Barriers to Enantiocontrol in Lewis Acid Catalyzed hetero-Diels-Alder Reactions

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Supplementary Information

General Materials and Methods. All reagents were obtained from commercial sources. The catalysts Rh_2(4*S*-MPPIM)$_4$,[1] Rh_2(5*S*-MEPY)$_4BF_4$[2] and (salen)-Chromium(III)-BF_4[3] were prepared according to the literature reports. NMR spectra were obtained with Bruker DRX-400 instrument. Enantioselectivity was measured by a Varian Prostar HPLC with a Chiralcel OD-H column. Anhydrous dichloromethane and tetrahydrofuran were obtained and dried by nitrogen forced-flow over activated alumina as described by Grubbs.[4]

General procedure for the hetero-Diels-Alder(HDA) reaction catalyzed by Rh_2(4*S*-MPPIM)$_4$ or Rh_2(5*S*-MEPY)$_4BF_4$.[5] An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with dirhodium catalyst (0.0025 mmol), *p*-nitrobenzaldehyde (37.8 mg, 0.25 mmol), and 1.00 mL DCM was added. The resulting solution was stirred for 20 min before the Danishefsky diene (49 µL, 0.25 mmol) was added by a syringe. The vial was capped and the solution was stirred at room temperature for 24 h, and then three drops of TFA were added. After stirring for another 30 min, 3 mL of DCM was added to dilute the solution. The mixture was washed with saturated $NaHCO_3$ and brine solution, then the organic layer was concentrated and chromatographed on silica gel with hexane:ethyl acetate (2:1) to yield the product. Percentage conversion was measured by H^1 NMR of the crude reaction solution. Enantiomeric excess was determined by HPLC (OD-H column). Characteristics of product can be found in literature.[2,5]

General procedure for HDA reaction catalyzed by (salen)-Chromium(III)-BF_4.[3] An oven-dried 2-dram vial equipped with a magnetic stir bar was charged with (salen)-Cr(III)-BF_4 (6.5 mg, 0.01 mmol), *p*-nitrobenzaldehyde (75.6 mg, 0.50 mmol) and 100 mg 4 Å Molecular Sieves. The vial was then sealed with a rubber septum. After purging the vial with dry N_2, 2.00 mL DCM was added by a syringe. The solution was stirred for 20 min., before Danishefsky diene (98 µL, 0.50 mmol) was added by a syringe. The vial was further sealed with parafilm. The mixture was allowed to stir at room temperature for 24 h, and then three drops of TFA were added. After stirring for another 30 min, 3 mL of DCM was added to dilute the solution. The mixture was washed with saturated $NaHCO_3$ and brine solution, then the organic layer was concentrated and chromatographed on silica gel with hexane:ethyl acetate (2:1) to yield the product. Percentage conversion was measured by H^1 NMR of the crude reaction solution. Enantiomeric excess was determined by HPLC (OD-H column).

General procedure for HDA reaction catalyzed by (*t*-Bu-Box)Cu(II).[6] $Cu(OTf)_2$ (9.0 mg, 0.025 mmol) and (*S*,*S*)-*t*-Bu-Box (8.0 mg, 0.027mmol) were stirred under vacuum in an oven-dried 10 mL Schlenk flask for 1 h. The flask was then purged with N_2, 2.00 mL of dry DCM was added by a syringe, and the resulting solution was stirred for 30 min. *p*-nitrobenzaldehyde (37.8 mg, 0.25 mmol) was added into the flask under a flow of N_2. The mixture was stirred for another hour at room temperature, and then Danishefsky diene (49 µL, 0.25 mmol) was added. The solution was stirred for 24 h at room temperature. Three drops of TFA was added, and after stirring for another 30 min, 3 mL of DCM was added to dilute the solution. The mixture was washed with saturated $NaHCO_3$ and brine solution, then the organic layer was concentrated and chromatographed on silica gel with hexane:ethyl acetate (2:1) to yield the product. Percentage conversion was measured by H^1 NMR of the crude reaction solution. Enantiomeric excess was determined by HPLC (OD-H column).

General procedure for catalytic asymmetric HDA reaction with excess equivalents of *p*-nitrobenzaldehyde. The experimental procedure was the same as the general procedure described above for each catalyst. At the step of adding *p*-nitrobenzaldehyde, the amount of aldehyde added was increased to 2.0, 3.0, 4.0 or 5.0 equivalents, while the amount of Danishefsky diene and catalyst were kept the same as described in each general procedure. Solvent volume was kept constant at 1.00 mL for catalysts Rh_2(4*S*-MPPIM)$_4$ and Rh_2(5*S*-MEPY)$_4$$BF_4$, and 2.00 mL for catalysts (salen)-Chromium(III)-BF_4 and (*t*-Bu-Box)Cu(II).

General procedure for study of co-solvent(either acetonitrile or tetrahydrofuran) influence on % conversion and % ee. The experimental procedure was the same as the general procedure described above for the catalyst Rh_2(4*S*-MPPIM)$_4$ or Rh_2(5*S*-MEPY)$_4$$BF_4$. The amount of *p*-nitrobenzaldehyde, Danishefsky diene, and catalyst were as stated in the footnotes of Tables 1 and 2. The total volume of solvent was kept at 1.00 mL.

Table 1. Influence of co-solvent for Rh_2(4*S*-MPPIM)$_4$ catalyzed hetero-Diels-Alder reactions of *p*-nitrobenzaldehyde with Danishefsky diene[a]

amount of co-solvent in DCM (total solvent volume = 1.00 ml)	conversion(%)[b]	ee(%)[c]
0	100	94
10 μL(0.19 M) acetonitrile	37(57[d])	72(68[d])
50 μL acetonitrile	19	40
100 μL acetonitrile	15	32
0.50 mL acetonitrile	7	20
1.00 mL acetonitrile (no DCM)	6	19
10 μL(0.12 M) THF	96	95
50 μL THF	93	95
100 μL THF	92	96
0.50 mL THF	73	96
1.00 mL THF (no DCM)	45	96

[a] Reactions were run with 0.0025 mmol catalyst, 0.25 mmol *p*-nitrobenzaldehyde, 0.30 mmol Danishefsky diene in 1.00 ml solvent at room temperature for 24 h. [b] Determined by H^1 NMR of the crude reaction mixture. [c] Determined by HPLC (OD-H column). [d] Reactions were run for 48 h.

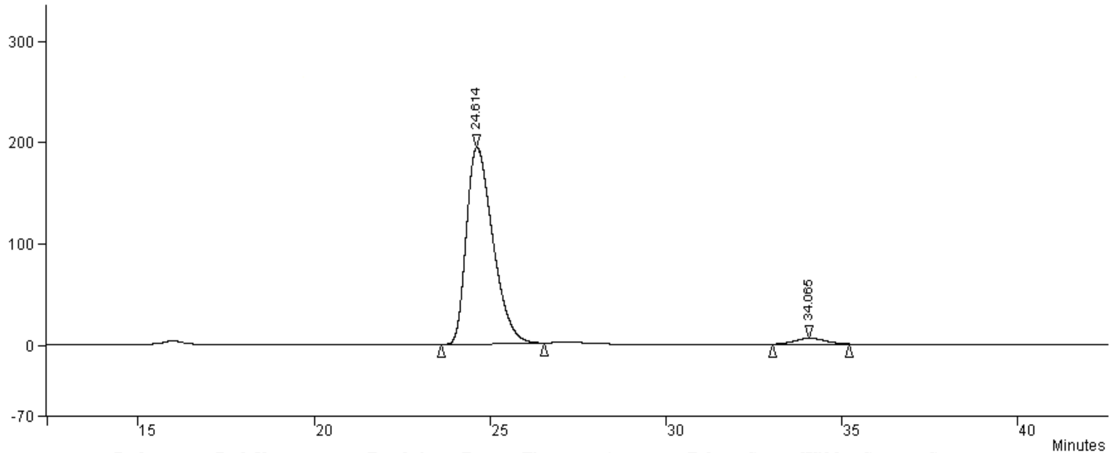
Table 2. Influence of co-solvent for Rh_2(5*S*-MEPY)$_4BF_4$ catalyzed hetero-Diels-Alder reactions of *p*-nitrobenzaldehyde with Danishefsky diene[a]

amount of co-solvent in DCM (total solvent volume = 1.00 ml)	conversion(%)[b]	ee(%)[c]
0	96	94
10 μL (0.19M) acetonitrile	91	90
50 μL acetonitrile	79	86
100 μL acetonitrile	69	82
0.50 mL acetonitrile	49	65
1.00 mL acetonitrile (no DCM)	19	46
50 μL (0.61 M) THF	95	94
100 μL THF	95	94
0.50 mL THF	92	94
1.00 mL THF (no DCM)	88	95

[a] Reactions were run with 0.0053 mmol catalyst, 0.53 mmol *p*-nitrobenzaldehyde, 0.63 mmol Danishefsky diene in 1.00 ml solvent at room temperature for 24 h. [b] Determined by H^1 NMR of the crude reaction mixture. [c] Determined by HPLC (OD-H column).

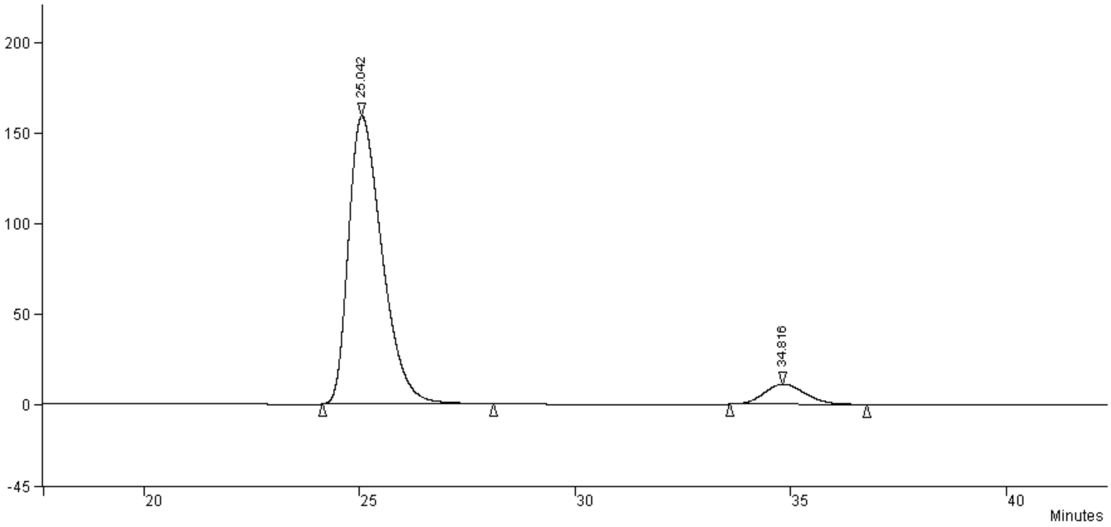
Selected HPLC chromatograms for the cycloadducts of *p*-nitrobenzaldehyde with Danishefsky diene:

1. Reaction with a mixture of 1.0 equiv (0.25 mmol) of *p*-nitrobenzaldehyde, 1.0 equiv of Danishefsky diene, and 1.0 mol% $Rh_2(4S\text{-}MPPIM)_4$ in 1.00 mL DCM at room temperature for 24 h: complete conversion, 94% ee. HPLC separation conditions: OD-H column; hexanes: isopropyl alcohol = 80:20, flow rate = 1.0 mL/min, detection wavelength = 254 nm, t_r (major enantiomer) = 24.6 min, t_r (minor enantiomer) = 34.1 min.



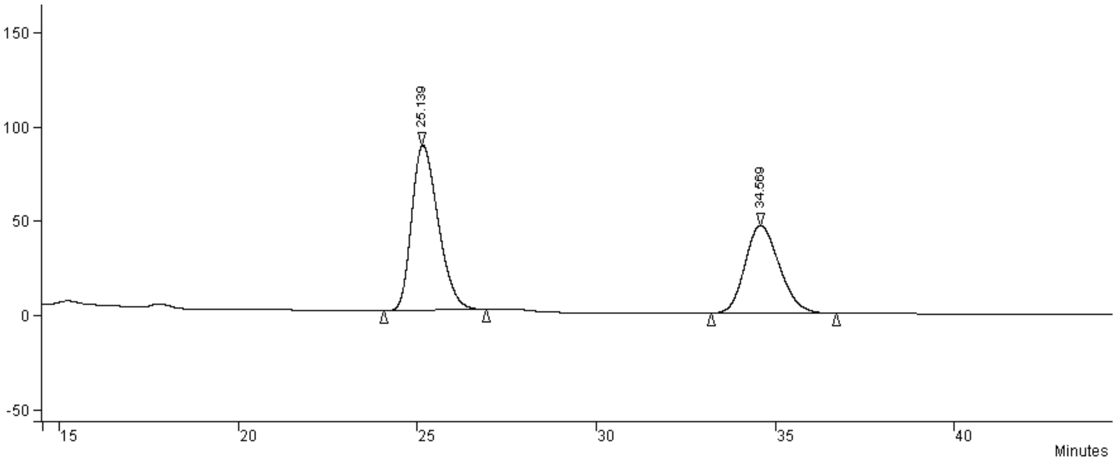
Peak No	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		96.7918	24.614	0.000	101444640	0.00	BB	51.9		0
2		3.2082	34.065	0.000	3362390	0.00	BB	58.4		0
	Totals	**100.0000**		**0.000**	**104807032**					

2. Reaction with a mixture of 1.0 equiv (0.25 mmol) of *p*-nitrobenzaldehyde, 1.0 equiv of *p*-anisaldehyde, 1.0 equiv of Danishefsky diene, and 1.0 mol% $Rh_2(4S\text{-}MPPIM)_4$ in 1.00 mL DCM at room temperature for 24 h: *p*-anisaldehyde did not react at all, *p*-nitrobenzaldehyde had 66% conversion, and the resulting cycloadduct had 85% ee (same conditions as above).



Peak No	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		92.2265	25.042	0.000	86414168	0.00	BB	53.2		0
2		7.7735	34.816	0.000	7283621	0.00	BB	61.8		0
	Totals	**100.0000**		**0.000**	**93697792**					

3. Reaction with a mixture of 1.0 equiv(0.25 mmol) of *p*-nitrobenzaldehyde, 1.2 equiv of Danishefsky diene and 1.0 mol% Rh_2(4*S*-MPPIM)$_4$ in 1.00 mL CH_3CN at r.t. for 24 h: 6% conversion, 19%ee.



Peak No	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Rel Ret Time	Sep. Code	Width 1/2 (sec)	Status Codes	Group
1		59.4429	25.139	0.000	45220584	0.00	BB	50.8		0
2		40.5571	34.569	0.000	30853416	0.00	BB	62.7		0
	Totals	**100.0000**		**0.000**	**76074000**					

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