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2-Alkenoyl Pyridine *N*-Oxides, Highly Efficient Dienophiles for the Enantioselective Cu(II)–Bis(oxazoline) Catalyzed Diels–Alder Reaction[†]

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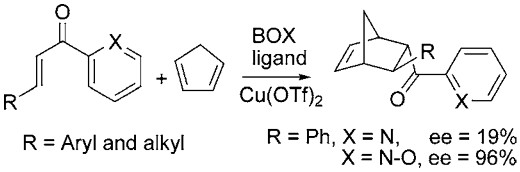
ABSTRACT



R = Aryl and alkyl

R = Ph, X = N, ee = 19%
X = N-O, ee = 96%

2-Alkenoyl pyridine *N*-oxides are introduced as a new kind of efficient dienophiles for the Cu(II)–bis(oxazoline) (BOX) catalyzed enantioselective Diels–Alder reaction affording higher reactivity and enantioselectivity (ee's up to 96%) than the corresponding nonoxidized 2-alkenoyl pyridines.

The Diels−Alder (DA) reaction is one of the most powerful organic transformations, and it constitutes a versatile method for the synthesis of many building blocks for the total synthesis of bioactive natural products.[1] The opportunity to generate up to four stereogenic centers in a stereocontrolled way has stimulated great interest in the development of enantioselective procedures for this transformation. Remarkable progress toward this goal has been achieved through the use of both chiral auxiliaries[2] and chiral catalysts.[3] Although some examples of organocatalytic reactions have appeared recently in the literature,[4] enantioselective DA reaction is most often effected by chiral Lewis acid catalysis. However, although a relatively large number of Lewis acid catalysts based on aluminum, boron, magnesium, and transition metals have been used for this purpose,[3] the overall substrate scope of the reaction remains limited. Earlier studies with monodentate dienophiles have focused mainly on the reaction of unsaturated aldehydes,[3] especially with an α-substituent, and in less extension on the reaction of alkylacrylates[5] and quinones.[6] Furthermore, a number of effective bidentate dienophiles have been reported. Thus, 3-alkenoyl-1,3-oxazolidin-2-ones have proven to be very efficient substrates with a large number of metal-based catalysts and have become the standard test for new catalyst development.[3] Examples of less studied chelating dienophiles include *N*-hydroxyacrylamides,[7] α′-hydroxyenones,[8] unsaturated α-ketoesters,[9] 2-alkylidene-1,3-dicarbonyl compounds,[10] or

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[†] Dedicated to Prof. Ramón Mestres on the occasion of his retirement.

(1) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(2) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261−4263. (c) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397−1401.

(3) (a) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3. (b) *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: New York, 2002. (c) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York. 2000; Vols. 1 and 2.

(4) (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. (b) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (c) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616−11617. (d) Kim, K. H.; Lee, K. S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991−5994. (e) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141−4144. (f) Sakakura, A.; Suzuki, K.; Nakano, K.; Ishihara, K. *Org. Lett.* **2006**, *8*, 2229−2232.

(5) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992−9993.

(6) (a) Jarvo, E. R. B.; Lawrence, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6043−6046. (b) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559−1562.

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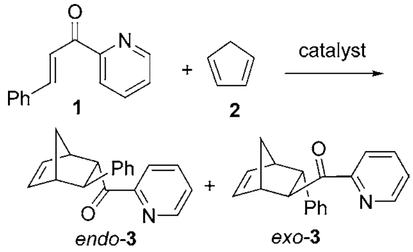
acrylimides.[11] The development of new templates which ensure a proper coordination of the substrate to the catalyst and allow an effective chirality transfer to the product constitutes an important goal.

2-Alkenoyl pyridines are bidentate substrates which can chelate to a metal center by virtue of the pyridine and carbonyl group lone electron pairs. Engberts et al. have reported DA reaction between aza-chalcones and cyclopentadiene in aqueous media (Scheme 1). The reaction is catalyzed by Lewis acid[12] and also by micelles.[13] Schreiner et al. have reported catalysis by neutral hydrogen bond donors for this reaction in either organic solvents or water.[14] The enantioselective version of this reaction was first reported by Engberts using Cu^{2+}−amino acid complexes obtaining moderate ee's up to 74%.[15] Jitsukawa et al. described the use of functionalized bis(oxazoline) complexes as catalysts, although these authors reported the reaction between benzylidine-2-acetylpyridine (**1**) and cyclohexadiene as the only example of reaction with their system.[16] Recently, Roelfes and Feringa have described DNA-based catalysis for this reaction using copper(II) complexes of heteroaromatic ligands in the presence of salmon testes or calf tymus DNA.[17] ee's up to 99% are obtained, although conversions are sometimes low depending on the aromatic substituent of the substrate. Results also depend on the heteroaromatic ligand coordinated to the metal. Remarkably, other bidentate dienophiles such as 3-alkenoyl-1,3-oxazolidin-2-ones fail to react. Finally, Reetz et al. have described copper−phthalocyanine conjugates of serum albumins as catalysts for this DA reaction, obtaining enantioselectivities up to 98% working at a 20 μmol scale which decrease upon increasing the scale of the reaction.[18] It should be noted that in the two last examples chirality is transferred from a bioorganic macromolecule, i.e., DNA or a protein, and not from the ligand which is directly linked to the metal ion. Despite these precedents, the substrate scope for the enantioselective DA reaction with 2-alkenoyl pyridines is very limited, cyclopentadiene being the only diene that has been studied so far. Therefore, the development of an efficient and highly enantioselective catalytic system for the DA reaction with 2-alkenoyl pyridines as dienophiles which relies on easily available catalysts and on general applicability to a large number of dienes is still under investigation.

Scheme 1. Diels−Alder Reaction of Azachalcone and Cyclopentadiene



Because metal complexes with bis(oxazoline) ligands (BOX)[19] have found successful application in a large number of enantioselective reactions with bidentate substrates, we decided to use this kind of ligand in our research. However, when we carried out the reaction between benzylidene-2-acetylpyridine (**1**) and cyclopentadiene (**2**) using the commercially available BOX ligand **6** in the presence of either Cu(II) or Zn(II) triflates, we obtained the expected product **3** but with low diastereo- and enantioselectivity (Table 1, entries 1 and 2). Very recently, Jørgensen et al.[20] have described that *N*-oxypyridin-2-carbaldehydes are better substrates than the corresponding pyridin-2-carbaldehydes in the Cu(II)−BOX catalyzed Mukaiyama reaction with silylketene acetals. In this communication, we describe for the first time the use of 2-alkenoyl pyridine *N*-oxides as dienophiles for the enantioselective DA reaction catalyzed by Cu(II)−BOX

Table 1. Results of the Diels−Alder Reaction of **1** and **4a** with Cyclopentadiene (**2**) According to Schemes 1 and 2[a]

entry	dienophile	L	M	temp (°C)	time (h)	endo/exo[b]	ee endo (%)[b]	ee exo (%)[b]
1	**1**	**6**	Zn	0	22	81.5:18.5	23	41
2	**1**	**6**	Cu	0	22	86:14	19	11
3	**4a**	**6**	Zn	0	2.5	96:4	91	35
4	**4a**	**6**	Cu	0	0.3	97.5:2.5	96	81
5	**4a**	**6**	Cu	−40	3	98.5:1.5	95	76
6	**4a**	**7**	Cu	0	1	96.5:3.5	−96[c]	−94[c]
7	**4a**	**7**	Cu	−40	3	92.5:7.5	−92[c]	−90[c]

[a] All experiments were carried out under nitrogen, dienophile (0.25 mmol), $M(OTf)_2$ (0.025 mmol), (*S,S*)-L (0.025 mmol), **2** (1.8 mmol), and CH_2Cl_2 (1.5 mL); full conversion in all cases (TLC). [b] Determined by HPLC using a chiralpack AD-H column. [c] The opposite enantiomers to those of entries 3−5 were obtained.

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(7) (a) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1731−1733. (b) Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002**, *4*, 1735−1738.

(8) Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942−13493.

(9) Zhou, J.; Tang, Y. *Org. Biomol. Chem.* **2004**, *2*, 429−433.

(10) Yamauchi, M.; Aoki, T.; Li, M.-Z.; Honda, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 3113−3118.

(11) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349−2352.

(12) Otto, S.; Bertoncin, F.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1996**, *118*, 7702−7707.

(13) (a) Otto, S.; Engberts, J. B. F. N.; Kwak, J. C. T. *J. Am. Chem. Soc.* **1998**, *120*, 9517−9525. (b) Rispens, T.; Engberts, J. B. F. N. *Org. Lett.* **2001**, *3*, 941−943. (c) Rispens, T.; Engberts, J. B. F. N. *J. Org. Chem.* **2002**, *67*, 7369−7377.

(14) Wittkopp, A.; Schreiner, P. R. *Chem.*−*Eur. J.* **2003**, *9*, 407−414.

(15) (a) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238−4239. (b) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798−6806.

(16) Matsumoto, K.; Jitsukawa, K.; Masuda, H. *Tetrahedron Lett.* **2005**, *46*, 5687−5690.

(17) (a) Roelfes, G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3230−3232. (b) Roelfes, G.; Boersma, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 635−637.

(18) Reetz, M. T.; Jiao, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 2416−2419.

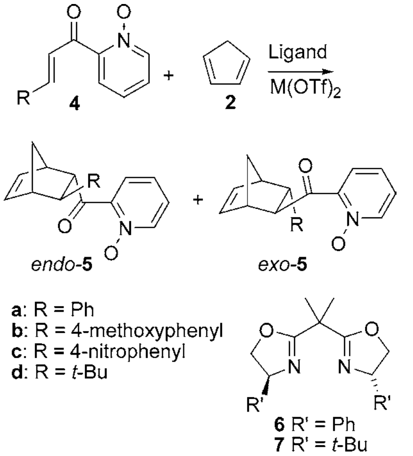
(19) For a review on BOX-catalyzed reactions, see: Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561−3651.

(20) (a) Landa, A.; Minnkilä, A.; Blay, G.; Jørgensen, K. A. *Chem.*−*Eur. J.* **2006**, *12*, 3472−3483. (b) Landa, A.; Richter, B.; Johansen, R. L.; Minkkilä, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 240−245.

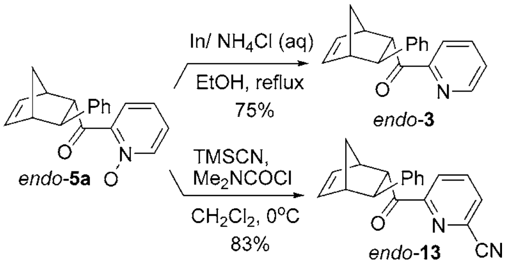
complexes, affording better results than the corresponding 2-alkenoyl pyridines.

2-Alkenoyl pyridine *N*-oxides **4a−d** were prepared by aldol reaction from 2-acetylpyridine *N*-oxide and aldehydes. When we subjected compound **4a** to the DA reaction with cyclopentadiene (**2**) in conditions identical to those for the corresponding aza-chalcone **1**, we found the reaction proceeding much faster and with higher diastereo- and enantioselectivity (Scheme 2). The major diastereomer product was determined to be *endo*-**5a** by NOE experiments and by its conversion into the known compound *endo*-**3** (see Scheme 3 below). Copper(II) triflate gave slightly better results than zinc(II) triflate (Table 1, entries 3 and 4), affording product **5a** with a 97.5:2.5 endo/exo ratio and 96% ee for the major endo diastereomer.

Scheme 2. Diels−Alder Reaction between Alkenoyl Pyridine *N*-Oxides and Cyclopentadiene

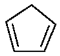
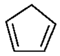
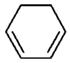
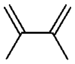
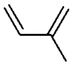
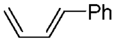


Scheme 3

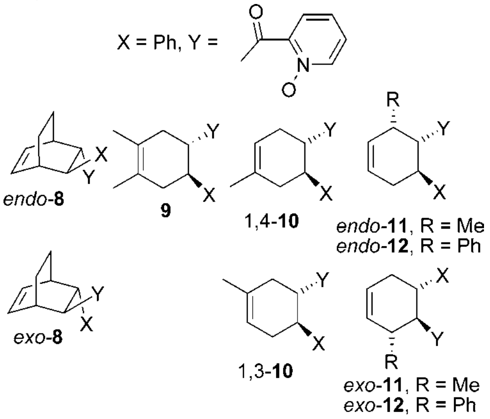


Both the Cu(II)−**6** and Zn(II)−**6** complexes yielded the same major enantiomer for *endo*-**5a**. Lowering the temperature to −40 °C did not change the result significantly. When *tert*-butyl bis(oxazoline) **7** was used instead of ligand **6**, the reaction also took place with high diastereo- and enantiomeric excess (entry 6), but the reaction yielded the opposite enantiomers as is the case with other reactions catalyzed by **6** or **7**.[21] Lowering the temperature with the Cu(II)−**7** complex gave rise to a slight decrease in both diastereo- and enantioselectivity.

Table 2. Results of the Diels−Alder Reaction between 2-Alkenoyl Pyridine *N*-Oxides **4a−d** and Different Dienes Catalyzed by Cu(II)−**6**[a]

entry	4	diene	time (h)	yield (%)[b]	dr[c]	ee (%)[c,d]
1	**4a**		0.3	**5a** 98	97.5: 2.5[e]	96
2[f]	**4a**		0.4	**5a** 94	97: 3[e]	95
3	**4b**		0.3	**5b** 95	97: 3[e]	95
4	**4c**		0.01	**5c** 93	95: 5[e]	96
5	**4d**		0.5	**5d** 92	78:22[e]	93
6	**4a**		30	**8** 99	85:15[e]	96
7	**4a**		21	**9** 95		93
8	**4a**		20	**10** 93	96:4[g]	92
9	**4a**		7.5	**11** 97	>99:1[e]	94
10	**4a**		0.5	**12** 99	>99:1[e]	94

[a] Reaction conditions as in Table 1, entry 4, unless noted otherwise. [b] Isolated product after column chromatography. [c] Determined by HPLC using chiral stationary phase columns. [d] ee for the major isomer. [e] Endo/exo ratio. [f] Reaction carried out with **1a** (0.7 mmol), **6** (0.007 mmol), and Cu(OTf)$_2$ (0.007 mmol). [g] 1,4-**10**/1,3-**10** ratio.



A preliminary study of the substrate scope of the reaction has been carried out using the Cu(II)−**6** complex as catalyst at 0 °C. The R group on the dienophile was amenable to variation. Substrates **4b** and **4c** bearing an aromatic ring were rapidly converted to the corresponding DA products with high yield, diastereo-, and enantioselectivity, regardless of the nature of the substituent on the phenyl ring (Table 2, entries 1−4). The dienophile also tolerates an alkyl group

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(21) (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. (b) Johansen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762.

attached to the double bond (entry 5). Thus, the reaction with the *tert*-butyl-substituted **4d** afforded the major *endo*-adduct in 93% ee together with the *exo*-adduct in 70% ee, in a short reaction time. Experiments also showed that the amount of catalyst can be reduced to as low as 1 mol % and the reaction scaled up at least three times without a noticeable effect on the yield and stereoselectivity (Table 2, entry 2).

Dienes other than cyclopentadiene were also studied using compound **4a** as the dienophile.[22] As expected, the less reactive cyclohexadiene required longer reaction time, although the reaction was complete in 30 h affording the corresponding adduct **8** with fair diastereoselectivity and high enantioselectivity for the *endo*-adduct (Table 2, entry 6). It should be mentioned that the nonoxidized benzylidene-2-acetylpyridine (**1**) does not react with cyclohexadiene in the presence of the Cu(II)−**6** complex even at room temperature.[16] 2,3-Dimethyl butadiene also required 21 h of reaction to afford the expected product **9** with excellent yield and enantioselectivity (Table 2, entry 7). Of major significance were the results with more problematic dienes. With isoprene, the DA reaction gave a 96:4 mixture of two regioisomeric products **10** having the methyl and carbonylpyridyl groups in 1,4- and 1,3-relative positions on the cyclohexene ring, respectively. The major 1,4-regioisomer was obtained in 92% ee (Table 2, entry 8). Similar levels of selectivity were obtained with other difficult dienes such as piperylene (entry 9) and 1-phenylbutadiene (entry 10). In these cases, the reaction yielded primarily the corresponding *endo*-adducts having a cis disposition between the carbonylpyridyl group and the substituent (methyl or phenyl) proceeding from the diene. No regioisomeric products were observed in the reaction mixtures. In both cases, the major diastereomers *endo*-**11** and *endo*-**12** were obtained in 94% ee.

An important aspect related with the chemistry reported here is that the optically active pyridine *N*-oxide adducts can be deoxygenated to the corresponding pyridine adducts by treatment with In/NH_4Cl without noticeable loss of enantiomeric purity. Thus, a 91% enantiomerically pure *endo*-**5a** (Table 1, entry 3) was converted into compound *endo*-**3**, having identical optical purity, with 75% yield (Scheme 3). Compound *endo*-**3** obtained in this way showed spectral features identical to those described by Engberts[12] for the *endo*-adduct obtained by reaction of compound **1** with cyclopentadiene (**2**), therefore confirming the structural assignment for the major diastereomer obtained from the reaction with **4a** in Scheme 2. Furthermore, a comparison of the retention times in HPLC shows that compound *endo*-**3** obtained according to Scheme 3 is the enantiomer of the product obtained by Engberts from **1** and **2** upon catalysis with Cu(II)−*N*-methyl-L-tyrosine.[15b] On the other hand, the characteristic chemistry of pyridine *N*-oxides can be used to perform transformations on the heterocyclic ring. As an example, we have carried out the regioselective cyanation of *endo*-**5a** by a modified Reissert−Henze reaction[23] to give *endo*-**13** in 83% yield (Scheme 3).

In summary, we have presented here a new type of dienophile for the Cu(II)−BOX catalyzed enantioselective Diels−Alder reaction. 2-Alkenoyl pyridine *N*-oxides not only showed increased reactivity but also had higher levels of enantioselectivity than the corresponding nonoxidized 2-alkenoyl pyridines. Unlike other related catalytic systems, high conversions and ee's are obtained regardless of the nature of the substituent on the double bond of the dienophile, allowing either aryl or alkyl groups. The high efficiency of the reaction is also maintained with dienes other than cyclopentadiene. We have shown that the DA adducts can be deoxygenated to the corresponding pyridine adducts without loss of optical purity, but it could also be possible to take advantage of the characteristic pyridine *N*-oxide chemistry to carry out transformations on the heteroaromatic ring which could be otherwise difficult to perform. Research on this regard as well as on expanding the scope of the DA reaction with these substrates is under development.

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Supporting Information Available: General experimental procedures, characterization data, and ^1H NMR and ^{13}C NMR spectra for compounds **4a**−**d** and for the major Diels−Alder products **3**, **5**, and **8**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[22] No DA reaction took place between the poorly reactive diene furan and compound **4a**. Instead, a sluggish Michael addition of furan to enone **4a** was observed at room temperature.

[23] Fife, K. F. *J. Org. Chem.* **1983**, *48*, 1375−1377.