Unexpected Temperature, Time and Solvent Effects in the Catalytic Asymmetric aza-Diels–Alder Reaction of an Ethyl Glyoxylate-derived *N*-Aryl Imine with Danishefsky's Diene Catalysed by a BINOL–Zinc Complex

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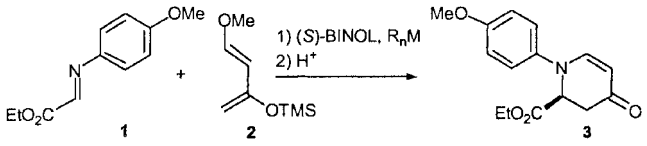
Abstract: : The catalytic asymmetric aza-Diels–Alder reaction of an ethyl glyoxylate-derived *N*-aryl imine with Danishefsky's diene using a BINOL–zinc complex provides the corresponding cycloadduct with moderate to high enantioselectivity, depending on the solvent, temperature and reaction time.

Key words: heterodienophile, Diels–Alder reaction, asymmetric induction, BINOL–zinc



Scheme 1 BINOL–zinc complex catalysed aza-Diels–Alder reaction of imine **1** with Danishefsky's diene.

A number of optically active nitrogen-containing heterocyclic compounds such as piperidines have shown biological properties.[1] One of the most powerful methods for the synthesis of chiral piperidines is the Lewis acid-catalysed asymmetric aza-Diels–Alder reaction. In 1992, Yamamoto et al. reported the first example of the asymmetric aza-Diels–Alder reaction using a chiral boron-based Lewis acid, however, stoichiometric amounts were needed.[2] The first catalytic enantioselective aza-Diels–Alder reaction was achieved by Kobayashi et al.,[3] but since this report, only a few further examples of catalytic asymmetric aza-Diels–Alder reactions using imino dienophiles have been reported.[4]

Of the catalysts used for these reactions, several have used BINOL (1,1′-bi-2-naphthol) derivatives as the chiral sources.[3,4b,d] BINOL derivatives have already shown their potential in different asymmetric reactions.[5] As part of an ongoing programme aimed at developing robust, efficient and reproducible catalytic aza-Diels–Alder reactions, we present herein our recent results on the asymmetric reaction of ethyl glyoxylate-derived imine **1** and Danishefsky's diene **2**[6] using (*S*)-BINOL as the chiral source (Scheme 1).

Initially, we screened different BINOL-metal complexes prepared in situ by mixing (*S*)-BINOL and different Lewis acids and applied the resulting complexes to the aza-Diels–Alder reaction of imine **1** and diene **2** in dichloromethane at room temperature (Scheme 1). Only the diethylzinc and triethylaluminium-derived complexes (entries 1 and 3, Table 1) afforded the piperidine **3** in moderate yield and with low to moderate enantiomeric excesses. Although the diethyl zinc–BINOL complex[7] has been recently reported as an efficient catalyst for enantioselective Diels–Alder[8] and oxo-Diels–Alder reactions,[9] this complex, to the best of our knowledge has not been used for catalytic aza-Diels–Alder reactions of imino dienophiles.

With the corresponding boron complexes (entries 4 and 5, Table 1), the piperidine **3** was obtained, but as a racemic mixture. The other complexes (entries 2, 6 and 7, Table 1) either failed to produce consumption of the imine or produced complete degradation without cycloadduct formation. We therefore decided to study the potential of the BINOL–zinc(II) complex for the reaction shown in Figure 1 in more detail.

Table 1 Asymmetric aza Diels–Alder Catalysed by Various BINOL–Metal Complexes[a]

Entry	Lewis acid R_nM	Yield (%)[b]	ee (%)[c]
1	Et_3Al	65	15
2	Et_2AlCl	–	–
3	Et_2Zn	57	36
4	Et_3B	53	0
5	$(i\text{-PrO})_3B$	56	0
6	$(PhO)_3B$	–	–
7	$(i\text{-PrO})_4Ti$	<5	0

[a] All reactions were performed on a 0.1 mmol scale by using 10 mol % of each complex.
[b] Isolated yields after silica gel chromatography.
[c] Determined by HPLC using a Chiralcel OD column.

We therefore tested the BINOL–zinc complex for the reaction of the imine **1** and diene **2** using different solvents, temperatures and at different catalyst loadings. The results are summarised in Table 2.

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Table 2 Amount of the Complex, Solvent and Temperature Effect on the aza-Diels–Alder Reaction of Imine **2** and Danishefsky's Diene **3**

Entry	Catalyst (mol%)	Solvent	T (°C)	Yield (%)[a]	ee (%)[b]
1[c]	100	CH_2Cl_2	r.t.	78	93
2[d]	10	CH_2Cl_2	r.t.	62	40
3	10	THF	r.t.	61	12
4	10	CH_3CN	r.t.	67	24
5	10	Toluene	r.t.	52	84
6[e]	10	Toluene	r.t.	35	42
7[f]	10	Toluene	r.t.	56	17
8	10	Toluene	0	47	68
9	10	Toluene	–40	45	23
10	10	Toluene	–78	38	12
11	10	CH_2Cl_2	0	50	37
12	10	CH_2Cl_2	–78	38	7
13[c]	100	CH_2Cl_2	0	72	92
14[c]	100	CH_2Cl_2	–40	66	88
15[c]	100	CH_2Cl_2	–78	63	72

[a] Isolated yields after silica gel chromatography.
[b] Determined by HPLC using a Chiralcel OD column.
[c] Reaction time: 2.5 h.
[d] All reactions carried out using 10 mol% of the Lewis acid over 15 h.
[e] Reaction time: 36 h.
[f] Reaction time: 60 h.

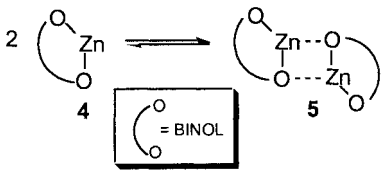
At room temperature and using a stoichiometric amount of the zinc–BINOL Lewis acid in dichloromethane, the piperidine **3** was obtained in 78% yield and 93% ee (entry 1, Table 2). By comparison with a previous report, the absolute configuration was proved to be (*S*) on the basis of HPLC peak assignment.[4c] When the Lewis acid loading was reduced to 10 mol% (entry 2, Table 2), the yield and the ee decreased significantly to 62% and 40% respectively. In an aim to improve the enantioselectivity of the reaction, we examined the effect of solvent polarity, temperature and time on the reaction (Table 2).

Varying the solvent has a significant effect on the reaction outcome. The use of more polar solvents such as tetrahydrofuran and acetonitrile afforded the piperidine **3** with low ee, 12% and 24% respectively (entries 3 and 4). In contrast however, was the finding that toluene resulted in the highest ee of 84% (entry 5, Table 2) with moderate yield (52%). We also noticed that the reaction carried out in toluene proceeded more slowly than the corresponding reaction carried out in dichloromethane, which reinforces the view that a more polar solvent assists catalyst turnover, but at the expense of asymmetric induction. Interestingly from a mechanistic point of view, is the fact that the reaction in toluene does not show a predictable level of asymmetric induction over time, as shown by entries 5, 6 and 7 (Table 2). At longer reaction times (36 and 60 h versus 15), the ee is reduced by half at 42% (36 h) from 84%, and a further reduction in ee to 17% after 60 hours. The approximate conservation of the yield over these reaction times suggests a slow epimerisation process occurring over time and also shows the importance of optimising the reaction time, as well as temperature and solvent in these types of reactions.

We carried out a further optimisation of the reaction by examining the effect of decreasing the temperature, since this generally results in increased asymmetric induction, for example, as observed in substituted BINOL–zinc catalysed oxa-Diels–Alder reactions.[10] However, we were surprised to find that the ee decreased at lower temperatures. Indeed, at 0 °C, the ee decreased to 68% (entry 8, Table 2) from 84% (entry 5, Table 2) under identical conditions, with further decreases in ee at –40 °C and –78 °C to 23% and 12% respectively (entries 9 and 10). The same temperature effect was observed when the reactions were carried out in dichloromethane under the same conditions (entries 11 and 12, Table 2). Such effects are unusual and in stark contrast to the corresponding aldehyde-based reaction, but not unknown, as observed for example by Buono et al. in asymmetric diethyl zinc-aldehyde additions involving amino alcohol-derived alkyl zinc complexes[10] and oxazaphospholidine-borane-mediated ketone reductions for example.[11] These observations are compatible with the likelihood that more than one catalytic species may be present in the reaction.

We further examined the effect of temperature on the reaction using the stoichiometric BINOL–zinc catalysed reactions conditions in dichloromethane. Although the temperature effect was less significant in this case than for the catalytic version, the same trend was observed (compare entries 13–15, Table 2). The ee dropped from 92% (r.t.) to 72% (–78 °C) with only a small concomitant reduction in yield.

The finding that the BINOL–zinc(II) complex-mediated reactions show unusual solvent polarity, time and temperature effects raises interesting mechanistic questions. Aza-Diels–Alder reactions involving electron deficient imino dienophiles and electron rich dienes are either relatively concerted cycloadditions, or more likely stepwise addition-cyclisation processes. The results presented herein are compatible with at least two possible competing effects: 1) the presence of catalyst oligomers,[9a] possibly involving monomer and dimer complexes **4** and **5** respectively (Scheme 2); and 2) the likelihood that in the catalytic reaction, that an acyclic addition product such as **6** (or its bidentate zinc–ester carbonyl complex) might act as a silicon electrophile, activating a further imine via N-silylation producing an iminium ion **7**. Such a process could produce racemic product via a silicon chain-transfer reaction, which may predominate at lower temperatures due to slowing of the zinc-mediated catalytic process. In addition, extended reaction times might also produce the



Scheme 2 Possible dimerisation of the BINOL–zinc complex.

same effect, assuming the formation of intermediate **6** is reversible. Further studies are required to probe the exact mechanism operating.

In conclusion, we have shown that BINOL–zinc efficiently catalyses the aza-Diels–Alder reaction of an electon-deficient imine with an electron rich, oxygenated diene efficiently producing good enantioselectivity. The ready availability of BINOL, ease of preparation and reproducibility of this catalyst system makes this process highly attractive for future piperidine alkaloid and related compound syntheses, and for application to other aza-Diels–Alder reactions involving different imine-diene combinations.

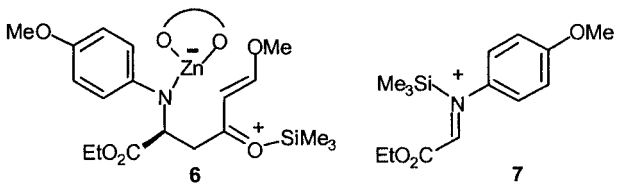


Figure 1 Intermediates **6**, which may cause generation of activated imine **7**, which would produce racemic cycloadduct **3**.

Further studies on the catalytic asymmetric aza-Diels–Alder reaction and the effects of competing silyl transfer reactions are underway.

General procedure (entry 5, Table 2):
(*S*)-BINOL (4.9 mg, 0.017 mmol) was dried under vacuum (1 h), dissolved in dry toluene (0.5 mL) under Ar and treated with Et_2Zn (15 L of a 1 M soln in hexanes). After 1 h, a solution of freshly distilled imine **1** (31 mg, 0.15 mmol) in toluene (1 mL) was added, followed by diene **2** (43 μL, 0.225 mmol). After completion, the reaction was hydrolysed with aq HCl (1%, 2 mL), separated, washed with H_2O, dried ($MgSO_4$) and evaporated. Purification by SiO_2 chromatography (hexanes–EtOAc, 1:1) gave **3** (21.5 mg, 52%) as a yellow oil. Ee's were determined by chiral HPLC using a Daicel Chiralcel OD column: eluant, hexane–*i*-PrOH, 7:3; flowrate, 1.0 mL/min; retention times, (*R*) 17.2 min, (*S*) 25.6 min.

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