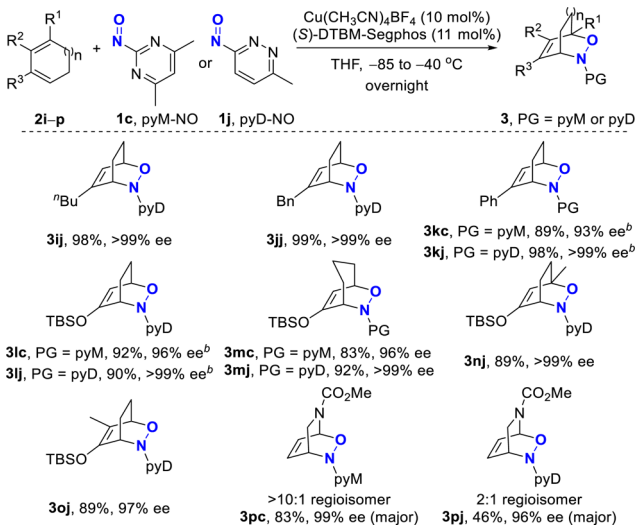
with previously reported data, hence allowing the absolute configuration of the NDA product **3hj** to be determined. The absolute configurations of the adducts **3** in Chart 3 were assigned by analogy. Importantly, **11** could easily be transformed to tetracetylated conduramine A-1 (**5**) in one step.[4f,22]

NDA Reactions with Unsymmetrical 1,3-dienes. Next, 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 the optimal conditions, the NDA reactions of 2-butyl- and 2-benzylcyclohexa-1,3-diene (**2i** and **2j**) delivered the cycloadducts **3ij** and **3jj** in very high yields with perfect regio- and enantioselectivities (d.r. > 99:1 and >99% ee). Likewise, a high regioselectivity (d.r. > 99:1) was observed for the NDA reaction of 2-phenylcyclohexa-1,3-diene (**2k**) using 5 mol % catalyst. 2-*tert*-Butyldimethylsiloxy-1,3-cyclohexadiene (**2l**) and 2-*tert*-butyldimethylsiloxy-1,3-cycloheptadiene (**2m**) similarly underwent the NDA reaction with very high regio- and enantioselectivities. We then studied the regioselectivity of the NDA reactions of 2,4- and 2,3-disubstituted 1,3-cyclohexadienes (**2n** and **2o**, respectively). 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 on the basis of NMR spectroscopy and comparisons with similar structures in the literature. The high proximal selectivities of these reactions were in accordance with the results of computational studies for the related Cu(I)-catalyzed NDA reaction of 2-nitrosopyridines.[23d] Finally, the NDA reaction of *N*-CO_2Me-substituted azacyclohexadiene **2p** with **1c** and **1j** resulted in the formation of mixtures 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).

Jana and Studer[4d] reported a Cu(I)–Walphos-CF_3-catalyzed divergent reaction of racemic 5-substituted 1,3-cyclohexadienes in which only two products (out of eight possible stereoisomers) were formed with very high enantioselectivities. 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 hoped in this case that the regioselectivity would be governed by the 2-substituents and hence that one of the enantiomers of the racemic diene would react with the nitroso compounds faster than the other.

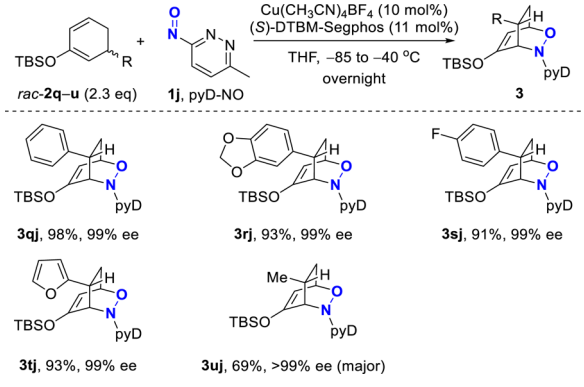
As shown on page S34 in the Supporting Information, the five representative 2,6-disubstituted 1,3-cyclohexadienes **2q–u** were synthesized in good yields over three steps. The NDA reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes **2q–u** were conducted in THF using 10 mol % Cu(I)–DTBM-Segphos catalyst and 2.3 equiv of the diene (Chart 5). Pleasingly, the NDA reaction proceeded smoothly, and only one regioisomer of each product (**3qj–3tj**) was formed in high

Chart 4. Enantioselective NDA Reaction with Unsymmetrical Dienes 2i–p[a]



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

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** and 0.23 mmol of 1,3-diene **2q–u** in 1.5 mL of THF. Yields of the isolated products are given. The ee values were determined by HPLC using a chiral stationary phase.

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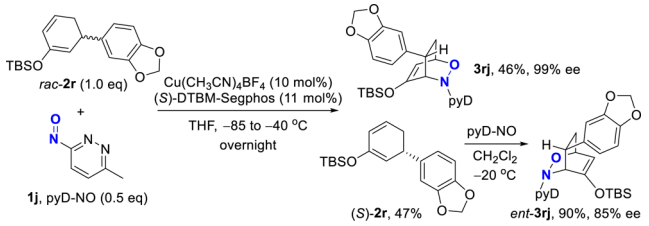
yield (91−98%) with excellent diastereo- (d.r. > 99:1) and enantioselectivity (99% ee). The only exception to this was the reaction with 6-methyl-substituted diene **2u**, for which the major isomer **3uj** was formed in 69% yield with >99% ee as a 4:1 mixture with another isomer whose structure has not been determined.

When exactly 2 equiv of diene **2r** was used for the NDA reaction, efficient kinetic resolution of the racemates took place (Scheme 3). The NDA adduct **3rj** was obtained in 46% yield

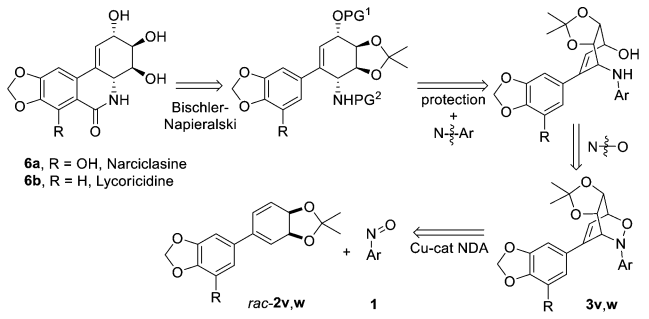
Scheme 3. Kinetic Resolution of Racemic Diene 2r via Enantioselective NDA Reaction



with 99% ee, whereas the unreacted diene was recovered in 47% yield and its enantioselectivity was determined by converting it to the corresponding NDA adduct *ent*-**3rj** (90% yield, 85% ee). This result corresponds to a selectivity factor (*s*) of >500 for the kinetic resolution of diene **2r**, which is remarkably high.[24] To the best of our knowledge, this represents the first example of kinetic resolution in asymmetric nitroso Diels−Alder chemistry.

Motivated by the high regio-, diastereo-, and enantioselectivities of the NDA reaction of racemic 2,6-disubstituted 1,3-cyclohexadienes *rac*-**2q−u**, we wanted to extend the reaction to more challenging 2-aryl-5,6-dihydroxy-1,3-cyclohexadienes *rac*-**2v** and *rac*-**2w**. Retrosynthetically, the NDA adducts **3v** and **3w** could easily be connected to the hydroxylated phenanthridones narciclasine (**6a**) and lycoricidine (**6b**)[25] via N−O bond cleavage and Bischler−Napieralski cyclization[26] (Scheme 4).

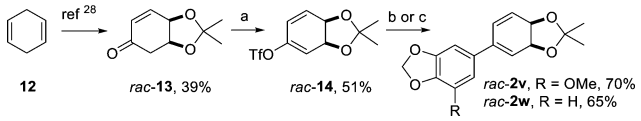
Scheme 4. Retrosynthetic Analysis of the Synthesis of Narciclasine and Lycoricidine



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]

The syntheses of dienes **2v** and **2w** are shown in Scheme 5. The racemic cyclohexenone derivative *rac*-**13** was prepared on a large scale from 1,4-cyclohexadiene (**12**) using the procedure reported by Krow et al.[28] The required dienes *rac*-**2v** and *rac*-

Scheme 5. Syntheses of Dienes 2v and 2w[a]

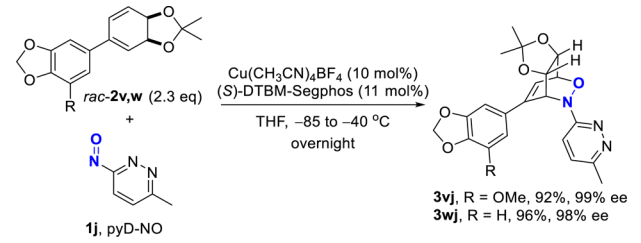


[a]Reagents and conditions: (a) LiHMDS, 5-Cl-PyNTf$_2$, THF; (b) (7-methoxybenzo[*d*][1,3]dioxol-5-yl)magnesium bromide, CuI (10 mol %), THF; (c) (benzo[*d*][1,3]dioxol-5-yl)magnesium bromide, CuI (10 mol %), THF.

2w were then prepared in moderate yields from **13** in two steps.[29]

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

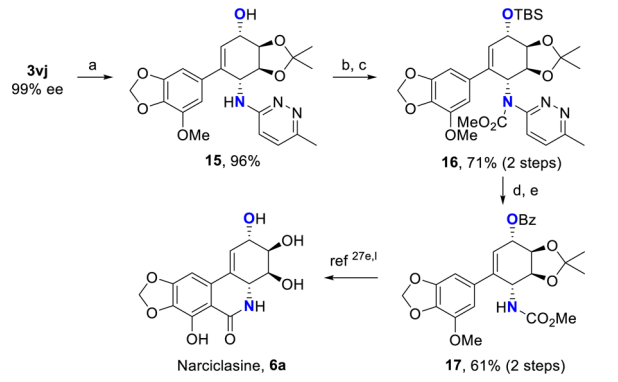
Scheme 6. Enantioselective NDA Reaction of *rac*-2v and *rac*-2w



proceeded smoothly, and the NDA adducts **3vj** and **3wj** were formed in 92 and 96% yield, respectively, with excellent regio-, diastereo-, and enantioselectivities (>99:1 regioselectivity, d.r. > 99:1, and 99 and 98% ee, respectively).

The N−O bond of the adduct **3vj** was cleaved easily using Mo(CO)$_6$/NaBH$_4$ in CH$_3$CN/H$_2$O to give intermediate **15** in 96% yield (Scheme 7).[21] The O-protection using TBSOTf took

Scheme 7. Formal Synthesis of Narciclasine 6a[a]



[a]Reagents and conditions: (a) Mo(CO)$_6$, NaBH$_4$, CH$_3$CN/H$_2$O; (b) TBSOTf, NEt$_3$, CH$_2$Cl$_2$; (c) LiHMDS, ClCO$_2$Me, THF; (d) I(CH$_2$)$_3$OTf, CH$_2$Cl$_2$, then NaBH$_4$, MeOH, then 2 N NaOH, MeOH; (e) BzCl, DMAP, NEt$_3$, CH$_2$Cl$_2$.

place smoothly within 1 h in CH$_2$Cl$_2$, and N-carbamoylation was performed by treatment of the corresponding lithium amide with ClCO$_2$Me in THF to give intermediate **16** in 71% yield over the two steps. Next, cleavage of the pyridazinyl group under conditions similar to those described in Scheme 2 and benzoyl protection delivered **17** in 61% yield over the two

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steps. Intermediate **17** could then be transformed to narciclasine (**6a**) following the method in the literature.[27e,l]

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 of the cases studied, the cycloadducts were obtained in high yields and the enantioselectivities exceeded those previously reported. As an application of this methodology, we have presented formal syntheses of conduramine A-1 and narciclasine.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11273.

Complete experimental procedures and full compound characterization, including NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514. (b) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131. (c) Baidya, M.; Yamamoto, H. *Synthesis* **2013**, *45*, 1931.

(2) (a) Waldmann, H. *Synthesis* **1994**, *1994*, 535. (b) Streith, J.; Defoin, A. *Synthesis* **1994**, *1994*, 1107. (c) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317. (d) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, *2006*, 2031. (e) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595.

(3) (a) Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5630. (b) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 11146. (c) Carosso, S.; Miller, M. J. *Org. Biomol. Chem.* **2014**, *12*, 7445. (d) Calvet, G.; Dussaussois, M.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2004**, *6*, 2449. (e) Li, F.; Yang, B.; Miller, M. J.; Zajicek, J.; Noll, B. C.; Möllmann, U.; Dahse, H.-M.; Miller, P. A. *Org. Lett.* **2007**, *9*, 2923. (f) Mineno, T.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 6591. (g) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *J. Org. Chem.* **1998**, *63*, 8397. (h) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, *1995*, 873. (i) Lin, W.; Gupta, A.; Kim, K. H.; Mendel, D.; Miller, M. J. *Org. Lett.* **2009**, *11*, 449. (j) Lin, W.; Virga, K. G.; Kim, K.-H.; Zajicek, J.; Mendel, D.; Miller, M. J. *J. Org. Chem.* **2009**, *74*, 5941.

(4) (a) Chow, C. P.; Shea, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 3678. (b) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128. (c) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082. (d) Jana, C. K.; Studer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6542. (e) Jana, C. K.; Studer, A. *Chem. - Eur. J.* **2008**, *14*, 6326. (f) Jana, C. K.; Grimme, S.; Studer, A. *Chem. - Eur. J.* **2009**, *15*, 9078. (g) Sancibrao, P.; Gori, D.; Kouklovsky, C.; Vincent, G. *Chem. - Eur. J.* **2013**, *19*, 5557. (h) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (i) Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190. (j) Pous, J.; Courant, T.; Bernadat, G.; Iorga, B. I.; Blanchard, F.; Masson, G. *J. Am. Chem. Soc.* **2015**, *137*, 11950. (k) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2003**, *32*, 582.

(5) (a) Chatterjee, I.; Jana, C. K.; Steinmetz, M.; Grimme, S.; Studer, A. *Adv. Synth. Catal.* **2010**, *352*, 945. (b) Chatterjee, I.; Fröhlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11257.

(6) Gouverneur, V.; McCarthy, S. J.; Mineur, C.; Belotti, D.; Dive, G.; Ghosez, L. *Tetrahedron* **1998**, *54*, 10537.

(7) (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. (b) Iwasa, S.; Fakhruddin, A.; Nishiyama, H. *Mini-Rev. Org. Chem.* **2005**, *2*, 157. (c) Palmer, L. I.; Frazier, C. P.; Read de Alaniz, J. *Synthesis* **2014**, *46*, 269.

(8) (a) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, *0*, 2058. (b) Frazier, C. P.; Bugarin, A.; Engelking, J. R.; Read de Alaniz, J. *Org. Lett.* **2012**, *14*, 3620. (c) Chaiyaveij, D.; Cleary, L.; Batsanov, A. S.; Marder, T. B.; Shea, K. J.; Whiting, A. *Org. Lett.* **2011**, *13*, 3442.

(9) (a) Maji, B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 753. (b) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8714. (c) Maji, B.; Baidya, M.; Yamamoto, H. *Chem. Sci.* **2014**, *5*, 3941. (d) Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14472. (e) Maji, B.; Yamamoto, H. *Synlett* **2015**, *26*, 1528.

(10) Moskalenko, G. G.; Sedova, V. F.; Mamaev, V. P. *Chem. Heterocycl. Compd.* **1989**, *25*, 805.

(11) (a) Taylor, E. C.; Tseng, C. P.; Rampal, J. B. *J. Org. Chem.* **1982**, *47*, 552. (b) Faustino, H.; El-Shishtawy, R. M.; Reis, L. V. R.; Santos, P. F. S.; Almeida, P. A. *Tetrahedron Lett.* **2008**, *49*, 6907.

(12) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(13) (a) Saito, T.; Sayo, N.; Xiaoyaong, Z.; Yokozawa, T. (Takasago International Corporation). EP 0850945, 1998. (b) Shimizu, H.; Nagasaki, I.; Matsumura, K.; Sayo, N.; Saito, T. *Acc. Chem. Res.* **2007**, *40*, 1385.

(14) Xie, J.-H.; Zhou, Q.-L. *Acc. Chem. Res.* **2008**, *41*, 581.

(15) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363.

(16) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.

(17) Genet, J.-P.; Ayad, T.; Ratovelomanana-Vidal, V. *Chem. Rev.* **2014**, *114*, 2824.

(18) Kamaluddin, A.-R. Jia, W.; Lu, S.; Guo, R.; Chen, X.; Amaroso, D. (Kanata Chemical Technologies Inc.). US20130184479, 2013.

(19) Sedova, V. F.; Shkurko, O. P. *Chem. Heterocycl. Compd.* **1993**, *29*, 593.

(20) Werbitzky, O.; Klier, K.; Felber, H. *Liebigs Ann. Chem.* **1990**, *1990*, 267.

(21) Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351.

(22) (a) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077. (b) Leung-Toung, R.; Liu, Y.; Muchowski, J. M.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 1639. (c) Lu, P.-H.; Yang, C.-S.; Devendar, B.; Liao, C.-C. *Org. Lett.* **2010**, *12*, 2642.

(23) (a) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) Leach, A. G.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 5192. (c) Galvani, G.; Lett, R.; Kouklovsky, C. *Chem. - Eur. J.* **2013**, *19*, 15604. (d) Tran, A. T.; Liu, P.; Houk, K. N.; Nicholas, K. M. *J. Org. Chem.* **2014**, *79*, 5617.

(24) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5.

(25) (a) Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, *108*, 1982. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, *2005*, 365. (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111. (d) Chapleur, Y.; Chretien, F.; Ibn Ahmed, S.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 341.

(26) (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. (b) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303.

DOI: 10.1021/jacs.5b11273
J. Am. Chem. Soc. 2015, 137, 15957−15963

(27) (a) Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829. (b) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143. (c) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752. (d) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. (e) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726. (f) Pandey, G.; Murugan, A.; Balakrishnan, M. *Chem. Commun.* **2002**, 624. (g) Elango, S.; Yan, T.-H. *J. Org. Chem.* **2002**, *67*, 6954. (h) Poe, S. L.; Morken, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 4189. (i) McNulty, J.; Zepeda-Velázquez, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 8450. (j) Collins, J.; Rinner, U.; Moser, M.; Hudlicky, T.; Ghiviriga, I.; Romero, A. E.; Kornienko, A.; Ma, D.; Griffin, C.; Pandey, S. *J. Org. Chem.* **2010**, *75*, 3069. (k) Vshyvenko, S.; W'Giorgis, Z.; Weber, A.; Neverova, N.; Hedberg, B.; Hudlicky, T. *Adv. Synth. Catal.* **2015**, *357*, 83. (l) Gonzalez, D.; Martinot, T.; Hudlicky, T. *Tetrahedron Lett.* **1999**, *40*, 3077.

(28) Krow, G. R.; Carmosin, R.; Mancuso, A. *Org. Prep. Proced. Int.* **1977**, *9*, 285.

(29) (a) Mc Murry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (b) Karlström, A. S. E.; Rönn, M.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 2517.

NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, Scheme 2 was not corrected in the proof and has been corrected in the version reposted on December 15, 2015.

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