Barriers to enantiocontrol in Lewis acid catalyzed hetero-Diels–Alder reactions†‡

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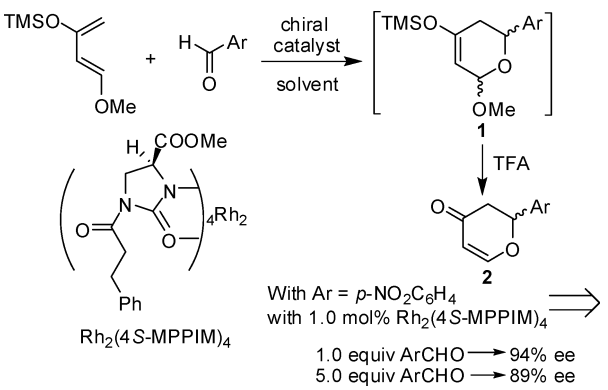
Lewis bases, including reactant aldehydes, inhibit the rate of conversion for cycloaddition and those, like aldehydes or nitriles, cause a decrease in enantiocontrol due to the Lewis acidity of the activated complex.

Hetero-Diels–Alder reactions between carbonyl compounds or imines and a reactive diene have constituted an important synthetic methodology, and the use of chiral catalysts in these reactions is a common platform for evaluation of catalyst effectiveness for enantiocontrol.[1,2] Lewis acids are employed as catalysts to activate the hetero-dienophile for cycloaddition, and with few exceptions, catalyst loading is between five and ten mole percent.[3] Optimized conditions are commonly reported, and they almost universally involve using the diene component in excess over the dienophile. In the course of our recent studies of the hetero-Diels–Alder reactions between aldehydes and the Danishefsky diene using chiral dirhodium carboxamidate catalysts,[4,5] knowing that the rate of reaction has first-order dependence on the concentration of aldehyde,[6] we increased the concentration of aldehyde in order to increase the rate for product formation. In these investigations we observed a decrease in enantioselectivity as the concentration of aldehyde was increased (Scheme 1).[7] We now report the extent and cause of this aldehyde-dependent selectivity and its potential generality.

Although there are several explanations for this phenomenon, the one that we chose to explore involved the possible utilization of the activated aldehyde as a Lewis acid catalyst in addition to the chiral ligated transition metal catalyst (Scheme 2). In such a case, with the activated aldehyde (**3**) able to coordinate with a second aldehyde, an intermediate diastereomeric complex (**4**) is produced that would be expected to diminish the enantiomeric excess of the final product. Previous studies showed that the Rh_2(4*S*-MPPIM)$_4$-catalyzed reaction was at least 100-fold faster than the background reaction which conflicted with an explanation of diminution of % ee due to the background reaction,[6] and this large rate differential was confirmed in this investigation.

To ascertain if this was a general phenomenon among Lewis acids from chiral transition metal catalysts we surveyed those of Rh(II)Rh(III),[8] Cu(II),[9] and Cr(III)[10] in the same hetero-Diels–Alder reaction, and representative examples of these applications are reported in Table 1. Reactions were performed under the same conditions, and catalyst amounts are as reported. As can be seen from these data, the change in enantiomeric excess as a function of excess aldehyde is relatively small, but the numbers are real. The variation in % ee over multiple runs (at least three per catalyst under each condition) performed under the same conditions show variations that are no more than ±0.5% in the reported values. In addition, % ee values from reactions performed between the two extremes of aldehyde use were between the two reported values of % ee in Table 1. When equal amounts of both *p*-nitrobenzaldehyde and *p*-anisaldehyde [K_{eq}(*p*-MeOC$_6$H$_4$CHO)/K_{eq}(*p*-NO$_2$C$_6$H$_4$CHO) = 12 for coordination with Rh_2(4*S*-MPPIM)$_4$][6] were used, only *p*-nitrobenzaldehyde reacted with the Danishefsky diene, but the rate of reaction was 2.6 times slower than that without *p*-anisaldehyde and the % ee for **2** was 86% ee (compare with Scheme 1). Although we could not find a reference to a study reporting lower enantioselection with increased ratio of aldehyde to diene,[2,3] that understanding appears to exist because these investigations uniformly report the use of only one equivalent of aldehyde even when the first-order dependence on aldehyde is known and the rate of reaction is low.[6]

If excess aldehyde can cause a decrease in enantioselectivity, then so should dipolar aprotic solvents. A clear indication of this is seen in the comprehensive report by Evans and co-workers on the effect of solvents on Diels–Alder reactions catalyzed by chiral bis(oxazoline)copper(II) complexes;[11] they found that acetonitrile, in particular, lowered the % ee by half the values found for reactions performed in dichloromethane. In preliminary studies of the hetero-Diels–Alder reaction



Scheme 1 Initial observation of a decrease in enantioselectivity as the aldehyde equivalent was increased.

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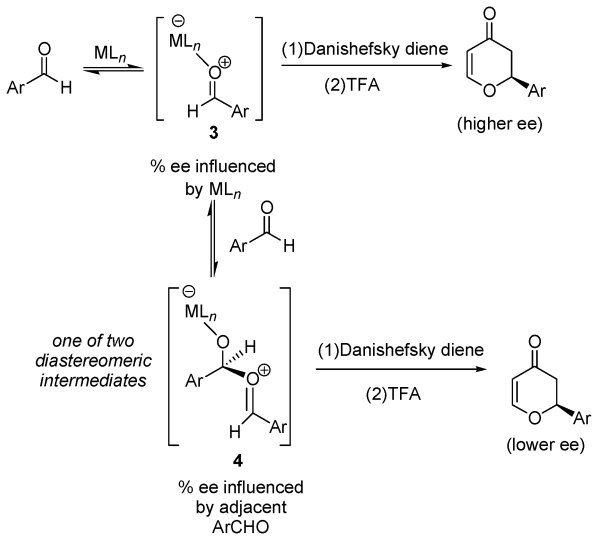


Scheme 2 Proposed mechanistic pathway causing the decrease of enantioselectivity.

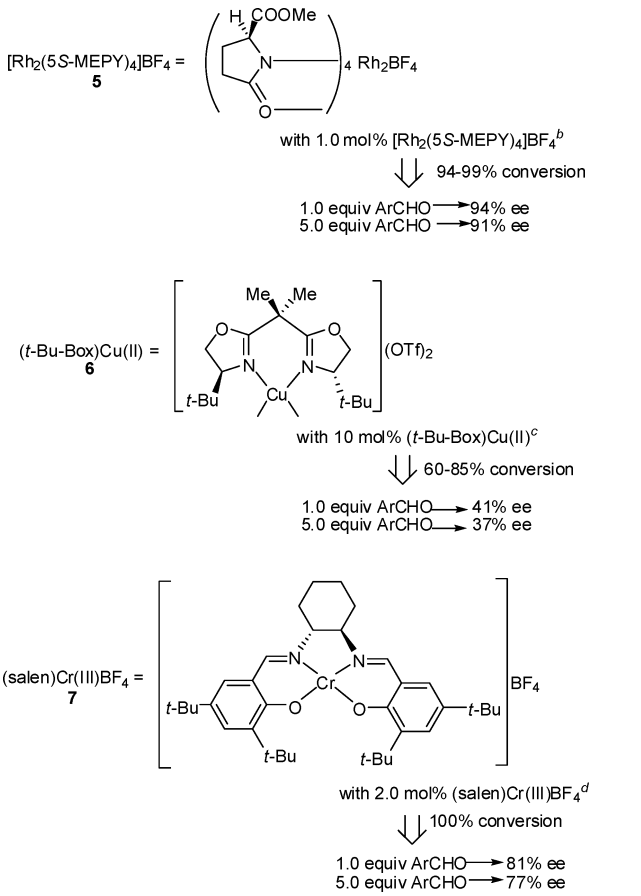
between *p*-nitrobenzaldehyde and the Danishefsky diene the use of acetone or nitromethane was found to drastically lower % ee, whereas the use of THF did not.[12] To further understand this phenomenon, we performed this hetero-Diels–Alder reaction in dichloromethane, catalyzed by Rh_2(4*S*-MPPIM)$_4$, in the presence of varying amounts of either acetonitrile or THF. The results of % conversion and % ee are reported in Fig. 1.

Both acetonitrile and tetrahydrofuran inhibit the reaction, and both are known to coordinate with the dirhodium(II) catalyst at the axial positions,[13] which are themselves the catalytically active Lewis acidic sites. In this coordination acetonitrile and THF block the catalyst's Lewis acid site and inhibit activation of the aldehyde (Scheme 3). However, consistent with what is observed with excess aldehyde (Scheme 1 and Table 1), the role of acetonitrile is also to act as a surrogate site for Lewis acid activity towards the hetero-Diels–Alder reaction. Even when the amount of acetonitrile is only 75% that of *p*-nitrobenzaldehyde, conversion decreased to 37% (24 h) and enantiomeric excess was only 72%. Both THF and acetonitrile can inhibit the background reaction as well as the catalyzed reaction: without catalyst over the same time reactions gave 6% conversion in DCM, 2% in THF, and 3% in acetonitrile demonstrating that the background reaction is too slow to account for the decrease of ee.

Similar results were obtained with chiral Rh_2(5*S*-MEPY)$_4$BF$_4$[8] (Fig. 2) as the catalyst with the same set of concentrations of acetonitrile or tetrahydrofuran as co-solvent as are described in Fig. 1. In this case, however, enantiomeric excess for reactions in acetonitrile decreased to 46% (in acetonitrile as the sole reaction solvent) in what appears to be a more complex pathway, and when the amount of acetonitrile was only 35% that of *p*-nitrobenzaldehyde, % ee decreased to 90% (as compared to an estimated 83% with Rh_2(4*S*-MPPIM)$_4$, Fig. 1).

A similar study was carried out with (salen)Cr(III)BF$_4$,[10] but enantioselectivity decreased with addition of either acetonitrile or THF. Subsequent experiments showed that the 4 Å molecular sieves, used to remove the pre-coordinated water molecule from (salen)Cr(III)BF$_4$, accelerated the background reaction as the rate of the hetero-Diels–Alder reaction was

Table 1 Influence of the relative amount of aldehyde on enantioselectivity in the hetero-Diels–Alder reactions of *p*-nitrobenzaldehyde (ArCHO) with the Danishefsky diene[a]



[a] Reactions were performed at room temperature with the specified amount of catalyst in dichloromethane for 24 h. [b] With 0.25 M Danishefsky diene in 1.0 mL dichloromethane. [c] With 0.125 M Danishefsky diene in 2.0 mL dichloromethane. [d] With 0.25 M Danishefsky diene and molecular sieves 4 Å (100 mg per 2 mL) in 2.0 mL dichloromethane.

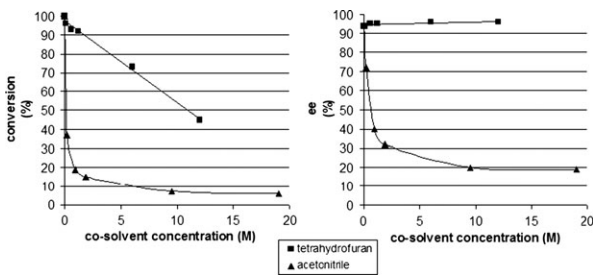
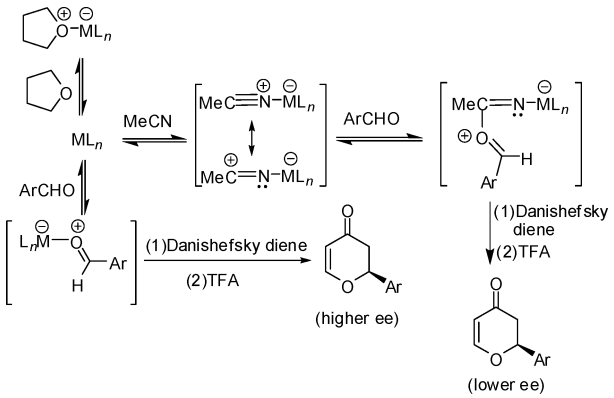


Fig. 1 Influence of co-solvent (either tetrahydrofuran or acetonitrile) on Rh_2(4*S*-MPPIM)$_4$ catalyzed hetero-Diels–Alder reactions of *p*-nitrobenzaldehyde with Danishefsky diene. Reaction conditions: aldehyde (0.25 mmol), diene (0.30 mmol), catalyst (0.0025 mmol), solvent (1.00 mL), rt, 24 h.



Scheme 3 Roles played by tetrahydrofuran and acetonitrile in Lewis acid catalyzed hetero-Diels–Alder reactions.

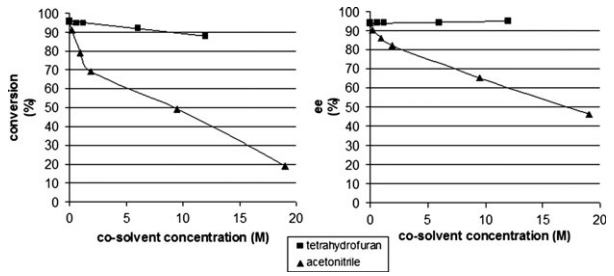


Fig. 2 Influence of co-solvent (either tetrahydrofuran or acetonitrile) on $Rh_2(5S\text{-MEPY})_4BF_4$ catalyzed hetero-Diels–Alder reactions of *p*-nitrobenzaldehyde with Danishefsky diene. Reaction conditions: aldehyde (0.53 mmol), diene (0.63 mmol), catalyst (0.0053 mmol), solvent (1.00 mL), rt, 24 h.

inhibited by both THF and acetonitrile. As mentioned earlier, the Evans group had reported that with chiral bis(oxazoline)-copper(II) complexes[11] acetonitrile lowered the % ee by half the values found for reactions performed in dichloromethane.

The results presented here provide a clear explanation for the loss of enantiocontrol when Lewis acid catalyzed reactions are performed in the presence of certain dipolar aprotic solvents, including nitriles, aldehydes, and ketones. As anticipated, these solvents cause a decrease in rate because they compete with the substrate for the catalytically active site. Furthermore, for those transformations involving activation of an aldehyde or ketone, the activated substrate may itself serve as the Lewis acid, causing less than optimum reactivity and selectivity. The implications of this outcome extend well beyond hetero-Diels–Alder reactions.

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