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Non-linear effects operate and dynamic ligand exchange occurs when chiral BINOL–boron Lewis acids are used for asymmetric catalysis

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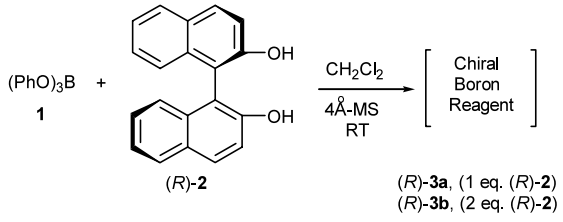
Abstract—Non-linear effects reveal that the use of chiral BINOL–boron reagents for aza-Diels–Alder reactions results in an enantioselective catalytic species containing at least 2 equiv. of BINOL. Dynamic ligand exchange and ligand accelerated catalysis occurs in these reactions, consistent with the formation of a cyclic borate ester of BINOL with enhanced Lewis acidity.

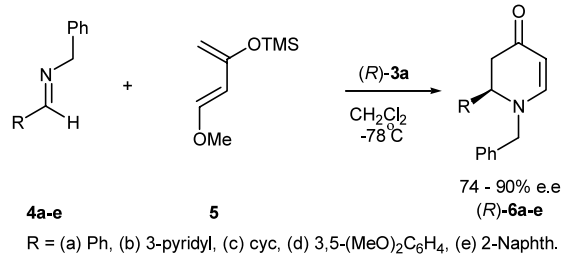
It is well known that boron–ligand complexes containing aryloxy ligands can undergo dynamic ligand exchange in solution,[1] and this fact has been exploited by Yamamoto et al., and others, in developing a range of boron complexes containing enantiopure 1,1′-binaphthol [BINOL] (and its derivatives) as chiral Lewis acids for asymmetric catalysis.[2–7] Their first report on the use of chiral boron reagents derived from BINOL described that mixing 1 equiv. of $(PhO)_3B$ **1** with 1 equiv. of BINOL (*R*)-**2** in dry CH_2Cl_2 resulted in a self-assembled chiral boron reagent (*R*)-**3a** that catalysed formal asymmetric aza-Diels–Alder reactions[8] in good e.e. (Scheme 1). Thus, treatment of a range of *N*-benzylaldimines **4a–e** and Danishefsky's diene **5** with a stoichiometric amount of chiral boron reagent (*R*)-**3a** in CH_2Cl_2 at −78°C gave a range of chiral *N*-benzyl-2,3-dihydro-1*H*-pyridin-4-ones (*R*)-**6a–e** in 74–90% e.e. (Scheme 2).[2]

Yamamoto et al. proposed that monomeric BINOL–boron complex (*R*)-**7** was the most likely active catalytic species in these reactions,[2a] however the possibility that other BINOL–boron species might be responsible for the observed enantioselectivity was not excluded.[9] Subsequently, this chiral boron reagent (*R*)-**3a** was employed as a stoichiometric chiral Lewis acid for diastereoselective aza-Diels–Alder,[2b,3] and aldimine–aldol reactions,[4] with complex (*R*)-**7** being invoked as the catalytically active species in each case.

Yamamoto et al. subsequently introduced an alternative protocol for the preparation of this type of chiral boron–BINOL reagent by refluxing 2 equiv. of (*R*)-



Scheme 1.



Scheme 2.

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BINOL with 1 equiv. of $(MeO)_3B$ in CH_2Cl_2 in the presence of 4 Å molecular sieves.[6] A crystalline precatalyst was isolated and characterised via spectroscopic and crystallographic analysis as a dimeric 'ate' species (*R*,*R*)-**8** that contained 2 equiv. of (*R*)-BINOL.[6] Chiral boron reagent (*R*,*R*)-**8**[7] was shown to demonstrate similar reactivity to chiral boron reagent (*R*)-**3a** catalysing the formation of (*R*)-**6a** in 86% e.e.[6] (compare with 82% e.e.[2] for formation of (*R*)-**6a** using (*R*)-**3a**).

Non-linear effects in asymmetric catalysis have previously been employed to probe whether enantioselective catalytic species contain 2 or more equiv. of chiral ligand.[10] Consequently, we chose to investigate whether the use of (*R*)-**3a** for formal aza-Diels–Alder reactions using scalemic BINOL would result in a non-linear effect, since the existence of this phenomena would establish that a complex containing 2 equiv. of (*R*)-BINOL was responsible for the high enantioselectivity in these reactions. The formal aza-Diels–Alder reaction between *N*-benzylphenylimine **4a** and Danishefsky's diene **5** for the formation of (*R*)-**6a** (R = Ph) was chosen as our model reaction and carried out using chiral boron reagent (*R*)-**3a** which was prepared via premixing (*R*)-BINOL (1 equiv.) and $(PhO)_3B$ (1 equiv.) in CH_2Cl_2 under anhydrous conditions at room temperature.[2] In our hands, this formal aza-Diels–Alder reaction at −78°C reproducibly gave (*R*)-**6a** in 77% e.e.,[11] which was inferior to the value of 82% e.e. previously reported for the formation of (*R*)-**6a** using (*R*)-**3a** under these conditions.[2]

Nevertheless, this formal aza-Diels–Alder reaction was repeated four times at −78°C using a chiral boron reagent (*R*)-**3a** derived from 1 equiv. of BINOL of varying enantiopurity (ranging from 0 to 80% e.e.) under otherwise identical conditions, and the enantiomeric excess of (*R*)-**6a** determined in each case. Analysis of the enantiomeric excess obtained for (*R*)-**6a** in these reactions clearly revealed the presence of a small but significant positive non-linear effect (Fig. 1), thus providing clear experimental evidence that the active catalyst responsible for asymmetric induction in this reaction contained more than 1 equiv. of (*R*)-BINOL.

Consequently, we next carried out the same formal aza-Diels–Alder reaction at −78°C using a chiral boron reagent (*R*)-**3b** prepared from $(PhO)_3B$ and 2 equiv. of (*R*)-BINOL, which reproducibly gave (*R*)-**6a** in an improved 81% e.e. Unsurprisingly, the use of scalemic BINOL for the preparation of (*R*)-**3b** resulted in the formation of (*R*)-**6a** with an even greater positive non-linear effect than that observed for (*R*)-**3a** (Fig. 1), thus providing compelling evidence that the enantioselective catalytic species present in both these reactions contains at least 2 equiv. of (*R*)-BINOL.[12]

Since the enantioselective catalytic species in these reactions must contain either a trivalent or tetravalent boron species and at least 2 equiv. of (*R*)-BINOL, we reasoned that the use of (*R*)-**3a** for catalysis must occur in the presence of significant amounts of unreacted achiral

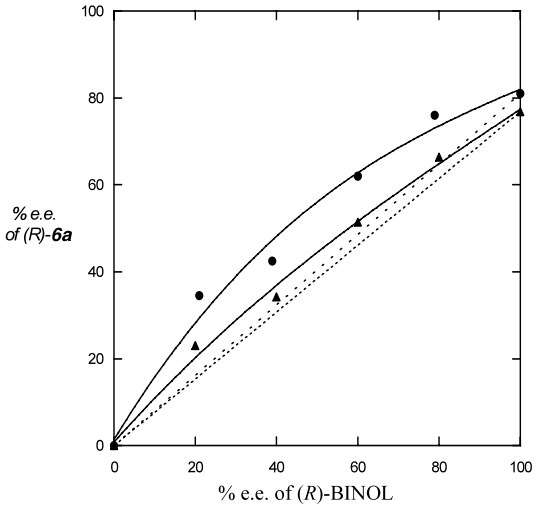
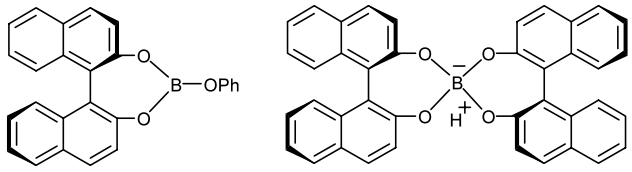
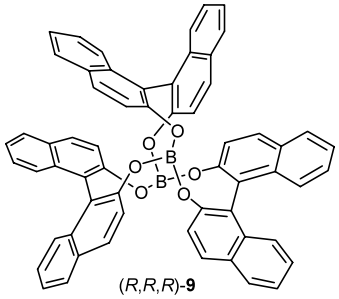


Figure 1. Graph of non-linear effects for conversion of **4a**+**5** into (*R*)-**6a** using chiral reagents (*R*)-**3a** and (*R*)-**3b**. (*R*)-**3a** prepared using 1 equiv. of (*R*)-BINOL (▲) and (*R*)-**3b** prepared using 2 equiv. of (*R*)-BINOL (●).





$(PhO)_3B$. This implied that the chiral catalyst generated in this reaction must catalyse the formation of (*R*)-**6a** at a significantly faster rate than $(PhO)_3B$ catalysed the background racemic reaction to afford (*rac*)-**6a**.

A potential explanation for the observed rate acceleration for (*R*)-**3a** and (*R*)-**3b** is the fact that cyclic borate esters are known to be stronger Lewis acids than the corresponding acyclic borate esters.[1b] Thus, if (*R*)-**3a** and (*R*)-**3b** afford an enantioselective catalytic species that contains a cyclic borate ester of (*R*)-BINOL then it would display enhanced Lewis acidity relative to acyclic $(PhO)_3B$, thus explaining both the rate enhancement and good enantioselectivity observed in this reaction.

Given the similar non-linear effects, enantioselectivity, and ligand acceleration effects[13] observed for the formation of (*R*)-**6a** using (*R*)-**3a** or (*R*)-**3b** in this reaction, it is reasonable to propose that the same

enantioselective catalytic species is operating to control stereoselectivity in both cases. The fact that (*R*)-**3b** (2 equiv. (*R*)-BINOL) affords (*R*)-**6a** in higher e.e. than (*R*)-**3a** (1 equiv. (*R*)-BINOL) would then simply be due to a higher concentration of the enantioselective catalytic species (2 equiv. (*R*)-BINOL) being present when (*R*)-**3b** is employed for reaction.

In order to probe how effectively dynamic ligand exchange was occurring in these reactions, we carried out a series of aza-Diels–Alder reactions using chiral boron reagents prepared from 1 equiv. of $(PhO)_3B$ and sub-stoichiometric quantities of (*R*)-BINOL. We reasoned that if dynamic ligand exchange was occurring, then turnover of (*R*)-BINOL between the different chiral and achiral boron–aryloxy complexes would occur in these reactions. Since chiral BINOL–boron complexes afford (*R*)-**6a** at a significantly faster rate than achiral $(Ph_3O)B$ complexes afford (*rac*)-**6a** then aryloxy ligand turnover should result in (*R*)-**6a** being formed in a significantly higher e.e. than expected if a simple linear relationship relating the concentration of (*R*)-BINOL to the e.e. of (*R*)-**6a** was in operation.

Consequently, the aza-Diels–Alder reaction between *N*-benzylphenylimine **4a** and **5** was carried out using 1 equiv. of a new chiral boron reagent prepared from 1 equiv. of $(PhO)_3B$ and 0.1 equiv. of (*R*)-BINOL (10 mol%) which resulted in formation of (*R*)-**6a** in 15% e.e. This value was clearly greater than the 7.7% e.e.[14] for (*R*)-**6a** that would have been expected if a linear relationship relating the concentration of (*R*)-BINOL to the e.e. of (*R*)-**6a** had occurred. We next carried out an inverse addition protocol in an attempt to minimise the background racemic reaction catalysed by $(PhO)_3B$, whereby dropwise addition of 1 equiv. of $(PhO)_3B$ in CH_2Cl_2 to a solution of (*R*)-BINOL (10 mol%), **4a** (1 equiv.) and **5** (1 equiv.) in CH_2Cl_2 at −78°C, over a period of 5 h, gave (*R*)-**6a** in an improved 42.5% e.e. Finally, use of a syringe pump enabled us to increase the length of time of inverse addition of PhO_3B to 16 h resulting in a further increase in the enantioselectivity of (*R*)-**6a** to 47% e.e. Thus, it was concluded that dynamic ligand exchange of (*R*)-BINOL between chiral and achiral boron–aryloxy complexes was occurring in solution, with (*R*)-**6a** being formed in an enhanced e.e. due to the increased rate of the enantioselective reaction.

Clearly, the principle of employing sub-stoichiometric amounts of a chiral ligand to amplify stereoselectivity in this manner is a potentially powerful atom efficient strategy,[15] that may be applicable in alternative reaction scenarios where other stoichiometric chiral reagents that undergo dynamic ligand exchange are employed for asymmetric synthesis.

In conclusion, we propose that the results described herein, and elsewhere,[2,3] are consistent with the following reaction mechanism. Firstly, non-linear effects obtained using scalemic BINOL demonstrate that the enantioselective species responsible for asymmetric induction contains at least 2 equiv. of (*R*)-BINOL. Potential catalytically active species that have been proposed previously that satisfy this criteria include (*R*,*R*)-**8** derived from 2 equiv. of (*R*)-BINOL and 1 equiv. of boron;[6] or (*R*,*R*,*R*)-**9** containing 3 equiv. of (*R*)-BINOL and 2 equiv. of boron.[5f] Secondly, the need for stoichiometric amounts of boron reagent in these reactions suggest that boron is coordinated to reactants or products (or both) throughout the course of the reaction.[16] Thirdly, a cyclic chiral boron–BINOL complex with enhanced Lewis acidity affords (*R*)-**6a** at a significantly faster rate than the corresponding acyclic complex $(PhO)_3B$ affords (*rac*)-**6a**. Finally, rapid dynamic ligand exchange of aryloxy ligands occurs between all of the aryloxy–boron complexes present in solution, thus ensuring that (*R*)-BINOL is always available for the competing formation of the more reactive enantioselective complex, even when (*R*)-BINOL is employed as a chiral ligand in sub-stoichiometric amounts.

It is likely that similar non-linear effects, dynamic ligand exchange and ligand accelerated catalysis are operating in other reaction scenarios where these type of chiral boron–BINOL reagents have been employed for asymmetric catalysis. Further investigations are currently underway in our laboratory to further delineate the mechanism of these reactions.

Acknowledgements

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11. Reactions were carried out according to the experimental protocol described in Refs. 2a and 2b. Thus, BINOL (*R*)-**2** (100 mg, 0.35 mmol, ranging from 0 to 100% e.e.) and $(PhO)_3B$ (101 mg, 0.35 mmol) were added to a suspension of powdered 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (10 ml) and the resulting suspension stirred under N_2 for 1 h at rt. The reaction mixture was cooled to 0°C and a solution of *N*-benzyl-α-phenylimine **4a** (68 mg, 0.35 mmol) in CH_2Cl_2 (1 ml) was then added and the reaction stirred for a further 10 min at 0°C, before cooling to −78°C followed by dropwise addition of diene **5** (0.084 ml, 0.42 mmol) in CH_2Cl_2 (1 ml). The reaction was stirred at −78°C for a further 5 h, before quenching with water and $NaHCO_3$(aq), dried ($MgSO_4$), and the solvent removed in vacuo to afford a crude product which was purified by chromatography over silica gel to afford pure dihydropyridone (*R*)-**6a** in 50–63% yield. The enantiomeric excess of (*R*)-**6a** was determined in each case via chiral HPLC analysis over a Daicel CHIRALPAK AD column using a mixed hexane/isopropanol (95:5) solvent at a flow rate of 1.0 ml min^{-1}, which gave baseline resolution with elution times for (*R*)-**6a** of 33 min, and (*S*)-**6a** of 36 min.
12. For a previous example where addition of scalemic (*R*)-BINOL to borane resulted in kinetic resolution via selective formation of homochiral 3:2 BINOL–boron complex (*R*,*R*,*R*)-**9** in enantiomerically enriched form, see: Ref. 5f.
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14. The theoretical value of 7.7% e.e. for (*R*)-**6a** is calculated from 10% of 77% e.e. obtained for (*R*)-**6a** using a chiral boron reagent (*R*)-**3a** derived from (*R*)-BINOL (100% e.e.).
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16. Use of 10 mol% of (*R*)-**3a** as catalyst for the aza-Diels–Alder reaction between **4a** and **5** resulted in formation of (*R*)-**6a** in less than 5% yield.