Asymmetric hetero-Diels–Alder reaction catalyzed by dirhodium(II) carboxamidates

Michael P. Doyle*, Marcela Valenzuela, and Penglin Huang

Department of Chemistry and Biochemistry, University of Maryland, College Park, MD 20742

Edited by Jack Halpern, University of Chicago, Chicago, IL, and approved February 10, 2004 (received for review October 31, 2003)

Chiral dirhodium(II) carboxamidates are highly efficient catalysts for reactions between a variety of aldehydes and activated dienes. Catalyst loadings as low at 0.01 mol % have been realized with enantioselectivities up to 97%. Kinetic investigations reveal a pronounced electronic influence on the rate of the hetero-Diels–Alder reaction with a Hammett $\rho$ value of +1.9 (versus $\sigma^+\)$. Inhibition of the catalyst by reactant aldehyde is apparent, but reactions show first-order dependence on aldehyde and diene, and there is a variable dependence on catalyst.

The catalytic enantioselective hetero-Diels–Alder (HDA) reaction between aldehydes and activated dienes is the transformation of choice for the production of chiral, nonracemic dihydropyrans (Eq. 1) (1–4), and examples of their application are found in the synthesis of natural products and those of pharmaceutical interest (5, 6). Since Danishefsky’s initial report of cyclo-addition reactions with 1-methoxy-3-[(trimethylsilyl)oxy]-butadiene (“Danishefsky’s diene”), this transformation has been a standard for evaluation of enantiocontrol with chiral Lewis acid catalysts (7–13). Although high selectivity has often been achieved, a high catalyst loading (TON $\leq$ 50) is required in virtually all cases (14). As a Lewis acid, the catalyst activates the aldehyde by coordination with a lone pair of electrons on the carbonyl oxygen (15, 16). This association provides a chiral environment that allows the approach of the diene from the less sterically hindered face.

We have previously reported the results of catalytic enantioselective HDA reactions between a variety of simple aldehydes and the Danishefsky diene catalyzed by air stable chiral dirhodium(II) carboxamidates (17). The product formed before treatment with trifluoroacetic acid (TFA) is cycloadduct 1 rather than the Mukaiyama-aldol adduct, confirming the cycloaddition pathway. Surprisingly, these catalysts are effective with catalyst loadings as low as 0.01 mol % [turnover number (TON) up to 10,000], but high enantioselectivities were achieved only with the most reactive aldehydes. Herein we report further optimization of the HDA reaction catalyzed by dirhodium(II) carboxamidate catalysts 3 and 4 with aromatic aldehydes whose reactivity toward cycloaddition extends to nearly three orders of magnitude and, for the first time, kinetic analyses that add additional insight into the mechanism of this reaction. Although there have been theoretical investigations pertaining to the mechanism of the catalytic enantioselective HDA reaction (18, 19) and extensive kinetic studies have been performed on the Diels–Alder reaction (20–23), to our knowledge, detailed kinetic studies have not been performed on the HDA reaction (24, 25). The dirhodium(II) catalytic system provides unique opportunities for these evaluations because they are amenable to determination of equilibrium constants for association between catalyst and aldehyde and to the monitoring of rates for reaction. The results obtained in our study portray a more complex process than that presently understood and suggest the need for more extensive evaluation of basic tenants of Lewis acid catalysis.

Materials and Methods

General. All aldehydes were obtained commercially and purified by distillation or recrystallization before their use. Dichloromethane, chloroform and dichloroethane were distilled before use according to established procedures (26). Rh$_2$(4S-MPPIM)$_4$ 3 (27), Rh$_2$(4S-MEOX)$_4$ 4 (28), Jacobsen’s chromium catalyst 5 (29), and Ding’s titanium(IV) catalyst 6 (30) were prepared according to literature methods. Danishefsky’s diene 7 and 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene 7 (32) were prepared according to published procedures.

Abbreviations: ee, enantiomeric excess; HDA, hetero-Diels–Alder; TFA, trifluoroacetic acid.

*To whom correspondence should be addressed. E-mail: mdoyle3@umd.edu.

© 2004 by The National Academy of Sciences of the USA
Fig. 1.  Pseudo-first-order kinetic plot for the reaction between p-nitrobenzaldehyde and Danishefsky’s diene at 23°C.

**General HDA Procedure.** Aldehyde (0.50 mmol) was added to an oven-dried 1.5-dram vial along with 1.0 mol % catalyst (0.0050 mmol) after which 0.50 ml of dry solvent was added, and the resulting solution was allowed to mix thoroughly by stirring. (If the aldehyde was a liquid, the reaction was performed without solvent.) Danishefsky’s diene (0.70 mmol) was then added, and the solution was stirred at the designated temperature. After the allotted reaction time, the solution was treated with a few drops of TFA and chromatographically purified by using a short silica column that removed the catalyst. Enantiomeric excesses (ee) were determined by HPLC analysis with a 0.46 × 25-cm Daicel Chiralpak OD column and a Varian Prostar HPLC instrument. The same procedure was used for catalytic reactions with diene 7.

**Kinetic Procedure.** To an oven-dried 2-dram vial was added aldehyde (0.25 mmol), biphenyl (gas chromatography standard, 0.25 mmol), 1.0 mol % catalyst, and 1.0 ml of the appropriate solvent. Danishefsky’s diene (2.5 mmol) was then added, and the solution was stirred at the designated temperature. The loss of aldehyde over time was measured by removing 100-µl aliquots from the solution and adding each of them to 4 ml of dichloroethane treated with three to four drops of TFA to desilylate both the product and the diene, thereby avoiding further reaction with the aldehyde. The acid was then neutralized with solid sodium bicarbonate, and samples were injected on a Hewlett-Packard 5890 gas chromatograph equipped with a Supelco SPB-5 column (30 m, 0.25 mm). The reaction was allowed to proceed through at least two half-lives. Kinetic measurements were determined in duplicate or triplicate trials. The same procedure as described above was used for the reaction with catalyst 5. The order with respect to the catalyst was determined from multiple experiments by varying the concentration of catalyst.

After kinetic measurement on the sample, the % ee value of the remaining product was measured by using HPLC to determine that the selectivity was consistent with that found in the nonkinetic measurement. Extraordinary efforts were used to maintain reactant purity because impurities in the catalyst, diene, and aldehyde demonstrably affected both the reaction rate as well as product selectivity. The rate constant, determined through at least one, and generally two, half-lives was calculated by linear least-squares regression from the linear pseudo-first-order kinetic plot. The half-life was determined by using the equation, \( t_{1/2} = 0.693/k \). An example of a kinetic plot is shown for the reaction between \( p \)-nitrobenzaldehyde and the Danishefsky diene at 23°C in a solution of dichloromethane (Fig. 1). The order with respect to diene was 1.0, but that with respect to \( \text{Rh}_2(4S-MPPIM) \) was 1.4 at 40°C in dichloromethane and 0.8 at 60°C in chloroform, and the order was also 0.8 for \( \text{Rh}_2(4S-MEOX) \) at 60°C in chloroform. The activation energy for the \( \text{Rh}_2(4S-MPPIM) \)-catalyzed reaction between \( p \)-nitrobenzaldehyde and the Danishefsky diene was determined by using the Arrhenius equation from the plot of \( \ln k_{\text{obs}} \) versus \( 1/T \), where \( k_{\text{obs}} \) is \( k_\text{d}[\text{diene}][\text{catalyst}] \) (Fig. 2) and \( T \) is in degrees Kelvin.

Equilibrium constants were measured on a Hewlett-Packard 8453 UV-Vis spectrophotometer at room temperature, following the published procedure (33). The axial-coordinating acetonitrile ligands of the catalysts were removed by dissolving the catalyst in dichloroethane and removing the volatile solvent under reduced pressure, followed by heating of the solid to 60°C under vacuum (<1 mm Hg) overnight before use; the color change from orange to blue indicated the absence of acetonitrile coordination. Aldehyde stock solutions were prepared by dissolving appropriate amounts of the aldehyde in dichloroethane. The acetonitrile-free solid was dissolved in 4.00 ml of dichloroethane, and 3.00 ml of the solution was transferred to a cuvette by syringe. A UV-visible spectrum was measured between 400 and 800 nm. Sequentially, a 5.0-µl aldehyde stock solution (for \( p \)-chlorobenzaldehyde and \( p \)-nitrobenzaldehyde, this was 10.0 µl) was added to the cuvette, and the process was repeated 10 times.

Equilibrium constants for \( K_1 \) were determined from a plot of \( 1/\Delta A \) versus \( 1/[\text{aldehyde}] \), which yielded a straight line. \( K_1 \) was calculated from the ratio between the intercept and the slope of this line (33). Wavelengths for the calculation of \( K_1 \) were chosen to be ~20 nm from the isosbestic point, which was 616 nm for \( p \)-anisaldehyde and benzaldehyde, 580 nm for \( p \)-chlorobenzaldehyde and \( p \)-nitrobenzaldehyde, and 613 nm for tolualdehyde. An example of the spectral overlay is shown in Fig. 3 for

**Fig. 2.** Arrhenius plot of \( \ln k_{\text{obs}} \) vs. \( 1/T \).

**Fig. 3.** Plot of absorbance vs. wavelength for \( p \)-anisaldehyde by using an initial concentration of 0.0024 M for \( \text{Rh}_2(4S-MPPIM) \) and incremental concentration changes of 0.0046 M with \( p \)-anisaldehyde.
as 0.01 mol % catalyst (Fig. 4). This decreased catalyst loading was effectively catalyzing the HDA reaction with catalyst loadings as low as 0.01 mol % when using 1.0 mol % of catalyst at 60°C (Table 1) were achieved routinely. Reactions with liquid aldehydes were carried out under solvent- and desiccant-free conditions, which are ideal for environmental safety and volumetric productivities (34). As can be seen from the data, all para-substituted aromatic aldehydes have enantioselectivities of 90% or greater with moderate to good isolated yields. Enantioselectivity changes slightly when the nitro group is at the ortho position instead of the para position. From the 1H NMR spectra of the reaction mixture taken before treatment with TFA, the cycloadduct is present exclusively, giving evidence for a concerted [4 + 2] mechanism. Dimethyl-substituted diene 7 has also been used to test the mechanistic pathway for the HDA reaction (35) with cis stereochemistry being the indicator of the [4 + 2] cycloaddition pathway. Accordingly, reactions between 5-nitro-2-thiophenecarboxaldehyde, 5-nitro-2-furanecarboxaldehyde, or p-nitrobenzaldehyde and diene 7 afford only the corresponding cis diastereomers (Table 2).

By using p-nitrobenzaldehyde and the Danishefsky diene as a model system, catalyst loading for the more reactive Rh2(4S-MPPIM)4 (catalyst 4) was examined. The aim of this study was to determine whether high selectivity and reactivity could be maintained as the amount of catalyst decreases. We were able to effectively catalyze the HDA reaction with catalyst loadings as low as 0.01 mol % catalyst (Fig. 4). This decreased catalyst loading was further extended to the comparable reaction between diene 7 and 5-nitro-2-thiophenecarboxaldehyde catalyzed by Rh2(4S-MEOX)4. In both cases the yield remains virtually unchanged with decreased catalyst loading from 1.0 mol % to 0.01 mol %.

During the course of this study we observed that electron-rich aldehydes such as p-tolualdehyde and p-anisaldehyde required significantly longer reaction times when compared to electron-withdrawing aldehydes such as p-nitrobenzaldehyde. A competitive reaction between p-nitrobenzaldehyde and p-chlorobenzaldehyde with the Danishefsky diene in the presence of catalyst 4 at room temperature showed a >20-fold reactivity difference, and this prompted our kinetic analyses.

The reaction mechanism is assumed to be that outlined in Scheme 1. Coordination of catalyst (Rh2L4) with the lone pair of electrons on the carbonyl oxygen of the aldehyde (A) lowers the energy barrier for addition of the diene (D) to the catalyst complex to give the HDA adduct (P) and regenerate the catalyst (36). The values for both the association constant and the rate constant for five aromatic aldehydes, catalyzed by Rh2(4S-MPPIM)4, are shown in Table 3. The more electron-withdrawing p-nitrobenzaldehyde has a reaction rate that is 20 times greater than that of the p-chlorobenzaldehyde, which is itself >30 times faster than that for p-anisaldehyde. The half-life of the background reaction of p-nitrobenzaldehyde in which no catalyst is present is at least 50 times slower than the reaction performed with 0.1 mol % Rh2(4S-MPPIM)4. p-Anisaldehyde, whose association constant of 74 M⁻¹ suggests that it is more tightly bound to the catalyst than p-nitrobenzaldehyde, which has an association constant of 6 M⁻¹, was expected to be an inhibitor for the reaction of p-nitrobenzaldehyde with Danishefsky’s diene. Thus, when equal amounts of both p-nitrobenzaldehyde and p-anisaldehyde are used at 25°C, only p-nitrobenzaldehyde reacts with Danishefsky’s diene, but the rate is measurably slower (1.87E-02 s⁻¹M⁻²) than that without p-anisaldehyde (4.87E-02 s⁻¹M⁻²). The coordinating acetonitrile ligands of the stock catalyst also act as an inhibitor; however, there is <15% difference in the rate constants when acetonitrile is removed compared to when it is not removed. Neither reactant diene nor product shows evidence of coordination with the catalyst.

### Results and Discussion

In our previous report the Rh2(4S-MPPIM)4 catalysts gave the highest level of enantiocontrol with nitro-substituted aromatic aldehydes (17). However, selectivity and reactivity were poor for less reactive aromatic aldehydes. We set out to optimize these reaction conditions and discovered that at higher temperatures we are able to increase the amount of dihydropyran formed without markedly affecting enantioselectivity. Stereoselectivities as high as 98% ee at 4.87E-02 s were achieved. Reactions with liquid aldehydes were carried out under solvent- and desiccant-free conditions, which are ideal for environmental safety and volumetric productivities (34). As can be seen from the data, all para-substituted aromatic aldehydes have enantioselectivities of 90% or greater with moderate to good isolated yields. Enantioselectivity changes slightly when the nitro group is at the ortho position instead of the para position. From the 1H NMR spectra of the reaction mixture taken before treatment with TFA, the cycloadduct is present exclusively, giving evidence for a concerted [4 + 2] mechanism. Dimethyl-substituted diene 7 has also been used to test the mechanistic pathway for the HDA reaction (35) with cis stereochemistry being the indicator of the [4 + 2] cycloaddition pathway. Accordingly, reactions between 5-nitro-2-thiophenecarboxaldehyde, 5-nitro-2-furanecarboxaldehyde, or p-nitrobenzaldehyde and diene 7 afford only the corresponding cis diastereomers (Table 2).

By using p-nitrobenzaldehyde and the Danishefsky diene as a model system, catalyst loading for the more reactive Rh2(4S-MPPIM)4 (catalyst 4) was examined. The aim of this study was to determine whether high selectivity and reactivity could be maintained as the amount of catalyst decreases. We were able to effectively catalyze the HDA reaction with catalyst loadings as low as 0.01 mol % catalyst (Fig. 4). This decreased catalyst loading was further extended to the comparable reaction between diene 7 and 5-nitro-2-thiophenecarboxaldehyde catalyzed by Rh2(4S-MEOX)4. In both cases the yield remains virtually unchanged with decreased catalyst loading from 1.0 mol % to 0.01 mol %.

During the course of this study we observed that electron-rich aldehydes such as p-tolualdehyde and p-anisaldehyde required significantly longer reaction times when compared to electron-withdrawing aldehydes such as p-nitrobenzaldehyde. A competitive reaction between p-nitrobenzaldehyde and p-chlorobenzaldehyde with the Danishefsky diene in the presence of catalyst 4 at room temperature showed a >20-fold reactivity difference, and this prompted our kinetic analyses.

The reaction mechanism is assumed to be that outlined in Scheme 1. Coordination of catalyst (Rh2L4) with the lone pair of electrons on the carbonyl oxygen of the aldehyde (A) lowers the energy barrier for addition of the diene (D) to the catalyst complex to give the HDA adduct (P) and regenerate the catalyst (36). The values for both the association constant and the rate constant for five aromatic aldehydes, catalyzed by Rh2(4S-MPPIM)4, are shown in Table 3. The more electron-withdrawing p-nitrobenzaldehyde has a reaction rate that is 20 times greater than that of the p-chlorobenzaldehyde, which is itself >30 times faster than that for p-anisaldehyde. The half-life of the background reaction of p-nitrobenzaldehyde in which no catalyst is present is at least 50 times slower than the reaction performed with 0.1 mol % Rh2(4S-MPPIM)4. p-Anisaldehyde, whose association constant of 74 M⁻¹ suggests that it is more tightly bound to the catalyst than p-nitrobenzaldehyde, which has an association constant of 6 M⁻¹, was expected to be an inhibitor for the reaction of p-nitrobenzaldehyde with Danishefsky’s diene. Thus, when equal amounts of both p-nitrobenzaldehyde and p-anisaldehyde are used at 25°C, only p-nitrobenzaldehyde reacts with Danishefsky’s diene, but the rate is measurably slower (1.87E-02 s⁻¹M⁻²) than that without p-anisaldehyde (4.87E-02 s⁻¹M⁻²). The coordinating acetonitrile ligands of the stock catalyst also act as an inhibitor; however, there is <15% difference in the rate constants when acetonitrile is removed compared to when it is not removed. Neither reactant diene nor product shows evidence of coordination with the catalyst.

### Table 1. HDA reactions of aromatic aldehydes with Danishefsky diene catalyzed by Rh2(4S-MPPIM)4

<table>
<thead>
<tr>
<th>Aldehyde, R</th>
<th>ee, %</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-MeOC6H4</td>
<td>93</td>
<td>47</td>
</tr>
<tr>
<td>p-CH3C6H4</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>C6H5</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>p-C6H4</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>p-CF3C6H4</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td>p-C6H4</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>p-C6H4</td>
<td>96</td>
<td>82</td>
</tr>
<tr>
<td>p-NO2C6H4</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>p-NO2C6H4</td>
<td>97</td>
<td>88</td>
</tr>
<tr>
<td>p-NO2C6H4</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>m-NO2C6H4</td>
<td>95</td>
<td>66</td>
</tr>
<tr>
<td>2-Naphthyl</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>Furfural</td>
<td>84</td>
<td>88</td>
</tr>
</tbody>
</table>

Reactions were carried out at the given temperature under solvent-free conditions, unless stated otherwise, with 1.0 mol % catalyst using 1.0 eq of aldehyde to 1.2 eq of Danishefsky’s diene. Treatment with TFA, followed by column chromatography, afforded the corresponding dihydropyran.

1| Determined by HPLC with a Chiralpak OD column.
2| Isolated yield after column chromatography.
3| Reaction was carried out in 0.5 ml of dry DCM.

### Table 2. Diastereoselectivity in catalytic cycloaddition of 7 with aldehydes

<table>
<thead>
<tr>
<th>Aldehyde, R</th>
<th>ee, %</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2N-</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>O2N-</td>
<td>84</td>
<td>95</td>
</tr>
<tr>
<td>O2N-</td>
<td>97</td>
<td>96</td>
</tr>
</tbody>
</table>

Reactions were carried out at room temperature for 24 h, with 1.0 mol % catalyst in a solution of dry CH2Cl2 with 1.0 eq of aldehyde to 1.2 eq of 7. Treatment with TFA after 24 h, followed by column chromatography, afforded the corresponding dihydropyran.

* Determined by HPLC with a Chiralpak OD column.
† Isolated yield after column chromatography.
‡ Reaction was carried out in 0.5 ml of dry DCM.

---

Doyle et al.
The activation energy was calculated to be 21 kcal/mol for the reaction between p-nitrobenzaldehyde and Danishefsky’s diene catalyzed by Rh₂(4-MPPIM)₄. A Hammett plot versus σ⁺ was found to give a p value of +1.9 (R² = 0.97).

When the kinetic studies were carried out with different concentrations of catalyst 3 over a range of 0.2–5.0 mol % at 40 °C, an order of 1.4 was found from the linear display (R² = 0.9954), and at 60 °C over a range of 0.2–2.6 mol % the order was 0.8 (R² = 0.9837). When the same was done with catalyst 4 over a range of 0.2–3.0 mol %, the order with respect to catalyst 4 was 0.8 (R² = 0.9793). Evans (21) has shown that competitive inhibition of catalyst transfer in the transition state for cycloaddition. However, the causative agent for the order in catalysis is 3.49E-01.

In summary, the enantioselective HDA reaction between aromatic aldehydes and the Danishefsky diene catalyzed by 1.0 mol % of catalyst 5 at 60 °C is 3.49E-01 ± 0.003 s⁻¹M⁻². The order for this catalyst has also been examined at 25 °C, and at catalyst loadings between 0.2 mol % and 1.0 mol % the order is 2.2 (R² = 0.9913), which is consistent with preliminary evidence obtained by Jacobsen and coworkers (29) that this catalyst operates in a dimeric form.

No association was seen between chromium catalyst 5 and p-tolualdehyde via NMR spectral shifts, and no isosbestic point is seen in UV-visible spectroscopy like that found with dirhodium(II) carboxamidate catalyst 3 (Fig. 3). Similarly, no isosbestic point is seen with titanium(IV) catalyst 6 and p-anisaldehyde. Feng and Jiang (30) have reported no change in the ¹H NMR spectrum or IR spectrum between 6 and a 5-fold excess of benzaldehyde, also confirming that there is no measurable interaction between 6 and the aldehyde. However, there is a modest association between catalyst 6 and the Danishefsky diene of 1.1 M⁻¹ that could be related to the formation of the active species, described by Feng and Jiang (30), which catalyzes the HDA reaction via a Mukaiyama-aldol process.

In summary, the enantioselective HDA reaction between aromatic aldehydes and the Danishefsky diene can be effectively catalyzed by using dirhodium(II) carboxamidates under mild conditions and with uncommonly high turnover numbers. This process is a [4 + 2] cycloaddition reaction that occurs with characteristically high enantiocontrol. Kinetic measurements for reactions with para-substituted aromatic aldehydes show a pronounced electronic influence on the rate of the HDA reaction with a Hammett ρ value of +1.9. Electron-withdrawing p-nitrobenzaldehyde reacts >700 times faster than does electron-donating p-anisaldehyde. The variable reaction rate order with respect to the catalyst in dirhodium(II)-catalyzed reactions raises questions as to the exact role of the catalyst, but this may be related to considerations of competitive inhibition. However, dirhodium(II) catalysts uniquely offer the opportunity to investigate multiple mechanistic aspects of the Lewis acid-catalyzed HDA reaction under well-defined conditions.

Table 3. Experimental rate and equilibrium constants of the HDA reaction catalyzed by Rh₂(4-MPPIM)₄ at 60 °C in CHCl₃

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>10⁻³ kₐ</th>
<th>s⁻¹M⁻²</th>
<th>kₑ(ref)</th>
<th>Kₑ(eq)</th>
<th>M⁻¹⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-NO₂C₆H₄CHO</td>
<td>133</td>
<td>0.7</td>
<td>722</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>C₆H₅CHO</td>
<td>9.67</td>
<td>0.13</td>
<td>53</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>p-CIC₆H₄CHO</td>
<td>6.58</td>
<td>0.35</td>
<td>36</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>p-Ch₃C₆H₄CHO</td>
<td>0.866</td>
<td>0.166</td>
<td>5</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>p-MeOCC₆H₄CHO</td>
<td>0.184</td>
<td>0.074</td>
<td>1</td>
<td>74</td>
<td>5</td>
</tr>
</tbody>
</table>

The reactions were carried out at 60 °C in CHCl₃ with 1.0 mol % Rh₂(5-MPPIM)₄ and 1.0 eq of aldehyde to 10 eq of Danishefsky’s diene.

*The rate of the reaction for p-nitrobenzaldehyde and Danishefsky’s diene with no catalyst present at 60 °C is 1.66E-06 (1.66 × 10⁻⁶) s⁻¹M⁻¹.

We are grateful to the National Science Foundation and the National Institutes of Health (Grant GM-46503) for their support of this research. M.V. thanks Pfizer Global Research and Development for a 2003 Research Fellowship Supporting Diversity in Organic Chemistry.