Asymmetric approach to the pentacyclic skeleton of *Aspidosperma* alkaloids via enantioselective intramolecular 1,3-dipolar cycloaddition of carbonyl ylides catalyzed by chiral dirhodium(II) carboxylates

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Abstract: This paper describes asymmetric tandem carbonyl ylide formation–intramolecular 1,3-dipolar cycloaddition reaction of diazo imides containing a tethered indole catalyzed by chiral dirhodium(II) carboxylates as an approach to the pentacyclic skeleton of *Aspidosperma* alkaloids. The cycloaddition of carbonyl ylides derived from indolyl-substituted 2-diazo-5-imido-3-ketoesters under the influence of dirhodium(II) tetrakis([N-tetrachlorophthaloyl-((S)-tert-leucinate], Rh$_2$(S-TCPTTL)$_4$, provides cycloadducts in moderate yields and enantioselectivities of up to 66% ee as well as with perfect *endo* diastereoselectivity. This is the first example of asymmetric induction in an intramolecular cycloaddition of a carbonyl ylide across an indolyl $\pi$-bond.

Over the past four decades, *Aspidosperma* alkaloids have been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis. Efficient and elegant strategies for the total synthesis of various members of this alkaloid family have been reported.\(^1,2\) Padwa and co-workers demonstrated that the tandem cyclic carbonyl ylide formation–1,3-dipolar cycloaddition reaction\(^3\) of diazo imides catalyzed by Rh$_2$(OAc)$_4$ is one of the most powerful methods for the rapid construction of the pentacyclic ABCDE framework of (−)-vindoline (1)\(^4,5\) and (−)-vindorosine (2)\(^6,7\) (eq. 1).\(^8\) The same group has

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accomplished the total synthesis of (±)-aspidophytine\(^9\) employing an intramolecular 1,3-dipolar cycloaddition of carbonyl ylide across the indole \(\pi\)-bond.\(^{10}\)

\[\text{(Please Insert Eq. 1 here:)}\]

The synthetic utility of the carbonyl ylide cycloaddition strategy has also been demonstrated in its application to the synthesis of a variety of natural products.\(^{11}\) Over the past decade, considerable effort has been directed to the development of an enantioselective version of carbonyl ylide formation–1,3-dipolar cycloaddition catalyzed by chiral dirhodium(II) complexes.\(^{12-15}\) In this process, the chiral dirhodium(II) catalyst must be capable of associating with carbonyl ylide intermediates in the cycloaddition step, because catalyst-free carbonyl ylides are achiral. Hodgson and co-workers were the first to demonstrate high levels of asymmetric induction (up to 90% ee) in intramolecular cycloadditions of carbonyl ylides derived from unsaturated \(\alpha\)-diazo-\(\beta\)-ketoesters using binaphtholphosphate catalyst \(\text{Rh}_2(R\text{-DDBNP})_4\) (4) (Figure 1).\(^{13a-c,f,h,i}\) Recently, we reported catalytic enantioselective intermolecular cycloadditions of 2-diazo-3,6-diketoesters-derived carbonyl ylides with arylacetylene, alkoxyacetylene, and styrene dipolarophiles using \(\text{Rh}_2(S\text{-TCPTTL})_4\) (3a),\(^{16a,d,e}\) the chlorinated analogue of \(\text{Rh}_2(S\text{-PTTL})_4\) (3c),\(^{17}\) wherein high levels of asymmetric induction (up to 99% ee) as well as perfect \textit{exo} diastereoselectivity for styrenes were achieved.\(^{14d}\) In this context, our interest was centered on an asymmetric approach to the pentacyclic skeleton of 1 and 2 by means of chiral dirhodium(II) complex-catalyzed carbonyl ylide formation–intramolecular cycloaddition across an indolyl \(\pi\)-bond. To the best of our knowledge, no examples of an enantioselective version of this sequence have been identified to date.\(^{18}\) Herein, we report the first example of catalytic enantioselective intramolecular 1,3-dipolar cycloaddition of carbonyl ylides derived from indolyl-substituted 2-diazo-5-imido-3-ketoesters, wherein \(\text{Rh}_2(S\text{-TCPTTL})_4\) (3a) provides cycloadducts in up to 66% ee and with perfect \textit{endo} diastereoselectivity.

\[\text{(Please Insert Figure 1 here:)}\]

Our carbonyl ylide cycloaddition approach to 1 and 2 based on Padwa’s effective route to the pentacyclic framework of 1 and 2\(^8\) is illustrated in Scheme 1. The
construction of the D-ring would be achieved by ring-closing metathesis (RCM) of diene 5. It was anticipated that an ethyl group at C5 might be formed by ring opening of the cyclopropyl ketone. On the basis of Padwa’s work,\textsuperscript{8} we envisioned that Rh(II)-catalyzed reaction of indolyl-substituted 2-diazo-5-imido-3-ketoester 7 would provide endo cycloadduct 6. The carbonyl ylide precursor 7 could be formed through N-acylation of diazo amide 8a with N-methylindole-3-acetyl chloride (9).\textsuperscript{10} α-Diazo-β-ketoester 8a could be prepared from commercially available dimethyl 1,1-cyclopropanedicarboxylate (11).

((Please Insert Scheme 1 here:))

The carbonyl ylide cycloaddition precursors 7a–d were prepared from 11 as shown in Scheme 2. Selective saponification of 11 followed by condensation with allylamine via the acid chloride and saponification of the methyl ester provided carboxylic acid 10 in 63% yield. Treatment of 10 with 1,1′-carbonyldiimidazole (CDI) followed by reaction with the dianion derived from a variety of half esters of malonic acid afforded the corresponding β-ketoesters 12a–c in 85–90% yields.\textsuperscript{19} 2-Phenylethyl ester derivative 12d was prepared by transesterification of tert-butyl β-ketoester 12b with 2-phenylethanol.\textsuperscript{20} Diazot transfer to 12a–d with methanesulfonyl azide\textsuperscript{21} (for 12a and 12b) or p-acetamidebenzenesulfonyl azide\textsuperscript{22} (p-ABSA) (for 12c and 12d) using Et3N as a base in CH3CN gave α-diazo-β-ketoesters 8a–d in 78–85% yields. Since attempted coupling of diazo amides 8 with acid chloride 9 using a variety of bases resulted in the recovery of starting materials 8, we prepared diazo imides 7 according to the procedure of Weinstock.\textsuperscript{10,23} Thus, N-acylation of 8a–d with 9 in the presence of 4 Å molecular sieves (MS) as an acid scavenger in CH2Cl2 at reflux provided the desired diazo imides 7a–d in 54–70% yields.

((Please Insert Scheme 2 here:))

On the basis of our previous work,\textsuperscript{14d} we initially explored the reaction of methyl ester 7a using 1 mol % of Rh2(S-TCPTTL)4 (3a)\textsuperscript{16a,d,e} (Table 1, entry 1). The reaction in α,α,α-trifluorotoluene at 60 °C proceeded to completion within 1 h, giving endo cycloadduct 6a in 42% yield, along with 42% of bicyclic epoxide 13a.\textsuperscript{24} The endo
stereochemistry of 6a was established by the 1H NOE between the C5 cyclopropyl group proton and C14–H (Figure 2). The enantiomeric excess of 6a was determined to be 37% by HPLC using a Daicel Chiralcel OD-H column. The enantiomeric purity of epoxide 13a, [α]D<sub>22</sub> = –8.0 (c 0.80, CHCl<sub>3</sub>), was not determined. Transformation of epoxide 13a to cycloadduct 6a under the same conditions did not occur, suggesting that the cycloaddition did not proceed via formation of epoxide 13 as an intermediate. We next examined the effect of the ester moiety. The use of tert-butyl ester 7b increased the product yield at the expense of enantioselectivity (66% yield, 20% ee, entry 2). Gratifyingly, the use of benzyl ester 7c greatly improved the enantioselectivity to provide cycloadduct 6c in 50% yield with 63% ee (entry 3), whereas a low level of asymmetric induction was obtained in the reaction of 2-phenylethyl ester 7d (36% ee, entry 4). Using the benzyl ester 7c, we then evaluated the performance of Rh₂(S-TFPTTL)₄ (3b) and Rh₂(S-PTTL)₄ (3c). Catalysis with Rh₂(S-TFPTTL)₄ (3b) exhibited lower product yield and enantioselectivity than those found with Rh₂(S-TCPTTL)₄ (3a) (42% yield, 53% ee, entry 5). The use of Rh₂(S-PTTL)₄ (3c) enhanced the product yield, but there was a marked decrease in enantioselectivity (55% yield, 22% ee, entry 6). A survey of solvents with 3a revealed that α,α,α-trifluorotoluene was the optimal solvent for this cycloaddition in terms of both product yield and enantioselectivity (entry 3 vs entries 7 and 8). Lowering the reaction temperature to 40 °C led to a modest improvement in enantioselectivity, though a slight drop in product yield was observed (43% yield, 66% ee, entry 9). The reaction at 80 °C resulted in a decrease in enantioselectivity with the same product yield (50% yield, 57% ee, entry 10).

While there was clearly room for improvement, we next examined the cyclopropane ring opening of cycloadduct 6c (Scheme 3). After considerable experimentation, we found that treatment of 6c with trimethylsilyl iodide (TMSI) led to the formation of tetracyclic compound 14 in 76% yield. The conversion of 6c to 14 involving cleavage of the cyclopropane bond and oxabicyclic ring may proceed via formation of an intermediate N-acyl iminium ion followed by nucleophilic attack of iodide ion on the
cyclopropane ring. Reductive removal of the iodine atom in 14 with Zn–Cu and acetic acid provided enamidone 15 in 81% yield.28

In summary, we have demonstrated the first example of asymmetric induction (up to 66% ee) in an intramolecular 1,3-dipolar cycloaddition of carbonyl ylides derived from the diazo decomposition of indolyl-substituted 2-diazo-5-imido-3-ketoesters under the influence of Rh2(S-TCPTTL)4. We have also achieved a sequential opening of cyclopropane and oxabicyclic rings with TMSI, forming the [6.5.6.5]-ABCE ring system of vindorosine. Efforts directed at improving the enantioselectivity and product yield as well as the total synthesis of (−)-vindorosine are currently in progress.

Acknowledgments

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Supplemental data

Supplementary data associated with this article can be found, in the online version, at doi:

References and notes


6. For total synthesis of (±)-vindorosine, see: Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* 1971, 93, 3299–3301. See also ref 4c.


18. Muthusamy and co-workers reported Rh2(OAc)4-catalyzed intermolecular cycloaddition of carbonyl ylides with indoles as dipolarophiles. (a) Muthusamy, S.; Gunanathan, C.; Babu, S.


24. Padwa and Curtis reported that ester-carbonyl ylide dipoles derived from \(\alpha\)-diazo-\(\beta\)-ketoesters underwent dimerization to furnish head to tail dimers. Padwa, A.; Curtis, E. A. ARKIVOC 2001, (ii), 51–60. Although compound 13 seemed to be dimer, we assigned 13 as a bicyclic epoxide on the basis of spectroscopic data (\(^1\)H and \(^{13}\)C NMR, IR, and ESI-HRMS). See Supplementary data.

25. The preferred absolute stereochemistry of cycloadducts 6a–d was not determined.


27. Padwa and Mejia-Oneto reported that BF\(_3\)\(\cdot\)OEt\(_2\)-promoted opening of an oxabicyclic ring led to the formation of a transient \(N\)-acyl iminium ion. See ref 10.

Legends for Figure 1

[Please insert Graphic for Figure 1]

**Figure 1.** Chiral dirhodium(II) catalysts.

Legends for Figure 2

[Please insert Graphic for Figure 2]

**Figure 2.** Key NOE interactions for cycloadduct 6a.

Legends for Scheme 1

[Please insert Graphic for Scheme 1]

**Scheme 1.** Synthetic strategy.

Legends for Scheme 2

[Please insert Graphic for Scheme 2]

**Scheme 2.** Reagents and conditions: (a) KOH, MeOH–H₂O (3:1), 3 h; (b) SOCl₂, CH₂Cl₂, reflux, 1 h; (c) allylamine, Et₃N, CH₂Cl₂, 0 °C, 0.5 h; (d) KOH, MeOH–H₂O (3:1), 2 h, 63% (4 steps); (e) CDI (1.1 equiv), THF, 1 h; (f) i-PrMgBr, RO₂CCH₂CO₂H, THF, 0.5–4 h, 85–90% (2 steps); (g) PhCH₂CH₂OH (3 equiv), toluene, 110 °C, 2 h, 76%; (h) MsN₃ (for 12a and 12b) or p-ABSA (for 12c and 12d), Et₃N, CH₃CN, 30 min, 78–85%; (i) 4 Å MS (powder), CH₂Cl₂, reflux, 15–24 h, 54–70%.
Legends for Scheme 3

[Please insert Graphic for Scheme 3]

Scheme 3. Reagents and conditions: (a) TMSI (1.5 equiv), CH$_3$CN, 10 min, 76%; (b) Zn–Cu, AcOH, MeOH–Et$_2$O (1:1), 1 h, 81%.

Table 1:

Table 1
Enantioselective intramolecular 1,3-dipolar cycloaddition of 2-diazo-5-imido-3-ketoesters 7a–d catalyzed by chiral dirhodium(II) carboxylates$^a$

[Please insert Graphic for Table 1]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazo imide 7</th>
<th>Rh(II) catalyst</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Cycloadduct 6 Yield$^b$ (%) ee$^c$ (%)</th>
<th>Epoxide 13 Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>Me</td>
<td>60</td>
<td>1</td>
<td>6a 42 37</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>t-Bu</td>
<td>60</td>
<td>1</td>
<td>6b 66 20</td>
</tr>
<tr>
<td>3</td>
<td>7c</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>Bn</td>
<td>60</td>
<td>1</td>
<td>6c 50 63</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>PhCH$_2$CH$_2$</td>
<td>60</td>
<td>1</td>
<td>6d 48 36</td>
</tr>
<tr>
<td>5</td>
<td>7e</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>Bn</td>
<td>60</td>
<td>1</td>
<td>6e 55 22</td>
</tr>
<tr>
<td>7</td>
<td>7e</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>Toluene</td>
<td>60</td>
<td>1</td>
<td>6e 44 60</td>
</tr>
<tr>
<td>8</td>
<td>7e</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>(CH$_2$Cl)$_2$</td>
<td>60</td>
<td>2</td>
<td>6e 42 44</td>
</tr>
<tr>
<td>9</td>
<td>7e</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>CF$_3$C$_6$H$_5$</td>
<td>40</td>
<td>3</td>
<td>6e 43 66</td>
</tr>
<tr>
<td>10</td>
<td>7e</td>
<td>PhCH$_2$CH$_2$</td>
<td>Rh$_2$(S-TCPTTL)$_2$(3a)</td>
<td>CF$_3$C$_6$H$_5$</td>
<td>80</td>
<td>1</td>
<td>6e 50 57</td>
</tr>
</tbody>
</table>

$^a$ All reactions were carried out as follows: a solution of 7 (0.1 mmol) in the indicated solvent (1 mL) was added over 5 min to a solution of Rh(II) catalyst (1 mol %) in the indicated solvent (1 mL) at the indicated temperature.

$^b$ Isolated yield.

$^c$ Determined by HPLC.
Graphic for Eq. 1:

\[
\text{Rh}_2(\text{OAc})_4 \xrightarrow{\text{benzene}, 50 \degree \text{C}} \end{equation}
\]

\[
\text{R} = \text{OMe}: (-)-\text{vindoline (1)}
\]

\[
\text{R} = \text{H}: (-)-\text{vindorosine (2)}
\]
Graphic for Figure 1:

\[
\begin{align*}
X &= \text{Cl: } \text{Rh}_2(S\text{-TCPTTL})_4 \text{ (3a)} \\
X &= \text{F: } \text{Rh}_2(S\text{-TFPTTL})_4 \text{ (3b)} \\
X &= \text{H: } \text{Rh}_2(S\text{-PTTL})_4 \text{ (3c)} \\
\end{align*}
\]
Graphic for Figure 2:
Graphic for Scheme 1:

R = OMe: (–)-vindoline (1)
R = H: (–)-vindorosine (2)
Graphic for Scheme 2:

\[ \text{MeO}_2\text{CCHO}_2\text{Me} \overset{a-d}{\rightarrow} \text{HO}_2\text{C} \overset{e,f}{\rightarrow} \]

\[ \text{RO}_2\text{C} \overset{h}{\rightarrow} \text{RO}_2\text{C} \]

\[ \text{g} \]

\[ 8a-d + \begin{array}{c} \text{I} \\ \text{Me} \\ \text{9 (1.2 equiv)} \end{array} \overset{i}{\rightarrow} \begin{array}{c} \text{Me} \\ \text{N}_2\text{CO}_2\text{R} \end{array} \]

\[ 12a: R = \text{Me} \\
12b: R = \text{t-Bu} \\
12c: R = \text{Bn} \\
12d: R = \text{PhCH}_2\text{CH}_2 \]
Graphic for Scheme 3:

6c (66% ee)

14: R = I
15: R = H
Graphic for Table 1:

\[
\text{Rh}_2(\text{S-TCPTTL})_4 (1 \text{ mol} \%) + \text{MeO} \rightarrow \text{Me}_2 \text{H}_6 \text{endo} + \text{Me}_{137} \text{RhO}_2 \text{C}
\]