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Catalytic Enantioselective Tandem Carbonyl Ylide Formation/1,3-Dipolar Cycloaddition Reactions of α-Diazo Ketones with Aromatic Aldehydes using Dirhodium(II) Tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-valinate]

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

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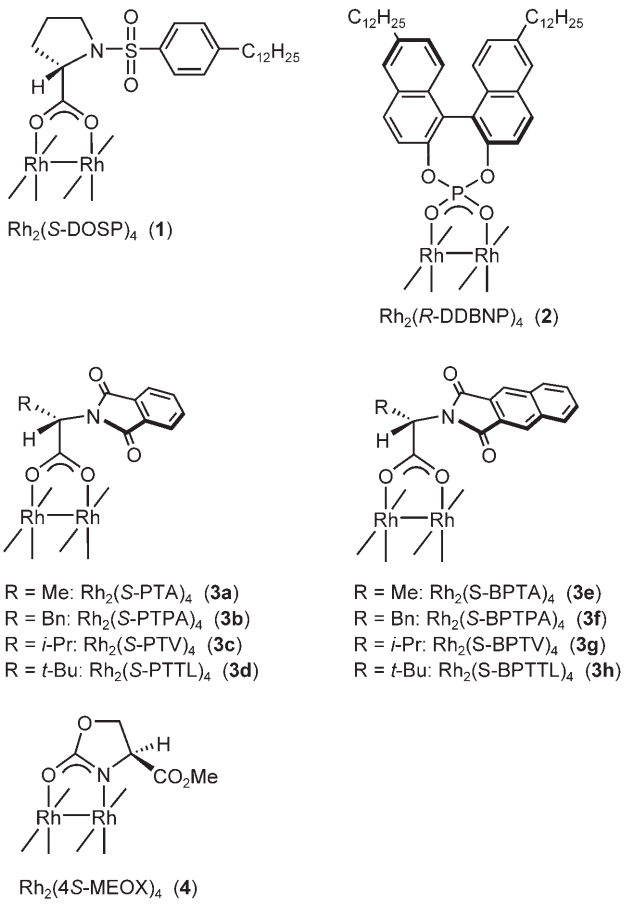
Abstract: The first successful example of the enantioselective intermolecular 1,3-dipolar cycloaddition of a chiral dirhodium(II) catalyst-associated carbonyl ylide with an aromatic aldehyde dipolarophile is described. The tandem carbonyl ylide formation/cycloaddition reactions of 1-diazo-5-aryl-2,5-pentanediones with aromatic aldehydes using dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-valinate] as a catalyst provide exclusively *exo* cycloadducts in up to 92% *ee*.

Keywords: aldehydes; asymmetric catalysis; carbonyl ylides; chiral dirhodium(II) carboxylates; α-diazo ketones; 1,3-dipolar cycloaddition

Rhodium(II)-catalyzed tandem carbonyl ylide formation/1,3-dipolar cycloaddition reactions of α-diazocarbonyl compounds with a range of dipolarophiles, developed and extensively advanced by the Padwa group, have become an attractive and effective method for the construction of complex oxapolycyclic systems containing embedded di- or tetrahydrofuran rings.[1] The exceptional power of the carbonyl ylide cycloaddition strategy has recently been demonstrated by a growing number of syntheses of diverse natural products such as brevicomin,[2] illudins,[3] phorbol esters,[4] zaragozic acids,[5] epoxysorbicillinol,[6] colchicine,[7] nemorensic acids,[8] aspidophytine,[9] pseudolaric acid[10] and polygalolides.[11] Consequently, the development of a catalytic enantioselective version of this sequence has become a challenging objective. Although high levels of enantiocontrol in C–H insertions and cyclopropanations have been achieved in a number of systems using well-designed dirhodium(II) carboxylate and carboxamidate catalysts,[12] such enantioselective transformations are relatively underdeveloped. In this process, a prime requirement for asymmetric induction is the use of chiral dirhodium(II) catalyst-associated carbonyl ylide intermediates in the cycloaddition step, because the catalyst-free carbonyl ylides are achiral and the reactions lead to the formation of racemic products. In 1997, Hodgson and co-workers demonstrated the first example of asymmetric induction (up to 52% *ee*) in the tandem carbonyl ylide formation/intramolecular cycloaddition of unsaturated 2-diazo-3,6-diketo esters using Davies' prolinate catalyst Rh_2(*S*-DOSP)$_4$ (**1**)[13] (Scheme 1).[14] They subsequently reported high levels of enantioselection (up to 90% *ee*) when the dirhodium(II) binaphtholphosphate catalyst Rh_2(*R*-DDBNP)$_4$ (**2**) was used.[15] Using Rh_2(*R*-DDBNP)$_4$, they recently achieved a significant asymmetric induction (up to 92% *ee*) in the intermolecular cycloadditions of 2-diazo-3,6-diketo ester-derived carbonyl ylides with strained alkene dipolarophiles.[16] In 1999, we demonstrated the first successful examples of the catalytic enantioselective intermolecular cycloaddition of carbonyl ylides derived from α-diazo ketones with dimethyl acetylenedicarboxylate (DMAD) using dirhodium(II) tetrakis[*N*-benzene-fused-phthaloyl-(*S*)-valinate], Rh_2(*S*-BPTV)$_4$ (**3g**), where significant enantiomeric excesses (up to 92% *ee*) were achieved.[17] We also reported high levels of enantioselection (up to

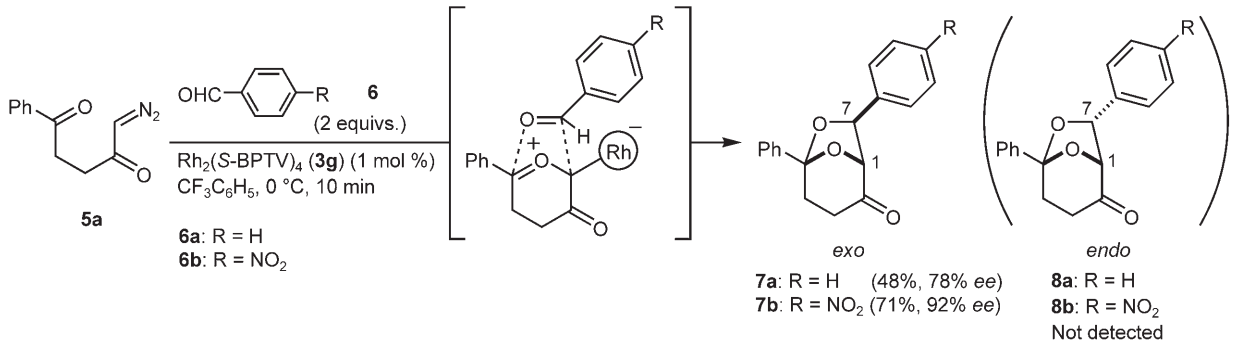


Scheme 1. Chiral dirhodium(II) complexes.

93% *ee*) for the intermolecular cycloaddition of ester-derived carbonyl ylides with DMAD using dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**3d**).[18] However, the reactions have serious limitations in that the nature of the dipolarophiles has a profound effect on enantioselectivity as well as the efficiency of the cycloaddition, in which only DMAD has met with success. In continuation of our interest in expanding the scope of the reaction with respect to the type of dipolarophiles, we herein report the first successful examples of enantioselective intermolecular carbonyl ylide cycloadditions with aromatic aldehydes as dipolarophiles, in which Rh_2(*S*-BPTV)$_4$ (**3g**) provides the *exo* cycloadducts exclusively, in up to 92% *ee*.

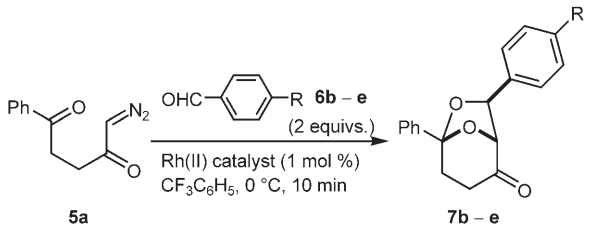
Only two examples of the catalytic enantioselective 1,3-dipolar cycloaddition of carbonyl ylides with aldehydes as a dipolarophile have been reported.[2,5a–c,19] Doyle and co-workers reported that the tandem intermolecular carbonyl ylide formation/cycloaddition of ethyl diazoacetate and *p*-nitrobenzaldehyde in the presence of the chiral dirhodium(II) carboxamidate catalyst Rh_2(4*S*-MEOX)$_4$ (**4**) afforded the all-*cis* trisubstituted 1,3-dioxolane as the major product with 28% *ee*.[20] Suga and co-workers developed a conceptually different approach and demonstrated highly enantioselective 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olate generated from the $Rh_2(OAc)_4$-catalyzed decomposition of *o*-methoxycarbonyl-α-diazoacetophenone with several benzyloxyacetaldehyde derivatives using the Sc(III)-Pybox-*i*-Pr complex as a chiral Lewis acid catalyst, in which *endo* cycloadducts were obtained as the major product in up to 93% *ee*.[21]

Following our previous work, we initially explored the formation of a six-membered cyclic carbonyl ylide from 1-diazo-5-phenyl-2,5-pentanedione (**5a**) and the subsequent cycloaddition with benzaldehyde (**6a**) (2 equivs.) using 1 mol% of Rh_2(*S*-BPTV)$_4$ (**3g**) in benzotrifluoride at 0 °C (Scheme 2). The reaction proceeded to completion within 10 min, giving the *exo* cycloadduct **7a**[2a] as the sole product in 48% yield. The assignment of *exo* cycloaddition was made upon inspection of the ^{1}H NMR spectrum; the bridgehead H-1 and benzylic H-7 protons of **7a** appeared as singlets at 4.49 and 5.29 ppm without any coupling. No evidence for the *endo* cycloadduct **8a** (doublets at 4.86 and 5.51 ppm for the bridgehead H-1 and benzylic H-7 protons with a coupling constant of $J = 5.3$ Hz) could be detected in the crude reaction mixture (see below). The enantioselectivity of this reaction was determined to be 78% *ee* by HPLC using Daicel Chiral-



Scheme 2. Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of **5a** with **6a** and **6b** catalyzed by Rh_2(*S*-BPTV)$_4$ (**3g**).

Table 1. Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of **5a** with **6b–e** catalyzed by chiral dirhodium(II) carboxylates **3a–h**.



Entry	Aldehyde		Rh(II) catalyst	Product	Yield [%][a]	*ee* [%][b]
	No.	R				
1	**6b**	NO_2	Rh_2(*S*-PTA)$_4$ (**3a**)	**7b**	55	61
2	**6b**	NO_2	Rh_2(*S*-PTPA)$_4$ (**3b**)	**7b**	51	67
3	**6b**	NO_2	Rh_2(*S*-PTV)$_4$ (**3c**)	**7b**	66	66
4	**6b**	NO_2	Rh_2(*S*-PTTL)$_4$ (**3d**)	**7b**	70	75
5	**6b**	NO_2	Rh_2(*S*-BPTA)$_4$ (**3e**)	**7b**	55	86
6	**6b**	NO_2	Rh_2(*S*-BPTPA)$_4$ (**3f**)	**7b**	65	87
7	**6b**	NO_2	Rh_2(*S*-BPTV)$_4$ (**3g**)	**7b**	71	92
8	**6b**	NO_2	Rh_2(*S*-BPTTL)$_4$ (**3h**)	**7b**	63	54
9	**6c**	CF_3	Rh_2(*S*-BPTV)$_4$ (**3g**)	**7c**	69	91
10	**6d**	Cl	Rh_2(*S*-BPTV)$_4$ (**3g**)	**7d**	68	88
11	**6e**	MeO	Rh_2(*S*-BPTV)$_4$ (**3g**)	**7e**	26	76

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiral OD-H column).

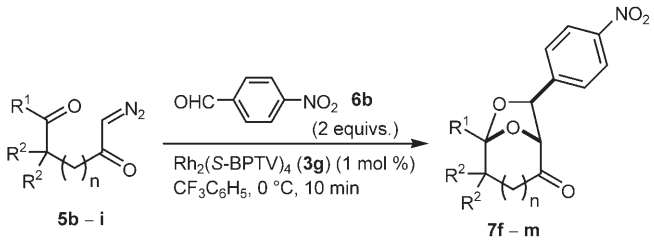
pak AD-H column. Gratifyingly, switching the dipolarophile from benzaldehyde to *p*-nitrobenzaldehyde (**6b**) greatly improved the product yield and enantioselectivity, providing the cycloadduct **7b** in 71% yield with complete *exo* selectivity and 92% *ee* (the *ee* value was determined by HPLC with a Daicel Chiralcel OD-H column).[22]

Using *p*-nitrobenzaldehyde as a dipolarophile, we next evaluated the performance of two classes of dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- and *N*-benzene-fused-phthaloyl-(*S*)-amino acids as the bridging ligands (Table 1). While a uniform sense of asymmetric induction and perfect *exo* selectivity were observed in all cases, the *ee* values were found to be dependent on the catalyst. With the exception of Rh_2(*S*-BPTTL)$_4$ (**3h**), dirhodium(II) catalysts **3e–g**, characterized by an extension of the phthalimido wall with one additional benzene ring, provided much higher enantioselectivities than the respective parent dirhodium(II) catalysts **3a–c** (entries 1–3 *vs.* 5–7). While Rh_2(*S*-PTTL)$_4$ (**3d**)[23,24] displayed the highest enantioselectivity of the parent dirhodium(II) catalysts (75% *ee*, entry 4), Rh_2(*S*-BPTV)$_4$ (**3g**) proved to be by far the best choice (92% *ee*, entry 7). It is interesting to note that the reaction using $Rh_2(O_2CCH_3)_4$ afforded an 83:17 mixture of *exo* and *endo* cycloadducts **7b** and **8b**, while the use of $Rh_2(O_2CCPh_3)_4$ with an exceptionally bulky ligand[25] markedly increased the proportion of *exo* isomer (**7b**:**8b** = 92:8). While the mechanistic profile for this reaction is not clear at this time, these results suggest that the presence of phthalimido or benzene-fused phthalimido groups in the bridging ligands of our dirhodium(II) catalysts **3a–h** is responsible for the complete *exo* selectivity in this process.

With the superiority of Rh_2(*S*-BPTV)$_4$ as a catalyst verified, we then explored the reaction of α-diazo ketone **5a** with aromatic aldehydes other than benzaldehyde and *p*-nitrobenzaldehyde. The use of electron-poor aromatic aldehydes including *p*-(trifluoromethyl)benzaldehyde (**6c**) and *p*-chlorobenzaldehyde (**6d**) afforded the corresponding *exo* cycloadducts **7c** and **7d** as the sole products in similar yields and asymmetric induction as was found for *p*-nitrobenzaldehyde (91% and 88% *ee*, entries 9 and 10). In contrast, the use of *p*-anisaldehyde (**6e**) as an electron-rich aldehyde resulted in a noticeable drop in product yield and enantioselectivity (26% yield and 76% *ee*, entry 11). It is noteworthy that the *ee* value is still comparable to that observed for benzaldehyde. Disappointingly, the use of aliphatic aldehydes gave a complex mixture of products.

Using Rh_2(*S*-BPTV)$_4$ as a catalyst and *p*-nitrobenzaldehyde as a dipolarophile, we finally investigated the tandem carbonyl ylide formation/cycloaddition of α-diazo ketones possessing substituents other than a phenyl group at the C-5 position or with a different length of the tether separating the two functionalities.

Table 2. Enantioselective tandem carbonyl ylide formation/1,3-dipolar cycloaddition of **5b–i** with **6b** catalyzed by Rh_2(*S*-BPTV)$_4$ (**3g**).



Entry	Substrate				Product	Yield [%][a]	*ee* [%][b]
	No.	n	R^1	R^2			
1	**5b**	1	4-MeO-C_6H_4	H	**7f**	74	89
2	**5c**	1	4-Me-C_6H_4	H	**7g**	60	88
3	**5d**	1	4-Cl-C_6H_4	H	**7h**	80	89
4	**5e**	1	4-CF_3-C_6H_4	H	**7i**	67	88
5	**5f**	1	Me	H	**7j**	14	19
6	**5g**	0	Me	Me	**7k**	74	12
7	**5h**	0	Ph	Me	**7l**	62	<1
8	**5i**	2	Ph	H	**7m**	60	79

[a] Isolated yield.
[b] Determined by HPLC (Daicel Chiralpak AD-H or Chiralcel OD-H column).

The results are summarized in Table 2. Aside from complete *exo* selectivity, a high enantioselectivity was consistently observed with either electron-donating or electron-withdrawing groups present at the *para*-position on the benzene ring at C-5 (88–89% *ee*, entries 1–4). However, switching the substituent at C-5 to a methyl group sharply decreased the product yield as well as the enantioselectivity (14% yield and 19% *ee*, entry 5). Reactions *via* five-membered cyclic carbonyl ylide intermediates derived from α-diazo ketones **5g** and **5h** proceeded smoothly to give the corresponding cycloadducts **7k** and **7l** in good yields with perfect *exo* selectivity, but it was disappointing to find that there was only poor to no asymmetric induction (12% *ee* and <1% *ee*, entries 6 and 7). On the other hand, the present protocol was found to be applicable to the seven-membered carbonyl ylide system, providing cycloadduct **7m** in 60% yield with 79% *ee* (entry 8).[26]

In summary, we have achieved a high enantioselectivity and complete *exo* selectivity in 1,3-dipolar cycloadditions of the six-membered carbonyl ylides derived from 1-diazo-5-aryl-2,5-pentanediones with electron-poor aromatic aldehydes using Rh_2(*S*-BPTV)$_4$ as a catalyst. The high levels of asymmetric induction (up to 92% *ee*) for this system have demonstrated that Rh_2(*S*-BPTV)$_4$ is intimately bound to carbonyl ylides during the cycloaddition process. The findings also show that enantioselectivity is highly sensitive to the substitution pattern at the ylide carbonyl and the electronic nature of the aromatic aldehyde dipolarophiles as well as the length of the tether. Further studies on the scope of the reaction as well as mechanistic and stereochemical studies are currently in progress.

Experimental Section

Representative Procedure for the Tandem Carbonyl Ylide Formation/1,3-Dipolar Cycloaddition (Scheme 2, Entry 7 in Table 1)

Rh_2(*S*-BPTV)$_4$·2THF (4.6 mg, 0.003 mmol, 1 mol%) was added to a solution of **5a** (60.6 mg, 0.30 mmol) and **6b** (90.7 mg, 0.60 mmol) in benzotrifluoride (3.0 mL) at 0 °C. After stirring for 10 min, the mixture was concentrated and the residue purified by column chromatography (silica gel, 1:2 hexane/benzene → benzene) to give 7-*exo*-(4-nitrophenyl)-5-phenyl-6,8-dioxabicyclo[3.2.1]octan-2-one (**7b**) as a white solid; yield: 69 mg (71%); R_f=0.31 (5:1 benzene/Et_2O); mp 160.0–161.0 °C; $[\alpha]_D^{24}$: +60.8 (*c* 1.15, $CHCl_3$); IR (KBr): ν=3441, 2994, 2936, 1738, 1603, 1524, 1343 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$): δ=2.42–2.61 (2H, m, CH_2), 2.71 (1H, dddd, *J*=17.8, 7.8, 3.2, 1.3 Hz, CH_2), 2.83 (1H, dt, *J*=17.8, 8.6 Hz, CH_2), 4.49 (1H, s, COC*H*), 5.37 (1H, s, ArC*H*), 7.33 (2H, d, *J*=8.6 Hz, *Ar*), 7.44–7.51 (3H, m, *Ar*), 7.63–7.68 (2H, m, *Ar*), 8.11 (2H, d, *J*=8.6 Hz, *Ar*); ^{13}C NMR (67.8 MHz, $CDCl_3$): δ=32.9 (CH_2), 36.9 (CH_2), 79.6 (CH), 86.5 (CH), 110.3 (C), 123.6 (CH), 124.8 (CH), 126.8 (CH), 128.5 (CH), 129.0 (CH), 138.7 (C), 147.0 (C), 147.7 (C), 203.9 (C=O); EI-LR-MS: *m/z*=325 (M^+), 268, 204, 174, 115, 105, 77; EI-HR-MS: *m/z*=325.0969, calcd. for $C_{18}H_{15}NO_5$ (M^+): 325.0950; anal. calcd. for $C_{18}H_{15}NO_5$: C 66.46, H, 4.65, N 4.31; found: C 66.06, H 4.87, N 4.10.

The enantiomeric excess of **7b** was determined to be 92% by HPLC using a Daicel Chiralcel OD-H column (5:1 hexane/2-propanol, flow rate = 1.0 mL min^{-1}): t_R = 18.1 min for the minor enantiomer; t_R = 21.6 min for the major enantiomer.

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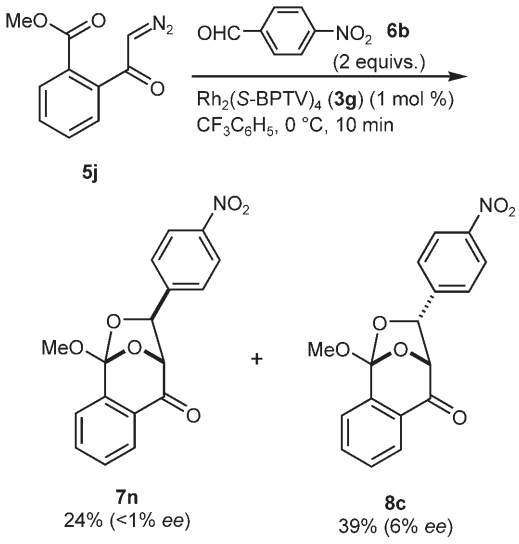

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