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 π-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 π-bond.[10]

((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 α-diazo-β-ketoesters using binaphtholphosphate catalyst Rh_2(*R*-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 Rh_2(*S*-TCPTTL)$_4$ (**3a**),[16a,d,e] the chlorinated analogue of Rh_2(*S*-PTTL)$_4$ (**3c**),[17] wherein high levels of asymmetric induction (up to 99% ee) as well as perfect *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 π-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 Rh_2(*S*-TCPTTL)$_4$ (**3a**) provides cycloadducts in up to 66% ee and with perfect *endo* diastereoselectivity.

((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,[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**).[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.[19] 2-Phenylethyl ester derivative **12d** was prepared by transesterification of *tert*-butyl β-ketoester **12b** with 2-phenylethanol.[20] Diazo transfer to **12a**–**d** with methanesulfonyl azide[21] (for **12a** and **12b**) or *p*-acetamidebenzenesulfonyl azide[22] (*p*-ABSA) (for **12c** and **12d**) using Et_3N as a base in CH_3CN 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.[10,23] Thus, N-acylation of **8a**–**d** with **9** in the presence of 4 Å molecular sieves (MS) as an acid scavenger in CH_2Cl_2 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,[14d] we initially explored the reaction of methyl ester **7a** using 1 mol % of Rh_2(*S*-TCPTTL)$_4$ (**3a**)[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**.[24] The *endo*

stereochemistry of **6a** was established by the ^{1}H 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.[25] The enantiomeric purity of epoxide **13a**, $[\alpha]_D^{22}$ −8.0 (*c* 0.80, $CHCl_3$), 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 Rh_2(*S*-TFPTTL)$_4$ (**3b**)[16b,c] and Rh_2(*S*-PTTL)$_4$ (**3c**).[17] Catalysis with Rh_2(*S*-TFPTTL)$_4$ (**3b**) exhibited lower product yield and enantioselectivity than those found with Rh_2(*S*-TCPTTL)$_4$ (**3a**) (42% yield, 53% ee, entry 5). The use of Rh_2(*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).

((Please Insert Table 1 here:))

((Please Insert Figure 2 here:))

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)[26] 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[27] 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]

((Please Insert Scheme 3 here:))

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 Rh_2(*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.

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Supplemental data

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

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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–H_2O (3:1), 3 h; (b) $SOCl_2$, CH_2Cl_2, reflux, 1 h; (c) allylamine, Et_3N, CH_2Cl_2, 0 °C, 0.5 h; (d) KOH, MeOH–H_2O (3:1), 2 h, 63% (4 steps); (e) CDI (1.1 equiv), THF, 1 h; (f) *i*-PrMgBr, $RO_2CCH_2CO_2H$, THF, 0.5–4 h, 85–90% (2 steps); (g) $PhCH_2CH_2OH$ (3 equiv), toluene, 110 °C, 2 h, 76%; (h) MsN_3 (for **12a** and **12b**) or *p*-ABSA (for **12c** and **12d**), Et_3N, CH_3CN, 30 min, 78–85%; (i) 4 Å MS (powder), CH_2Cl_2, 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_3CN, 10 min, 76%; (b) Zn–Cu, AcOH, MeOH–Et_2O (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]

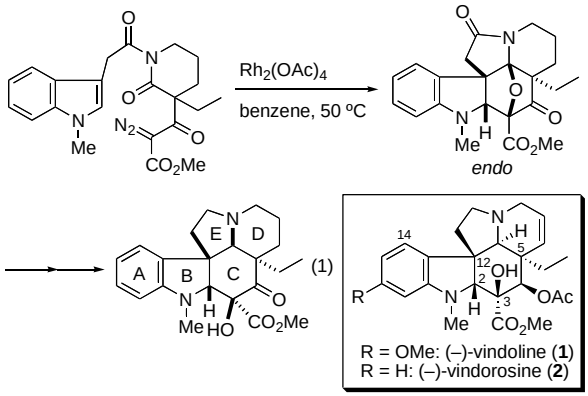
Entry	Diazo imide **7**		Rh(II) catalyst	Solvent	Temp (°C)	Time (h)	Cycloadduct **6**			Epoxide **13**	
		R						Yield[b] (%)	ee[c] (%)		Yield[b] (%)
1	**7a**	Me	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	60	1	**6a**	42	37	**13a**	42
2	**7b**	*t*-Bu	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	60	1	**6b**	66	20	**13b**	trace
3	**7c**	Bn	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	60	1	**6c**	50	63	**13c**	27
4	**7d**	$PhCH_2CH_2$	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	60	1	**6d**	48	36	**13d**	37
5	**7c**	Bn	Rh_2(S-TFPTTL)$_4$ (**3b**)	$CF_3C_6H_5$	60	1	**6c**	42	53	**13c**	4
6	**7c**	Bn	Rh_2(S-PTTL)$_4$ (**3c**)	$CF_3C_6H_5$	60	1	**6c**	55	22	**13c**	16
7	**7c**	Bn	Rh_2(S-TCPTTL)$_4$ (**3a**)	Toluene	60	1	**6c**	44	60	**13c**	21
8	**7c**	Bn	Rh_2(S-TCPTTL)$_4$ (**3a**)	$(CH_2Cl)_2$	60	2	**6c**	42	44	**13c**	17
9	**7c**	Bn	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	40	3	**6c**	43	66	**13c**	34
10	**7c**	Bn	Rh_2(S-TCPTTL)$_4$ (**3a**)	$CF_3C_6H_5$	80	1	**6c**	50	57	**13c**	23

[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.

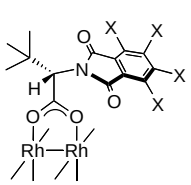
[b] Isolated yield.

[c] Determined by HPLC.

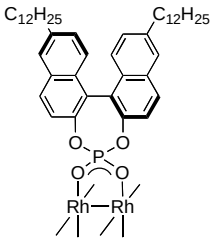
Graphic for Eq. 1:



Graphic for Figure 1:

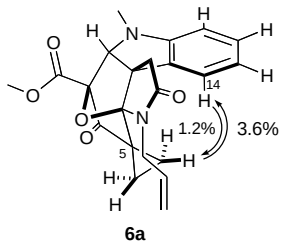


X = Cl: Rh_2(*S*-TCPTTL)$_4$ (**3a**)
X = F: Rh_2(*S*-TFPTTL)$_4$ (**3b**)
X = H: Rh_2(*S*-PTTL)$_4$ (**3c**)



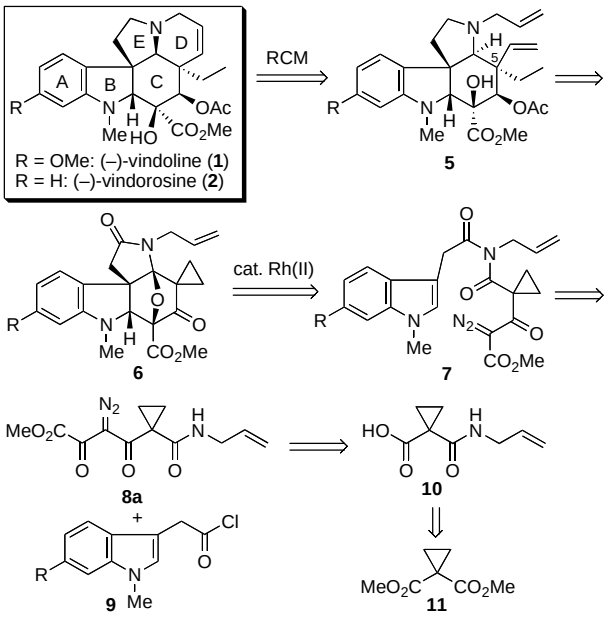
Rh_2(*R*-DDBNP)$_4$ (**4**)

Graphic for Figure 2:

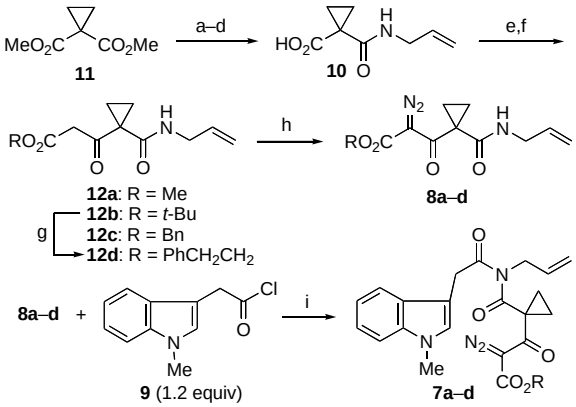


6a

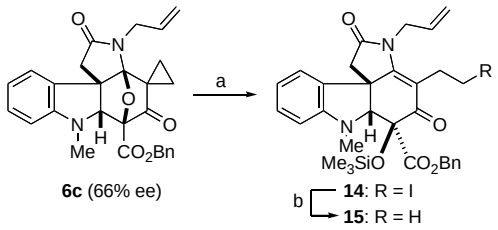
Graphic for Scheme 1:



Graphic for Scheme 2:



Graphic for Scheme 3:



6c (66% ee)

Graphic for Table 1: