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Notes

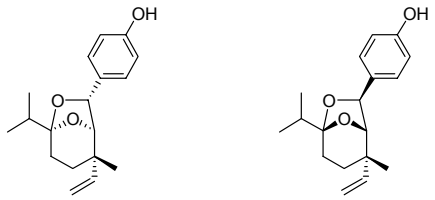
Catalytic Asymmetric Construction of the *exo*-7-Aryl-6,8-dioxabicyclo[3.2.1]octane Framework of Psoracorylifols B and C Using a Carbonyl Ylide Cycloaddition Strategy†

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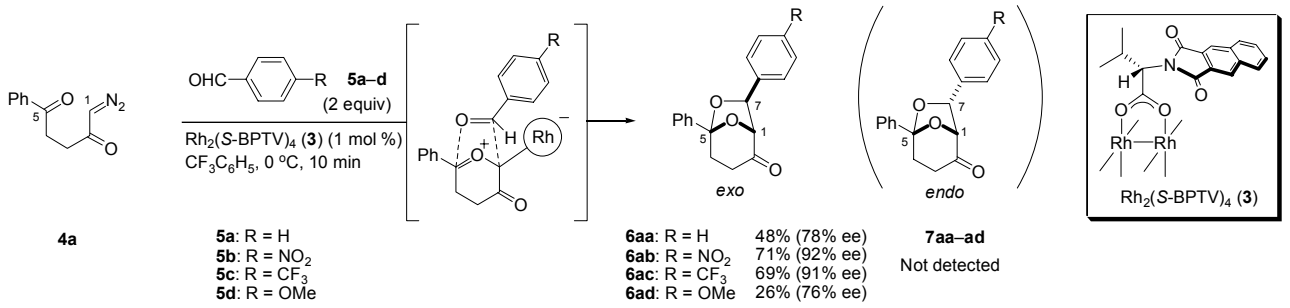
Key Words: Asymmetric reaction, 1,3-Dipolar cycloaddition, Carbonyl ylides, Chiral dirhodium(II) carboxylates, Aldehydes

Psoracorylifols A-E were isolated from the seeds of *Psoralea corylifolia* L., which is a well-known traditional Chinese medicine, by Yue and co-workers in 2006.[1] These compounds have been shown to exhibit significant inhibitory activity against two strains of *Helicobacter pylori* (SS1 and ATCC 43504) at the level of MICs of 12.5 ~ 25 μg/mL, especially against *H. pylori*-ATCC 43504, a drug-resistant strain with MIC of 128 μg/mL to resist metroniazole. In 2007, Yoshikawa and co-workers independently isolated psoracorylifols B (**1**) and C (**2**), possessing a 6,8-dioxabicyclo[3.2.1]octane ring system, from the same seeds.[2]



psoracorylifol B (**1**) psoracorylifol C (**2**)

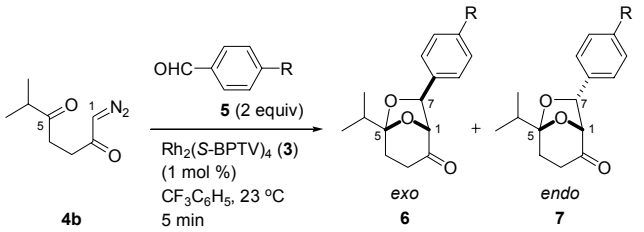
The 6,8-dioxabicyclo[3.2.1]octane skeleton is a common structural subunit in many biologically active natural products.[3] Among a variety of synthetic routes to such bicyclic ketals,[4] the dirhodium(II)-catalyzed tandem six-membered cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction of α-diazocarbonyl compounds with aldehydes as dipolarophiles[5,6] is one of the most direct and powerful methods for the construction of this ring system. As a seminal work, Padwa and co-workers reported a concise synthesis of *exo*- and *endo*-brevicomins employing the cycloaddition of a six-membered carbonyl ylide derived from 1-diazo-2,5-hexanedione with propionaldehyde in the presence of a catalytic amount of $Rh_2(OAc)_4$.[6d,e] Consequently, the development of an enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes has become a challenging objective. In this process, the chiral dirhodium(II) catalyst must be capable of associating with carbonyl ylide intermediates in the cycloaddition step,[7-9] because catalyst-free carbonyl ylides are achiral.[10] Recently, we reported catalytic enantioselective 1,3-dipolar cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-5-phenyl-2,5-pentanedione (**4a**) with aromatic aldehydes **5a-d** using dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-valinate], Rh_2(*S*-BPTV)$_4$ (**3**), in which electron-deficient dipolarophiles such as **5b** and **5c** provided exclusively *exo* cycloadducts **6ab** and **6ac** in good yields and with up to 92% ee (Scheme 1).[11] As a logical extension of our studies, we addressed a catalytic asymmetric construction of the *exo*-7-aryl-6,8-dioxabicyclo[3.2.1]octane framework of psoracorylifols B (**1**) and C (**2**). Herein, we report *exo*- and enantioselective cycloadditions of a six-membered carbonyl ylide derived from 1-diazo-6-methyl-2,5-heptanedione (**4b**) with aromatic aldehydes under the catalysis of Rh_2(*S*-BPTV)$_4$



Scheme 1. Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of **4a** with **5a-d** catalyzed by Rh_2(*S*-BPTV)$_4$ (**3**)

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.

Table 1. Enantioselective cycloaddition of **4b** with aldehydes **5a**, **b**, **d-h** catalyzed by Rh_2(*S*-BPTV)$_4$ (**3**)



entry	aldehyde		cycloadduct			
		R		yield (%)[a]	**6**:**7**[b]	ee of **6** (%)
1	**5a**	H	**6ba**+**7ba**	62	91:9	79[c]
2	**5b**	NO_2	**6bb**+**7bb**	63	93:7	30[d]
3	**5e**	OMs	**6be**+**7be**	72	95:5	74[d]
4	**5f**	OAc	**6bf**+**7bf**	63	94:6	77[e]
5	**5d**	OMe	**6bd**+**7bd**	57	94:6	87[e]
6	**5g**	OMOM	**6bg**+**7bg**	60	94:6	87[e]
7	**5h**	OBn	**6bh**+**7bh**	64	95:5	86[e]

[a]Combined yield of **6** and **7**. [b]Determined by ^{1}H NMR analysis of the crude product. [c]Determined by HPLC (Daicel Chiralpak IC). [d]Determined by HPLC (Daicel Chiralpak IA). [e]Determined by HPLC (Daicel Chiralpak AD-H).

(**3**), in which high levels of asymmetric induction (up to 87% ee) have been achieved by the use of electron-rich aromatic aldehydes.

On the basis of our previous work,[11] we initially explored the tandem carbonyl ylide formation/1,3-dipolar cycloaddition reaction of **4b** bearing an isopropyl substituent at C5 with benzaldehyde (**5a**) (2 equiv) using 1 mol % of Rh_2(*S*-BPTV)$_4$ (**3**) in benzotrifluoride at 23 °C (Table 1, entry 1). The reaction proceeded smoothly to completion in less than 5 min, giving *exo* and *endo* cycloadducts **6ba** and **7ba** in 62% combined yield. The assignment of *exo* and *endo* cycloadducts was made upon inspection of the ^{1}H NMR spectrum; the ratio of *exo* cycloadduct **6ba** (singlets at 4.44 and 5.04 ppm for the bridgehead H1 and benzylic H7 protons without any coupling) and *endo* cycloadduct **7ba** (doublets at 4.66 and 5.27 ppm for the bridgehead H1 and benzylic H7 protons with a coupling constant of J = 5.4 Hz) was determined to be 91:9 by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric excess of the *exo* isomer **6ba** was determined to be 79% by HPLC using Daicel Chiralpak IC column. Unexpectedly from the results with α-diazo ketone **4a** bearing a phenyl substituent at C5,[11] switching the dipolarophile from benzaldehyde to *p*-nitrobenzaldehyde (**5b**) significantly diminished the enantioselectivity for the *exo* isomer **6bb** (30% ee, entry 2), though little variation in combined yield or *exo*-selectivity was observed.

Since psoracorylifols B (**1**) and C (**2**) contain a hydroxy group at the *para* position on the benzene ring, we next explored the reaction of **4b** with a variety of protected *p*-hydroxybenzaldehyde derivatives **5d-h** as dipolarophiles. We found that the use of electron-poor aromatic aldehydes **5e** and **5f** carrying *p*-mesylate or acetate groups led to slightly lower enantioselectivities than that with benzaldehyde (74% and 77% ee, entries 3 and 4), whereas the reaction with an electron-rich *p*-methoxybenzaldehyde (**5d**) provided a 94:6 mixture of *exo* and *endo* cycloadducts **6bd** and **7bd** in 57% yield with 87% ee for **6bd** (entry 6). Thus, we then examined the reaction of *p*-hydroxybenzaldehyde derivatives **5g** and **5h** protected as more easily removable methoxymethyl (MOM) or benzyl (Bn) ethers. Gratifyingly, the use of these dipolarophiles **5g** and **5h** afforded the corresponding *exo* cycloadducts **6bg** and **6bh** in similar good yields and high enantioselectivities as those found with **5d** (87% and 86% ee, entries 7 and 8). While the discrepancy in reaction mode between carbonyl ylide cycloadditions of **4a** and **4b** with aromatic aldehydes remains to be elucidated, it is noteworthy that electron-rich and electron-poor aromatic aldehyde dipolarophiles can complement each other in this type of cycloaddition process.

In summary, we have achieved a highly efficient, catalytic asymmetric construction of the *exo*-7-aryl-6,8-dioxabicyclo-[3.2.1]octane framework of psoracorylifols B and C using the 1,3-dipolar cycloaddition reaction of a six-membered carbonyl ylide derived from 1-diazo-6-methyl-2,5-heptanedione with electron-rich aromatic aldehydes under the influence of Rh_2(*S*-BPTV)$_4$. This work, together with the previous finding, demonstrates that the extent of asymmetric induction is highly sensitive to both the substitution pattern (aryl or alkyl substituents) at the ylide carbonyl and the electronic nature of aromatic aldehyde dipolarophiles. Further efforts toward the total synthesis of psoracorylifols B and C are currently underway.

Experimental Section

Representative procedure for the tandem carbonyl ylide formation/1,3-dipolar cycloaddition (entry 7 in Table 1). Rh_2(*S*-BPTV)$_4$·2THF (3.1 mg, 0.002 mmol, 1 mol %) was added in one portion to a solution of **4b** (33.6 mg, 0.20 mmol) and **5h** (84.9 mg, 0.40 mmol) in benzotrifluoride (2.0 mL) at 23 °C. After stirring for 5 min, the mixture was concentrated in vacuo. The ratio of **6bh** and **7bh** was determined to be 95:5 by ^{1}H NMR of the crude product. The residue was purified by column chromatography (silica gel, 1:2 hexane/benzene → 10:1 hexane/Et_2O) to give *exo*-7-(4-benzyloxyphenyl)-5-isopropyl-6,8-dioxabicyclo[3.2.1]octan-2-one (**6bh**) (43.3 mg, 0.123 mmol, 62%) as a white solid, along with *endo* isomer **7bh** (1.6 mg, 0.04 mmol, 2%) as a white solid. **6bh**: TLC R_f 0.21 (4:1 hexane/EtOAc); mp 51.5 ~ 53.0 °C for 86% ee; $[\alpha]_D^{20}$ −37.5 (*c* 1.01, $CHCl_3$) for 86% ee; IR (neat) ν 2968, 1733, 1611, 1585, 1243 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, J = 6.9 Hz, 3H, $CH(CH_3)_2$), 1.10 (d, J = 6.9 Hz, 3H, $CH(CH_3)_2$), 2.09 (ddd, J = 4.6, 8.0, 13.8 Hz, 1H, CH_2), 2.24 (heptet, J = 6.9 Hz, 1H, $CH(CH_3)_2$), 2.26 (m, 1H, CH_2), 2.54 (dddd, J = 1.2, 4.6, 8.0, 16.0 Hz, 1H, $COCH_2C$), 2.61 (ddd, J = 8.0, 8.0, 16.0 Hz, 1H, CH_2), 4.41 (s, 1H, COC*H*), 4.98 (s, 1H, ArC*H*), 5.06 (s, 2H, $PhCH_2O$), 6.95 (d, J = 8.6 Hz, 2H, *Ar*), 7.29 (d, J = 8.6 Hz, 2H, *Ar*), 7.32-7.43 (m, 5H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6 (CH_3), 17.9 (CH_3), 28.7 (CH_2), 32.5 (CH_2), 35.6 (CH), 70.0 (CH_2), 79.4 (CH), 86.4 (CH), 112.6 (C), 114.8 (CH), 127.4 (CH), 127.6 (CH), 128.0 (CH), 128.6 (CH), 132.5 (C), 136.8

(C), 158.7 (C), 206.7 (C); EI-HRMS calcd for $C_{22}H_{24}O_4$ (M^+) 352.1675, found 352.1673. **7bh**: TLC R_f 0.30 (4:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, J = 7.3 Hz, 3H, $CH(CH_3)_2$), 1.12 (d, J = 7.3 Hz, 3H, $CH(CH_3)_2$), 2.11-2.22 (m, 4H, CH_2, $CH(CH_3)_2$), 2.37 (m, 1H, CH_2), 4.61 (dd, J = 1.4, 5.4 Hz, 1H, COC*H*), 5.03 (s, 2H, $PhCH_2O$), 5.21 (d, J = 5.4 Hz, 1H, ArC*H*), 6.93 (d, J = 8.6 Hz, 2H, *Ar*), 7.23 (d, J = 8.6 Hz, 2H, *Ar*), 7.33-7.43 (m, 5H, *Ar*).

The enantiomeric excess of **6bh** was determined to be 86% by HPLC using a Daicel Chiralpak AD-H column (19:1 hexane/2-propanol, flow rate: 1.0 mL/min; detection: 230 nm): retention time: 14.4 min (major enantiomer), 17.3 min (minor enantiomer).

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