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Copper(I)/TF-Biphamphos Catalyzed Asymmetric Nitroso Diels-Alders Reaction

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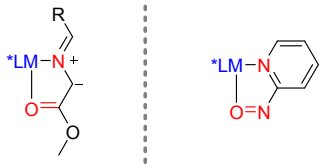
A highly efficient enantioselective Nitroso Diels-Alder reactions of 6-methyl-2-nitroso pyridine with various 1,3-dienes were successfully developed with Cu(I)/(S)-TF-BiphamPhos complex as the catalyst. For most of the cyclic dienes, the synthetically important heterocyclic 3,6-dihydro-1,2-oxazines were obtained in high yields with excellent regio-, diastereo- and enantioselectivities. Acyclic 2-silyloxy-1,3-diene also worked well in the reaction.

Asymmetric transition metal catalyzed reaction has become one of the most efficient tools for obtaining enantiopure compounds, and numerous of novel metal-chiral ligand complexes have been exploited for different asymmetric transformations.[1] The challenge in this field is matching the correct catalyst with the appropriate reaction to pursue high level of stereoselectivity and efficiency.[2] Nitroso Diels-Alder (NDA) reaction has attracted great attention due to the extensively utilization in natural product synthesis since it was discovered by Wichterle in 1947.[3] However, the instability of the nitroso compounds and extremely facile background reaction make the asymmetric approach become very difficult. To the best of our knowledge, few of the efficient catalyst systems for asymmetric metal catalyzed Nitroso Diels-Alder reaction has been discovered to date. The ground-breaking discovery came from Yamamoto's group, who reported a Cu(I)/Segphos-catalyzed highly efficient asymmetric NDA reaction of 2-nitrosopyridines with cyclic and acyclic dienes.[4] By introducing the additional cooperating site on the nitroso compound, 2-nitrosopyridine chelated to the copper metal center give a more stable and rigid complex which could suppress the dimerization of materials and enhance the stereoselective control. Base on this strategy, Studer and co-workers developed another catalysis system using Cu(I)/Walphos-CF_3 complex as the catalyst in the same reaction and obtained high enantioselectivity and diastereoselectivity.[5] Recently, our research group developed a serial of axially chiral N,P-ligands TF-BiphamPhos (N^2-(diphenylphosphanyl)-4,4',6,6'-tetrakis(tri-fluoromethyl)-[1,1'-biphenyl]-2,2'-diamine) based on the rigid biphenyl framework, which exhibited excellent asymmetric induction in the azomethine ylide-involved Cu(I) or Ag(I)-catalyzed asymmetric 1,3-dipolar cycloaddition,[6] Michael addition[7] and Mannich reaction.[8] Considering the structural similarity between the metalated azomethine ylide and 2-nitrosopyridine (Scheme 1), we envisioned the combination of copper or silver salts with chiral TF-BiphamPhos could realize the challenging asymmetric Nitroso Diels-Alder reaction in highly stereoselective control. To further expanding the application of our catalyst system in asymmetric catalysis, herein, we report a Cu(I)/TF-BiphamPhos-catalyzed asymmetric Nitroso Diels-Alder reaction of 6-methyl-2-nitroso pyridine with various 1,3-cyclic dienes, affording the synthetically important 3,6-dihydro-1,2-oxazines in high yields with exclusive regioselectivities and excellent diastereoselectivities and high enantioselectivities.

Scheme 1. Structural Similarity between Metalated Azomethine Ylide and 2-Nitroso Pyridine



Initially, 1,3-cyclohexadiene **1a** and 6-methyl 2-nitiroso-pyridine **2a** were selected as model substrates. The reaction was examined in the presence of catalytic amount of $Cu(MeCN)_4BF_4$ and various chiral (*S*)-TF-BiphamPhos (**L1-L5**) using dichloromethane as the solvent at -80 °C and gradually warmed to -50 °C in 5 h. All of the reactions went to completion with high yields and exclusive diastereoselectivities (Table 1, entries 1-5). The simplest ligand **L1** exhibited no enantioselectivity (Table 1, entry 1), and varying the groups on the nitrogen or phosphorous atom of the ligands delivered unsatisfactory enantioselectivities. To our delight, ligand **L5** bearing two bromine atoms in the 3,3'-position of the biphenyl backbone provided quantitative yield and high enantioselectivity (96% ee) (Table 1, entry 5). Switching the metal salts to Cu(II) or Ag(I) lower the enantioselectivity (Table

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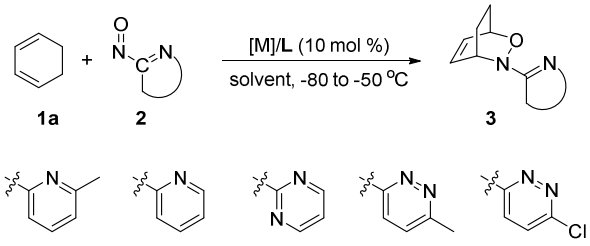
1, entries 6 and 7), while variation of the counter anion seems have no effect on the reactivity and enantioselectivity (Table 1, entry 8). Further solvent effects study found that best enantioselectivity was achieved with ethyl acetate and dichloromethane as the solvent, but less satisfactory results were obtained with toluene and THF (Table 1, entries 9-11). Subsequently, 2-nitiroso N-containing heterocycles **2b**-**2e** were synthesized according to the literature[9,4a] to investigate the influences of the steric and electronic properties of aryl nitroso compounds on the stereoselectivity control. It was found that removing the methyl group of pyridine or replacing the pyridine moiety with pyrimidine or pyridazine moiety resulted in low enantioselectivities (Table 1, entries 12-15). The steric effect of methyl group adjacent to cooperative nitrogen atom were proven to be crucial for this asymmetric catalytic reaction.

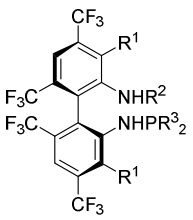
To gain further insight into the catalytic efficiency and stereoselectivity control of the catalyst system, a series of cyclic dienes were explored under the optimized experimental condition, and the results are shown in Table 2. Notably, the regioselectivity of the nitroso Diels-Alder reaction is an ineluctable challenge when it comes to unsymmetrical cyclic 1,3-dienes.[10] To our delight, unsymmetrical 2-substituted 1,3-cyclohexadiene **1b**-**1d** were tested in this catalytic system, and the corresponding cyclic products **3b-3d** were achieved in high yields and excellent enantioselectivities with exclusive regioselectivities (Table 2, entries 1-3). Perfect regioselectivity and good enantioselectivity were also achieved in the NDA reaction of 2,4-disubstituted 1,3-cyclohexadiene **1e** (Table 2, entry 4). N-Cbz protected aza-spirodiene **1f** was also proven to be a suitable substrate in the NDA reaction, affording the

Table 1. Screening Studies of Catalytic Asymmetric Nitroso Diels-Alder Reaction of 2-Nitroso Pyridine **1** with 1,3-Cyclohexadiene **2a**[a]



Entry	[M]	L	2	solvent	yield[b] (%)	ee[c] (%)
1	$Cu(MeCN)_4BF_4$	**L1**	**2a**	CH_2Cl_2	99	0
2	$Cu(MeCN)_4BF_4$	**L2**	**2a**	CH_2Cl_2	98	20
3	$Cu(MeCN)_4BF_4$	**L3**	**2a**	CH_2Cl_2	99	30
4	$Cu(MeCN)_4BF_4$	**L4**	**2a**	CH_2Cl_2	98	19
5	$Cu(MeCN)_4BF_4$	**L5**	**2a**	CH_2Cl_2	98	96
6	$Cu(OTf)_2$	**L5**	**2a**	CH_2Cl_2	90	80
7	AgOAc	**L5**	**2a**	CH_2Cl_2	86	2
8	CuOTf •1/2PhH	**L5**	**2a**	CH_2Cl_2	97	94
9	$Cu(MeCN)_4BF_4$	**L5**	**2a**	PhMe	89	90
10	$Cu(MeCN)_4BF_4$	**L5**	**2a**	EtOAc	96	94
11	$Cu(MeCN)_4BF_4$	**L5**	**2a**	THF	96	90
12	$Cu(MeCN)_4BF_4$	**L5**	**2b**	CH_2Cl_2	99	33
13	$Cu(MeCN)_4BF_4$	**L5**	**2c**	CH_2Cl_2	91	26
14	$Cu(MeCN)_4BF_4$	**L5**	**2d**	CH_2Cl_2	85	35
15	$Cu(MeCN)_4BF_4$	**L5**	**2e**	CH_2Cl_2	89	11

[a] All reactions were carried out with 0.24 mmol of **1** and 0.20 mmol of **2** in 5.0 mL of solvent. [b] Isolated yield. [c] Ee was determined by HPLC analysis.



L1: $R^1 = R^2 = H$, $R^3 = Ph$
L2: $R^1 = R^2 = H$, R^3 = 3,5-bis(methyl)phenyl
L3: $R^1 = R^2 = H$, R^3 = 3,5-bis(trifluoromethyl)phenyl
L4: $R^1 = H$, $R^2 = Et$, $R^3 = Ph$
L5: $R^1 = Br$, $R^2 = H$, $R^3 = Ph$

(*S*)-TF-BiphamPhos

Table 2. Cu(I)-Catalyzed Asymmetric Nitroso Diels-Alder Reaction of 2-Nitroso Pyridine **2a** with Various Cyclic Dienes **1**.[a]

Entry	Cyclic diene (**1**)	Prod (**3**)	yield[b] (%)	ee[c] (%)
1	R = Me (**1b**)	(**3b-d**)	95	94
2	R = Ph (**1c**)		98	96
3	R = OTBS (**1d**)		95	95
4	(**1e**)	(**3e**)	92	97
5	(**1f**)	(**3f**)	96	90
6	(**1g**)	(**3g**)	90	87
7	(**1h**)	(**3h**)	90	71
8	(**1i**)	(**3i**)	80	80

[a] All reactions were carried out with 0.20 mmol of **1** and 0.24 mmol of **2** in 5.0 mL of CH_2Cl_2. PG = 2-Me-Pyridyl. [b] Isolated yield. [c] Ee was determined by HPLC analysis.

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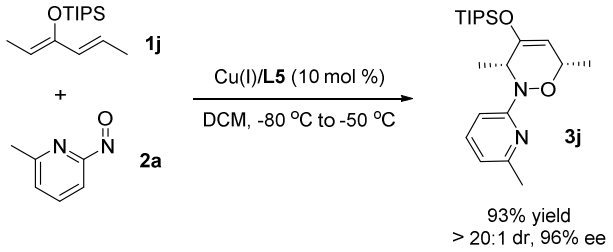
cycloadduct **3f** in 96% yield and 90% ee (Table 2, entry 5).[11] Five-membered cyclic diene 1,3-Cyclopentadiene **1g** was also a viable diene, and the corresponding cycloadduct **3g** was obtained in good yield with high diastereo-/enantioselectivity (Table 2, entry 6). Larger cyclic dienes, such as 1,3-Cycloheptadiene **1h** and *cis*,*cis*-1,3-cyclooctadiene **1i**, were next evaluated in the NDA reaction with the nitroso compound **2a** under the optimized reaction condition, and the reaction proceeded smoothly affording the desired cycloadducts **3h** and **3i** in high yields and excellent diastereoselectivities, albeit with moderate enantioselectivities, which probably resulted from the steric hindrances induced by the ring strains (Table 2, entries 7 and 8).

Encouraged by the results achieved with cyclic dienes, we further investigated acyclic diene in our catalytic system. Under the optimized reaction conditions, readily available 2-silyloxy-1,3-dienes **1j** was employed as an acyclic diene. The NDA reaction proceeded very well, delivering the corresponding cycloadduct **3j** in high yield (93%) with excellent stereoselectivity (> 20:1 dr and 96% ee) (Scheme 2). The absolute configuration of the cycloadducts were determined by comparison the optical rotation and the NMR spectroscopy with the literature results.[4,12]

Scheme 2. Cu(I)-Catalyzed Asymmetric Nitroso Diels-Alder Reaction of 2-Nitroso Pyridine **2a** with Acyclic Diene **1j**.



Based on the stereoselectivity of this Cu(I)/TF-BiphamPhos catalyzed NDA reaction and our previous research work,[13] a possible transition state was proposed in Figure 2. The chiral (*S*)-TF-BiphamPhos and nitrosopyridine chelated to copper metal center giving rise to an active tetrahedral complex. The methyl group on the 6-position of 2-nitiroso-pyridine maybe contribute to the stabilization of the metal complex. The steric congestion in the backside of nitrosopyridine caused by the bulky PPh_2 group of the chiral ligand forces the diene approach from the front side of the dienophile, which led to the observed cycloadducts with (1*R*,4*S*)-configuration in high diastereo- and enantioselectivity.

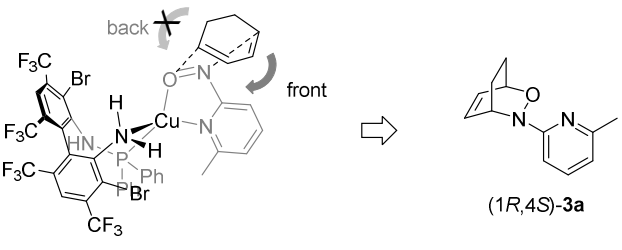


Figure 2. Proposed transition state leading to (1*R*,4*S*)-**3a**.

In summary, with Cu(I)/(*S*)-TF-Biphamphos complex as the catalyst we have successfully developed an efficient asymmetric nitroso Diels-Alder cycloaddition reaction of 6-methyl 2-nitrosopyridine and various cyclic and acyclic 1,3-dienes, leading to the cycloadducts in high yields and enantioselectivities in most cases. Further studies to investigate the mechanistic details and stereochemistry of this reaction are currently underway in our laboratory.

Acknowledgements

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