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Highly Enantio- and Diastereoselective Inverse Electron Demand Hetero-Diels–Alder Reaction using 2-Alkenoylpyridine *N*-Oxides as *Oxo*-Heterodienes

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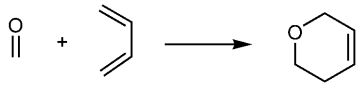
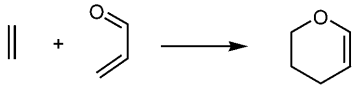
Abstract: A general catalytic inverse electron demand hetero-Diels Alder reaction for 2-alkenoylpyridine *N*-oxides is presented. 2-Alkenoylpyridine *N*-oxides react very efficiently with alkenes in the presence of bisoxazolidine-copper(II) [BOX-Cu(II)] complexes to give chiral dihydropyrans bearing a pyridine ring at the 6-position with very high yields and excellent diastereo- and enantioselectivity. These heterodienes exhibited higher reactivity and enantioselectivity than the corresponding non-oxidized 2-alkenoylpyridines.

Keywords: asymmetric catalysis; cycloaddition; hetero-Diels–Alder reaction; oxygen heterocycles; pyridines

The hetero-Diels–Alder (HDA) reaction with carbonyl compounds (Scheme 1) is a powerful procedure for the construction of six-membered oxygenated heterocycles, i.e., dihydropyrans and dihydropyranones,[1]

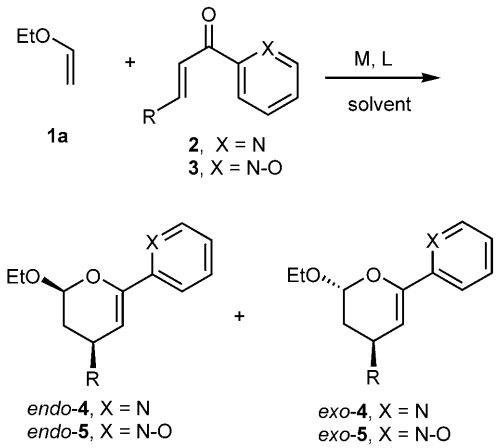




Scheme 1. HDA reaction with carbonyl compounds.

which are key structural elements in many bioactive natural products and important pharmaceuticals.[2]

Most of the recent developments for this reaction have mainly focused on enantioselective procedures leading to optically active compounds.[3] The reaction between carbonyl compounds and conjugated dienes, the direct electron demand HDA reaction, has received much attention and a good number of catalytic enantioselective systems have been developed for this reaction, especially with aldehydes[3,4] and, to a lesser extent, with ketones.[3,5] In contrast, the catalytic enantioselective inverse electron demand HDA, that is the reaction between unsaturated carbonyl compounds and electron-rich alkenes, has not been investigated to a great extent, and only few effective catalytic systems have been reported. Tietze et al.[6] published the first example of this class of reaction, an intramolecular cycloaddition catalyzed by a diacetone glucose derived-titanium(IV) Lewis acid. Later, Wada et al.[7] reported the first intermolecular catalytic enantioselective inverse electron demand HDA reaction with α′-arylsulfonyl enones as heterodienes catalyzed by a bulky TADDOL-Ti(IV) complex derivative. The chiral BOX-Cu(II) complexes have been found by Evans et al.[8] to catalyze the enantioselective HDA reaction of α,β-unsaturated acyl phosphonates with vinyl ethers. Simultaneously, the same catalytic system was applied by Jørgensen et al.[9] to HDA reactions of α,β-unsaturated acyl esters with different electron-rich alkenes. In both cases the resulting dihydropyrans were obtained in high yields and with excellent stereoselectivities. An HDA reaction with enals as heterodienes has been described by Jacobsen et al.[10] using a chiral Schiff base-Cr(III) complex as catalyst. This catalyst system has been extended by the groups of Carreaux and Hall[11] to 3-boronacrolein in a three-component [4+2]/allylboration sequence.



Scheme 2. Inverse electron demand HDA reaction with 2-alkenoylpyridine derivatives as heterodienes.

Finally, the concept of the HDA reaction has been also extended to organocatalyzed reactions *via* the participation of enamine intermediates as dienophiles by using proline derivatives as catalysts.[12]

2-Alkenoylpyridines **2** (Scheme 2) have been used as dienophiles in catalytic enantioselective DA reactions with a number of catalysts.[13] However, in a previous work,[14] we found that these substrates failed to give the DA reaction in the presence of the "privileged" BOX-Cu(II) complexes (Figure 1).[15] This problem could be overcome by using the related 2-alkenoylpyridine *N*-oxides **3** as dienophiles.[16] These substrates provided higher reactivity and enantioselectivity than the corresponding non-oxidized 2-alkenoylpyridines with the same catalyst, allowing one to obtain the expected cycloadducts with good yields and excellent enantioselectivities (up to 96% *ee*). Compounds **2** have been also used as heterodienes in a racemic HDA reaction catalyzed by yttrium(III) hexafluoroacetone.[17] However, an asymmetric version of this reaction has not been described so far.

In this communication, we present a new catalytic enantioselective inverse electron demand HDA reaction of compounds **3** as heterodienes, leading to optically active dihydropyrans bearing a pyridine ring at the 2-position of the oxygenated heterocycle. These kinds of compounds are useful synthetic precursors for bipyridines,[17] as well as flexible isosters of biologically active compounds.[18]

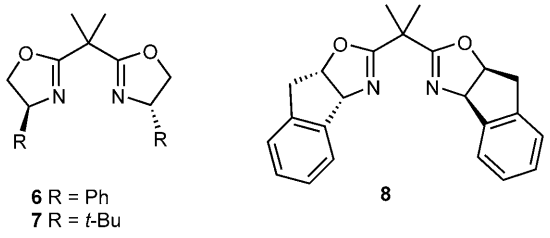


Figure 1. BOX ligands used in this study.

Our investigation started by checking the reaction between alkenoylpyridine **2a** (R = Ph) and ethyl vinyl ether (**1a**) in the presence of the **6**-Cu(OTf)$_2$ complex in dichloromethane. As anticipated from our previous experience, a sluggish reaction took place to give compound **4a** as an 85:15 *endo:exo* mixture with low enantioselectivity for both diastereomers (Table 1, entry 1). Therefore, we studied the reaction with alkenoylpyridine *N*-oxide **3a** (R = Ph). As expected, under almost identical reaction conditions (lower temperature) the pyridine oxide experienced a faster reaction to give the HDA adduct **5a** (R = Ph) with very good diastereo- and enantioselectivity (entry 2). Copper(II) triflate gave better results than zinc(II) triflate and magnesium triflate. Other solvents were tested, which gave similar or worse results than dichloromethane. The use of other BOX ligands (**7** and **8**) did not improve the enantioselectivity, although ligand **7** provided the opposite enantiomer to that obtained with **6**. Finally, with ligand **6** in dichloromethane, the reaction temperature could be lowered to −40 °C bringing about further improvement on the diastereo- and enantioselectivity of the reaction.

A preliminary study of the substrate scope for the heterodiene has been carried out using the Cu(II)-**6** complex as catalyst (Table 2). The R group on the heterodiene was amenable to variation. Substrates bearing an aromatic ring (**3a–d**) attached to the double bond reacted with ethyl vinyl ether (**1a**) to give the corresponding dihydropyrans **5a–d**, almost as a single diastereomer, with high yields, diastereo- and

Table 1. Enantioselective inverse-electron demand HDA reaction of ethyl vinyl ether (**1a**) and 2-alkenoylpyridine *N*-oxide **3a** (R = Ph) according to Scheme 2. Screening of ligands and conditions.[a]

Entry	M	L	Solv.	*T* [°C]	*t* [h]	*endo:exo*	*ee* [%][b]
1[c]	Cu(OTf)$_2$	**6**	CH_2Cl_2	r.t.	90	85:15	16 (15)[d]
2	Cu(OTf)$_2$	**6**	CH_2Cl_2	0	0.5	99:1	91
3	Cu(OTf)$_2$	**7**	CH_2Cl_2	0	0.5	94:6	−75[e]
4	Cu(OTf)$_2$	**8**	CH_2Cl_2	0	1	98:2	79
5	Cu(OTf)$_2$	**6**	Tol	0	3	>99:1	88
6	Cu(OTf)$_2$	**6**	$MeNO_2$	0	5	96:4	46
7	Cu(OTf)$_2$	**6**	THF	0	2.5	>99:1	87
8	Zn(OTf)$_2$	**6**	CH_2Cl_2	0	120	>99:1	51
9	Mg(OTf)$_2$	**6**	CH_2Cl_2	0	77	>99:1	0
10	Cu(OTf)$_2$	**6**	CH_2Cl_2	−20	4	>99:1	94
11	Cu(OTf)$_2$	**6**	CH_2Cl_2	−40	20	>99:1	96

[a] Full conversion of the heterodiene in all the cases.
[b] The *ee* for the major *endo* **5a** isomer determined by HPLC.
[c] Reaction carried out with **2a**.
[d] In brackets, *ee* for *exo*-**4a**.
[e] The opposite enantiomer was obtained

Table 2. Enantioselective inverse electron demand HDA reaction of ethyl vinyl ether (**1a**) and compounds **3** catalyzed by **6**-Cu(OTf)$_2$ according to Scheme 2.[a]

Entry	**3**	R	*t* [h]	Yield [%][b]	*endo*:*exo*	*ee* [%][c]
1	**a**	Ph	20	**5a**, 99	⩾99:1	96
2	**b**	4-MeOC$_6$H$_4$	48	**5b**, 80	⩾99:1	94
3	**c**	4-BrC$_6$H$_4$	14	**5c**, 99	⩾99:1	96
4[d]	**d**	4-NO$_2$C$_6$H$_4$	3	**5d**, 85	⩾99:1	96
5	**e**	2-furyl	70	**5e**, 99	99:1	96
6	**f**	3-fury	70	**5f**, 98	99:1	96
7	**g**	*t*-Bu	18	**5g**, 99	95:5	96 (37)[e]

[a] All reactions carried out at −40 °C, unless otherwise stated.
[b] Isolated yield after column chromatography.
[c] The *ee* for the major *endo* isomer determined by HPLC.
[d] Reaction carried out at −20 °C.
[e] In brackets, *ee* for *exo*-**5g**.

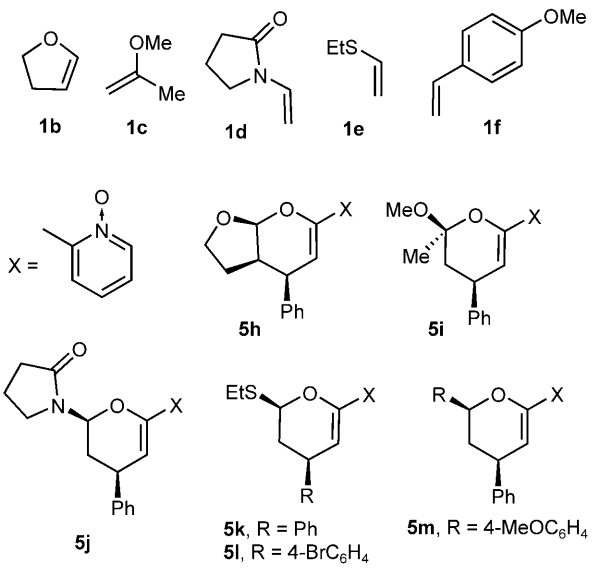


Figure 2. Structure of alkenes **1** and HDA products (*endo*) in Table 3.

enantioselectivities, regardless of the nature of the substituent on the phenyl ring (Table 2, entries 1–4). Compounds **3e** and **f**, bearing a heteroaromatic furan ring, reacted slower although very efficiently, affording the expected products **5e** and **f** with high diastereo- and enantioselectivity (entries 5 and 6), without any interference of the furan ring. The heterodiene also tolerates an alkyl group attached to the double bond. Thus, the reaction with the *tert*-butyl- substituted **3g** afforded the major *endo*-adduct in 96% *ee* together with a small amount of the *exo*-adduct (entry 7).

Next we carried out a preliminary study of the reaction with other electron-rich alkenes using compound **3a** as heterodiene (Figure 2, Table 3). Vinyl ethers (entries 1 and 2), *N*-vinyllactams (entry 3) and vinyl sulfides (entries 4 and 5) were found to be very efficient dienophiles in this reaction. In almost all the cases the HDA products **5h–l** were obtained with very high yields, diastereo- and enantioselectivities; only in the case of 2-methoxypropene (**1c**) was the product obtained with low diastereoselectivity, probably because of the methyl group exerting steric hindrance to the *endo* approach. The efficiency of the catalytic system was also demonstrated by the reaction with less reactive alkenes. Thus, 4-methoxystyrene (**1f**) reacted with **3a** to give quantitatively the HDA adduct **5m** with high diastereoselectivity and a meritorious 77% *ee* for the major *endo*-adduct.

The absolute stereochemistry of *endo*-**5l** (Table 2, entry 5) was elucidated by X-ray crystallographic analysis (Figure 3)[19] and for the rest of the products it was assigned on the assumption of a uniform mechanistic pathway. The stereochemistry of the products indicates the preference of the alkene to approach the heterodiene from the *si* face of the double bond.

Table 3. Enantioselective inverse-electron demand HDA reaction of different alkenes **1** with **3a** catalyzed by **6**-Cu(OTf)$_2$ according to Figure 2.[a]

Entry	**1**	*t* [h]	**5**	Yield [%][b]	*endo*:*exo*	*ee* [%][c]
1	**b**	7	**h**	99	⩾99:1	99
2	**c**	7	**i**	92	66:34	94 (95)[d]
3	**d**	25	**j**	93	⩾99:1	>99
4	**e**	7	**k**	98	⩾99:1	96
5[e]	**e**	5	**l**	99	98:2	97
6[f]	**f**	21	**m**	99	>97:3	77

[a] All reactions carried out in dichloromethane at −40 °C, unless otherwise stated.
[b] Isolated yield after column chromatography.
[c] The *ee* for the major *endo* isomer determined by HPLC.
[d] In brackets, *ee* for *exo*-**5i**.
[e] Reaction carried out with heterodiene **3c**.
[f] Reaction carried out at room temperature.

To show an example of potential transformations on the HDA adducts we subjected compound **5a** to catalytic hydrogenation in the presence of Pd/C (Scheme 3). Deoxygenation of the pyridine ring took place concomitantly with the stereoselective hydrogenation of the double bond to give a 92:8 mixture of diastereomers from which, the all-*cis*-trisubstituted tetrahydropyran **9** bearing three stereogenic centers was obtained without variation of *ee*, after chromatography.

In summary, we have presented here a new type of heterodienes for the Cu(II)-BOX-catalyzed enantioselective HDA reaction of enones with alkenes. 2-Al-

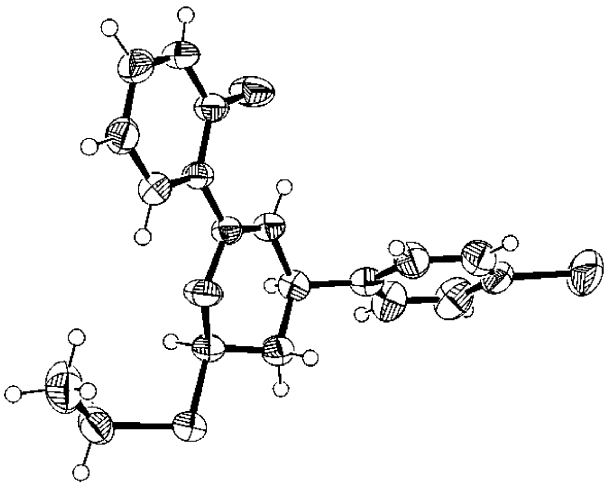
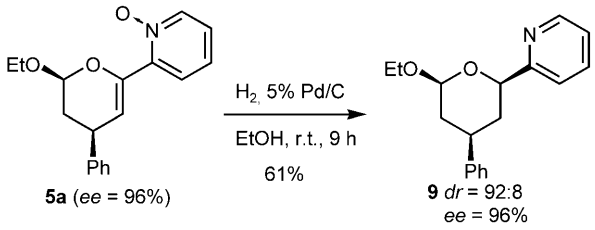


Figure 3. ORTEP plot for the X-ray structure of compound **5l**. Flack parameter 0.005(9).



Scheme 3. Hydrogenation of compound **5a**.

kenoylpyridine *N*-oxides show not only increased reactivity, but also higher levels of enantioselectivity than the corresponding non-oxidized 2-alkenoylpyridines. The reaction enhances the scope of the catalytic enantioselective inverse electron demand HDA reaction, which has been limited to a small number of heterodienes, so far. High conversions and *ee*s are obtained regardless of the nature of the substituent on the double bond of the heterodiene, allowing either aryl, heteroaryl or alkyl groups. The high efficiency of the catalytic system is also demonstrated by the reaction with less reactive alkenes. We have shown that the HDA 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 HDA reaction with these heterodienes is under development.

Experimental Section

Procedure for the Catalytic Enantioselective HDA Reaction

$Cu(OTf)_2$ (9.0 mg, 0.025 mmol) contained in a dry Schlenk tube was heated at 90 °C under vacuum for 1 h. After this time (*S*,*S*)-Ph-BOX **6** (8.4 mg, 0.025 mmol) and CH_2Cl_2 (1.5 mL) were added under a nitrogen atmosphere and the mixture was stirred for 1 h at room temperature. Then, alkenoylpyridine *N*-oxide **3a** (56 mg, 0.25 mmol) was added and the mixture stirred for 0.5 h. After this time, the solution was cooled to −40 °C and the ethyl vinyl ether (72 μL, 0.75 mmol) was added. After completion of the reaction (TLC), flash chromatography on silica gel eluting with hexane:EtOAc (3:7) afforded product **5a** (73.7 mg, 99%). Chiral HPLC analysis [Chiralpak AD-H, hexane:IPA (85:15), 1.0 mL min^{-1}]: e*xo* t_R = 10.3 min, *exo* t_R = 11.6 min, (+)-*endo* t_R = 16.5 min (major), (−)-*endo* t_R = 24.7 min (minor); *endo*/*exo* > 99.9:0.1; *ee* (*endo*) = 96%; $[\alpha]_D^{25}$: +98.8 (*c* 1.5, MeOH, 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (1H, dd, *J* = 0.8 Hz, *J* = 6.5 Hz), 7.80 (1H, dd, *J* = 2.1 Hz, *J* = 8.2 Hz), 7.40 (1H, dd, *J* = 1.1 Hz, *J* = 2.9 Hz), 7.24 (6H, m), 7.12 (1H, ddd, *J* = 2.1 Hz, *J* = 6.6 Hz, *J* = 7.4 Hz), 5.24 (1H, dd, *J* = 1.9 Hz, *J* = 9.0 Hz), 4.07 (1H, qd, *J* = 7.1 Hz, *J* = 9.5 Hz), 3.93 (1H, ddd, *J* = 2.9 Hz, *J* = 6.9 Hz, *J* = 10.1 Hz), 3.71 (1H, qd, *J* = 7.1 Hz, *J* = 9.5 Hz), 2.40 (1H, dddd, *J* = 1.3 Hz, *J* = 1.9 Hz, *J* = 6.9 Hz, *J* = 13.2 Hz), 1.99 (1H, ddd, *J* = 9.0 Hz, *J* = 10.8 Hz, *J* = 13.2 Hz), 1.29 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 143.56 (s), 143.05 (s), 141.58 (s), 141.06 (d), 128.43 (d), 127.36 (d), 126.48 (d), 125.01 (d), 124.25 (d), 123.43 (d), 112.73 (d), 100.31 (d), 64.67 (t), 38.87 (d), 36.93 (t), 15.12 (q); MS (FAB): *m*/*z* (%) = 298 (M^+ + 1, 100), 226 (47), 191 (23), 161 (58); HR-MS: *m*/*z* = 298.1457, calcd. for $C_{18}H_{20}NO_3$: 298.1443.

Acknowledgements

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[19] CCDC 704370 contains the supplementary crystallographic data (excluding structure factors) for the structure reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

