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Regulation of Orthogonal Functions in a Dual Catalyst System. Subservient Role of a Nonchiral Lewis Acid in an Asymmetric Catalytic Heteroatom Diels−Alder Reaction

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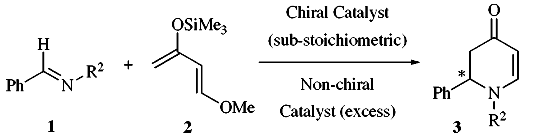
Attempts to develop chiral catalysts for asymmetric reactions of imines must confront the problem that the product is more basic than the starting imine, thus leading to difficulty in turnover.[1] A scenario in which both turnover and asymmetric induction could be realized would involve two catalysts, one chiral and one non-chiral (eq 1). If the nonchiral catalyst was in excess, then it could free up the chiral catalyst to turn over the reaction. Asymmetric induction could be achieved if the chiral catalyst has a larger binding constant than the nonchiral catalyst for imine **1** or if the chiral catalyst promotes the reaction at a sufficiently greater rate that it can overcome its molar disadvantage, or if both were to pertain. We report here the discovery of such a two-catalyst system where at least 20 turnovers can be achieved in a heteroatom Diels−Alder reaction with no loss of induction. This type of dual-Lewis acid catalyst system with orthogonal functions is to our knowledge unprecedented.[2,3]



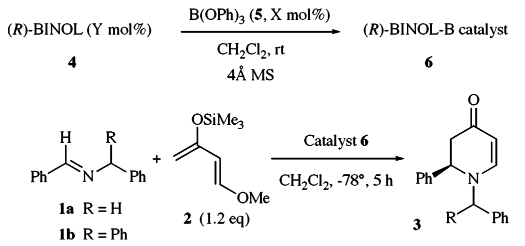
(1)

The first report of a heteroatom Diels−Alder reaction of an imine catalyzed by a chiral Lewis acid involved a catalyst prepared from (*R*)-BINOL and triphenylborate.[4,5] With a stoichiometric amount of catalyst **6**, the reaction produces the Diels−Alder adduct **3a** in 75% yield and 82% ee (Table 1, entry 1).[4a] However, if 10 mol % of the catalyst is used, less than 5% yield was observed.[4b] Interestingly, when 10 mol % of (*R*)-BINOL and 100 mol % $B(OPh)_3$ is used, the reaction proceeds but with a reduced asymmetric induction as might be expected as a result of a background reaction catalyzed by the excess $B(OPh)_3$.

On the basis of the results from the BINOL catalyst **6** (Table 1, entry 2), it was not unexpected to find that the same reaction with a catalyst prepared from 10 mol % of (*S*)-VAPOL[6] and 100 mol % of $B(OPh)_3$ gave a 50% yield of **3a** with 36% ee (Table 2, entry 1).[7] However, it was very surprising to find that the same reaction with imine **1b** (R = Ph) gave **3b** in 94% yield and 90% ee (Table 2, entry 2). It was further found that the % ee of the product does not decrease until a 40:1 ratio of $B(OPh)_3$ to (*S*)-VAPOL was used (entry 5). The reaction of a catalyst prepared from (*R*)-BINOL using the procedure for the preparation of catalyst **8** gave **3b** with low asymmetric induction and in a yield that is near that of the background reaction (entries 7 and 9).

The results from a series of experiments to examine the effect of varying amounts of excess $B(OPh)_3$ with 5 mol % of (*S*)-VAPOL proved to be quite informative (Chart 1). The % ee for **3b** rose to 90% with only 15 mol % of $B(OPh)_3$ and did not drop until 500 mol % was added (82% ee). The yield of the reaction continuously rose with each addition of more $B(OPh)_3$ from 58% at 15 mol % to 95% at 150 mol %. Since the % ee of **3b** remained constant over the same range, the increase in yield cannot be due to a background reaction with $B(OPh)_3$.

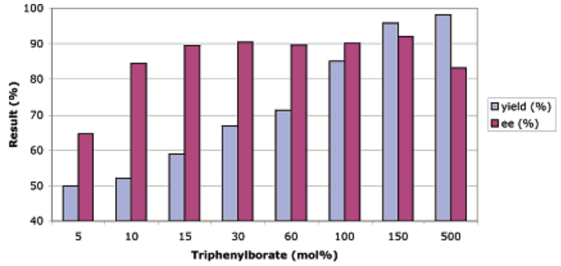
Table 1. Heteroatom Diels−Alder Reaction with Catalyst **6**[a]



entry	R	(*R*)-BINOL	$B(OPh)_3$	% yield **3**	% ee **3**	ref
1	H	100 mol %	100 mol %	68−75	77−86	4a,b, this work
2	H	10 mol %	100 mol %	41	15−40	4b, this work
3	H	10 mol %	10 mol %	<5	−	4b
4	Ph	100 mol %	100 mol %	0	−	4a, this work
5	Ph	10 mol %	100 mol %	0	−	this work

[a] All reactions were run at 0.03 M in **1**.

Chart 1. Effect of Triphenylborate Loading with 5 mol % of VAPOL



One explanation consistent with these results is that the increasing amounts of $B(OPh)_3$ can better compete with the chiral catalyst in binding to the product and thus liberate the sequestered chiral Lewis acid. The question is why does not the increasing amounts of $B(OPh)_3$ lead to a background reaction and loss of significant asymmetric induction. These observations could be explained simply by an increase in Lewis acidity that would be expected if catalyst **8** were a cyclic borate ester.[8] The question is whether the increase in the Lewis acidity of the VAPOL−$B(OPh)_3$ derived catalyst **8** would be sufficient to account for the results in Chart 1. In an attempt to answer this question, a study was undertaken to measure the binding constants of the catalyst **8** and $B(OPh)_3$ with

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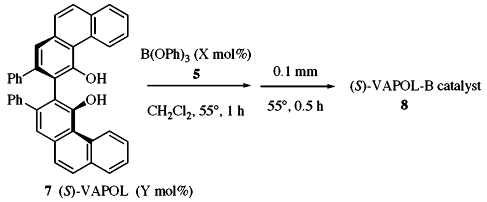
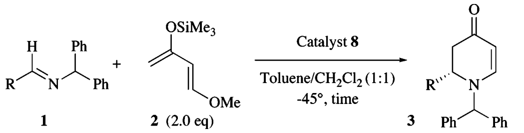
Table 2. Diels−Alder Reaction with Catalyst **8** with Excess $B(OPh)_3$[a]



entry	imine	(*S*)-VAPOL	(*R*)-BINOL	$B(OPh)_3$	% yield **3**	% ee **3**[b]
1	**1a** R = H	10 mol %	−	100 mol %	50	36 (*S*)
2	**1b** R = Ph	10 mol %	−	100 mol %	94	90 (*S*)
3	**1b** R = Ph	7.5 mol %	−	100 mol %	90	90 (*S*)
4	**1b** R = Ph	5 mol %	−	100 mol %	85	90 (*S*)
5	**1b** R = Ph	2.5 mol %	−	100 mol %	77	85 (*S*)
6	**1b** R = Ph	1 mol %	−	100 mol %	66	82 (*S*)
7	**1b** R = Ph	0 mol %	−	100 mol %	25	0
8	**1b** R = Ph	0 mol %	−	100 mol %	46[c]	0
9	**1b** R = Ph	−	10 mol %[d]	100 mol %	26	23 (*R*)
10	**1b** R = Ph	5 mol %	−	130 mol %	96[e]	84 (*S*)
11	**1b** R = Ph	5 mol %	−	130 mol %	97[f]	77 (*S*)
12	**1b** R = Ph	5 mol %	−	150 mol %	96	92 (*S*)

[a] All reactions were run at 0.2 M in **1** in a 1:1 mixture of toluene and CH_2Cl_2 at −45 °C for 24 h and with slow addition of 2 equiv of **2** over 3 h by syringe pump. If **2** was added all at once, the % ee of **3** in entry 2 is 88% ee. [b] Configuration of **3** is given in parenthesis. [c] $B(OPh)_3$ was not heated and evacuated according to the procedure for the preparation of **8**. [d] Catalyst prepared with procedure used for **8** except that (*R*)-BINOL was used. [e] Catalyst was prepared from 30 mol % of $B(OPh)_3$, and then an additional 100 mol % of $B(OPh)_3$ was added with the imine. [f] 0.5 equiv of phenol was added with the imine.

Table 3. Scope of Dual Catalyst Heteroatom Diels−Alder Reaction[a]



entry	R	mol % of (*S*)-VAPOL	reaction time (h)	series	yield[b] (%)	ee[c] (%)
1	Ph	5	24	b	85	90
2	2-MeC_6H_4	5	24	c	83	93
3	1-naphthyl	10	24	d	78	90
4	4-BrC_6H_4	5	24	e	84	89
5	4-$NO_2C_6H_4$	10	24	f	69	73
6	4-$MeOC_6H_4$	10	48	g	71	90
7	4-F,2-MeC_6H_3	5	50	h	84	89
8	*trans*-β-styryl	5	24	i	11	0
9	1-cyclohexenyl	10	46	j	45	93
10	*t*-butyl	5	47	k	0	−
11	cyclohexyl	10	24	l	90	93
12	*i*-propyl	10	48	m	64	90
13	*n*-heptyl	5	24	n	41[d]	0

[a] All reactions were performed at 0.2 M in imine. The diene was added over 3 h via syringe pump. Catalyst **8** was prepared from 100 mol % of $B(OPh)_3$ and the amount of (*S*)-VAPOL indicated in the table. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC analysis. [d] Background reaction with 100 mol % of $B(OPh)_3$ under the same conditions gives a 40% yield.

both the imine **1b** and product **3b**. The binding constants were determined by ^1H NMR titration experiments with increasing amounts of either catalyst **8** or $B(OPh)_3$ added to either imine **1b** or product **3b**. Monitoring the chemically induced shift of the benzhydryl proton in **1b** and the vinyl proton in **3b** adjacent to the carbonyl, the binding constant was determined for $B(OPh)_3$ to be $2.7 \pm 0.4\ M^{-1}$ with **3b** and $0.32 \pm 0.12\ M^{-1}$ with **1b** and for catalyst **8** to be $4.9 \pm 0.8\ M^{-1}$ with **3b** and $2.1 \pm 0.4\ M^{-1}$ with **1b**. Thus, the VAPOL catalyst **8** binds to the imine **1b** 7 times stronger than $B(OPh)_3$, while it binds to the product **3b** only about twice as strongly. While the nature of the binding of catalyst **8** to imine **1b** is not known, these binding constants alone are not sufficient to account for the data shown in Chart 1. Therefore, these data must be a result of a combination of the increased binding of the chiral catalyst and an increased rate of the reaction of imine **1b** with the chiral catalyst over that of the nonchiral catalyst. To explain these data, the difference in rate must be at least a factor of 100.

This catalyst system was found to have utility in providing turnover for the heteroatom Diels−Alder reaction with a variety of other benzhydryl imines (Table 3). The reaction was fairly general for imines prepared from aromatic aldehydes. α,β-Unsaturated imines appear to need a substituent in the α-position as high selectivity was observed for the imine of cyclohexene carboxaldehyde but not for cinnamyl aldehyde. Imines from unbranched aliphatic aldehydes gave racemic product, those from α-branched aliphatic aldehydes gave high ee, and those from α,α-disubstituted aldehydes were unreactive.

While the data can be explained by the scenario outlined in eq 1, it is possible that an ionic catalyst is involved that results from abstraction of a phenoxy group by the excess triphenylborate.[9] Further studies to shed light on the workings of this catalyst system are ongoing.

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Supporting Information Available: Spectroscopic data and experimental details are included (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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