Catalytic Enantioselective Intermolecular Cycloaddition of 2-Diazo-3,6-diketoester-Derived Carbonyl Ylides with Alkynes and Styrenes Using Chiral Dirhodium(II) Carboxylates
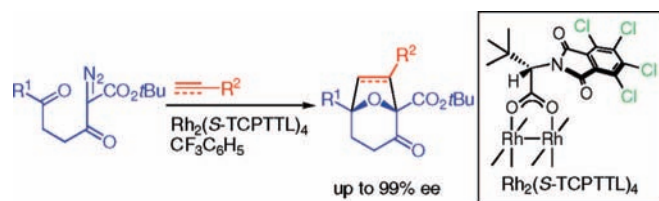
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ABSTRACT

Dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], Rh₂(*S*-TCPTTL)₄, is an exceptionally effective catalyst for enantioselective tandem carbonyl ylide formation−cycloaddition reactions of 2-diazo-3,6-diketoesters with arylacetylene, alkoxyacetylene, and styrene dipolarophiles, providing cycloadducts in good to high yields and with enantioselectivities of up to 99% ee as well as with perfect *exo* diastereoselectivity for styrenes.
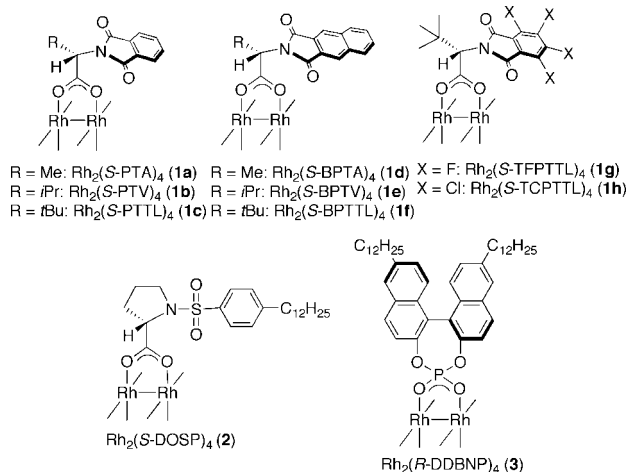
The dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation-1,3-dipolar cycloaddition reaction sequence extensively studied by the Padwa group represents one of the most efficient methods for the rapid assembly of complex oxapolycyclic systems containing embedded di- or tetrahydrofuran 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[2]

such as zaragozic acids,[2a,b] nemorensic acids,[2c] colchicine,[2d] aspidophytine,[2e] pseudolaric acid,[2f] polygalolides,[2g] 3*H*-epivincamine,[2h,i] indicol,[2j] and platensimycin.[2k] Consequently, the development of an enantioselective version of this sequence catalyzed by chiral dirhodium(II) complexes

(1) For books and reviews, see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223–269. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; Chapter 7. (c) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61. (d) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477–9504. (e) McMills, M. C.; Wright, D. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, 2003; Chapter 4. (f) Savizky, R. M.; Austin, D. J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 19. (g) Padwa, A. *Helv. Chim. Acta* **2005**, *88*, 1357–1374. (h) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–12275.

(2) For recent reports on the total syntheses of natural products via carbonyl ylide cycloaddition strategy, see: (a) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5351–5355. (b) Hirata, Y.; Nakamura, S.; Watanabe, N.; Kataoka, O.; Kurosaki, T.; Anada, M.; Kitagaki, S.; Shiro, M.; Hashimoto, S. *Chem. Eur. J.* **2006**, *12*, 8898–8925. (c) Hodgson, D. M.; Strat, F. L.; Avery, T. D.; Donohue, A. C.; Brückl, T. *J. Org. Chem.* **2004**, *69*, 8796–8803. (d) Graening, T.; Bette, V.; Neudörfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317–4320. (e) Mejía-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275–3278. (f) Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6197–6201. (g) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532–6535. (h) England, D. B.; Padwa, A. *Org. Lett.* **2007**, *9*, 3249–3252. (i) England, D. B.; Padwa, A. *J Org. Chem.* **2008**, *73*, 2792–2802. (j) Lam, S. K.; Chiu, P. *Chem. Eur. J.* **2007**, *13*, 9589–9599. (k) Kim, C. H.; Jang, K. P.; Choi, S. Y.; Chung, Y. K.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4009–4011.

has become a challenging objective. 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 catalyst-free carbonyl ylides are achiral.[3] 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 Rh₂(R-DDBNP)₄ (3) (Figure 1).[4] We

R = Me: Rh₂(S-PTA)₄ (1a) R = Me: Rh₂(S-BPTA)₄ (1d) X = F: Rh₂(S-TFPTTL)₄ (1g)
R = iPr: Rh₂(S-PTV)₄ (1b) R = iPr: Rh₂(S-BPTV)₄ (1e) X = Cl: Rh₂(S-TCPTTL)₄ (1h)
R = tBu: Rh₂(S-PTTL)₄ (1c) R = tBu: Rh₂(S-BPTTL)₄ (1f)

Rh₂(S-DOSP)₄ (2)

Rh₂(R-DDBNP)₄ (3)

Figure 1. Chiral dirhodium(II) complexes.

reported the first successful example of intermolecular cycloadditions of α-diazoketone-derived carbonyl ylides with dimethyl acetylenedicarboxylate (DMAD), in which Rh₂(S-BPTV)₄ (1e) proved to be the catalyst of choice for achieving enantioselectivities of up to 92% ee.[5,6] However, the reactions have serious limitations in that only highly electron-deficient dipolarophiles such as DMAD[6,7] and p-nitrobenzaldehyde[8] have met with any real success. Furthermore, Hodgson and co-workers reported that Rh₂(S-BPTV)₄ is less effective not only for the foregoing intramo-

lecular process but also for the intermolecular reaction of α-diazo-β-ketoester with DMAD.[4b,c] Later extensive studies by the same group demonstrated that a complex blend of electronic effects from the dipole and dipolarophile, together with the nature of the catalyst, contribute to the origin of asymmetric induction.[4e,9]

With respect to the dipole reactivity of cyclic carbonyl ylides derived from α-diazocarbonyl compounds, it is documented that the most dominant interaction in the case of α-diazo ketone is between the HOMO of the carbonyl ylide and the LUMO of electron-deficient dipolarophiles,[10] whereas the most favorable interaction in the case of α-diazo-β-ketoester is between the LUMO of the carbonyl ylide and the HOMO of more electron-rich dipolarophiles.[11] Recently, Hodgson and co-workers reported enantioselective intermolecular cycloadditions of 2-diazo-3,6-diketoester-derived carbonyl ylides with dipolarophiles that do not contain electron-withdrawing substituents on the π bond, using Rh₂-(S-DOSP)₄ (2)[12] and Rh₂(R-DDBNP)₄ (3).[13] In this process, high levels of asymmetric induction (up to 92% ee) were only achieved when strained alkene dipolarophiles such as norbornene and norbornadiene were used. As a logical extension of our previous studies, we addressed the issue of the scope of the reaction with respect to the dipolarophile component. Herein, we report the successful examples of enantioselective carbonyl ylide cycloadditions of 2-diazo-3,6-diketoester derivatives with arylacetylene, alkoxyacetylene, and styrene dipolarophiles, in which Rh₂(S-TCPTTL)₄ (1h),[14a,c] the chlorinated analogue of Rh₂(S-PTTL)₄ (1c),[15] has emerged as the catalyst of choice for achieving enantioselectivities of up to 99% ee.

Patterned after the original work of Hodgson,[13] we initially explored the reaction of tert-butyl 2-diazo-3,6-dioxoheptanoate (4a) with phenylacetylene (5a) (3 equiv) in benzotrifluoride at 23 °C using two classes of dirhodium(II) carboxylate catalysts (1 mol %), which incorporate N-

(3) Suga and co-workers developed a conceptually different approach and demonstrated highly enantioselective 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olates with a variety of dipolarophiles using chiral Lewis acid catalysts: (a) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836–14837. (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47–56.

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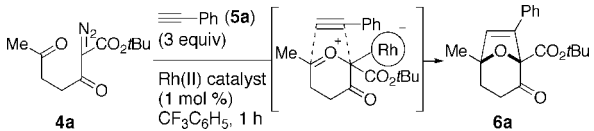
(5) For seminal works on enantioselective intermolecular cycloadditon of carbonyl ylides using chiral dirhodium(II) catalyst, see: (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935. (b) Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165–3166.

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(7) We reported high levels of enantioselection (up to 93% ee) in the intermolecular cycloaddition of ester-derived carbonyl ylides with DMAD using Rh₂(S-PTTL)₄ (1c): Kitagaki, S.; Yasugahira, M.; Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931–5935.

(8) Tsutsui, H.; Shimada, N.; Abe, T.; Anada, M.; Nakajima, M.; Nakamura, S.; Nambu, H.; Hashimoto, S. *Adv. Synth. Catal.* **2007**, *349*, 521–526.

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(11) Koyama, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185–9188.

(12) (a) Davies, H. M. L. *Aldrichm. Acta* **1997**, *30*, 107–114. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459–2469.

(13) (a) Hodgson, D. M.; Labande, A. H.; Glen, R.; Redgrave, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 921–924. (b) Hodgson, D. M.; Brückl, T.; Glen, R.; Labande, A. H.; Selden, D. A.; Dossetter, A. G.; Redgrave, A. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5450–5454.

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phthaloyl- and *N*-benzene-fused-phthaloyl-(*S*)-amino acids as the bridging ligands (Table 1, entries 1−6).[16] While a

entry	Rh(II) catalyst	T (°C)	yield[b] (%)	ee[c] (%)
1	Rh$_2$(*S*-PTA)$_4$ (**1a**)	23	35	70
2	Rh$_2$(*S*-PTV)$_4$ (**1b**)	23	45	80
3	Rh$_2$(*S*-PTTL)$_4$ (**1c**)	23	56	89
4	Rh$_2$(*S*-BPTA)$_4$ (**1d**)	23	53	75
5	Rh$_2$(*S*-BPTV)$_4$ (**1e**)	23	60	82
6	Rh$_2$(*S*-BPTTL)$_4$ (**1f**)	23	65	87
7	Rh$_2$(*S*-TFPTTL)$_4$ (**1g**)	23	80	92
8	Rh$_2$(*S*-TCPTTL)$_4$ (**1h**)	23	82	97
9	Rh$_2$(*S*-TCPTTL)$_4$ (**1h**)	60	80	95
10	Rh$_2$(*S*-TCPTTL)$_4$ (**1h**)	100	70	82

[a] All reactions were carried out as follows: a solution of **4a** (48.0 mg, 0.2 mmol) and **5a** (3 equiv) in CF$_3$C$_6$H$_5$ (1 mL) was added over 1 h to a solution of Rh(II) catalyst (1 mol %) in CF$_3$C$_6$H$_5$ (1 mL) at the indicated temperature. [b] Isolated yield. [c] Determined by HPLC.

uniform sense of asymmetric induction and perfect regioselectivity were observed in all cases, the ee values were dependent on the catalyst. Clearly, the best catalysts were Rh$_2$(*S*-PTTL)$_4$ (**1c**) and Rh$_2$(*S*-BPTTL)$_4$ (**1f**), which are characterized by a bulky *tert*-butyl group, as they provided cycloadduct **6a**[17] in 56% and 65% yields with 89% and 87% ee, respectively (entries 3 and 6). It is interesting to note that the substituents of the amino acids more markedly influenced enantioselectivity than the choice of *N*-phthaloyl- or *N*-benzene-fused-phthaloyl groups. It is also noteworthy that dirhodium(II) catalysts **1d−f** characterized by an extension of the phthalimido wall with one additional benzene ring provided even higher yields than the respective parent dirhodium(II) catalysts **1a−c** (entries 4−6 vs 1−3). We then evaluated the performance of Rh$_2$(*S*-TFPTTL)$_4$ (**1g**)[14b,d] and Rh$_2$(*S*-TCPTTL)$_4$ (**1h**),[14a,c] fluorinated and chlorinated analogues of Rh$_2$(*S*-PTTL)$_4$, which could bring about an electron deficiency on the rhodium(II) center (entries 7 and 8).[18] Gratifyingly, the halogenated catalysts noticeably improved the enantioselectivity and product yield obtained with Rh$_2$(*S*-PTTL)$_4$, 97% ee with Rh$_2$(*S*-TCPTTL)$_4$ being the highest achievement (entry 8). A survey of solvents with Rh$_2$(*S*-TCPTTL)$_4$ revealed that benzotrifluoride was the optimal solvent for this transformation in terms of both product yield and enantioselectivity.[19] An examination of the temperature

(16) Hodgson and co-workers reported that the reaction of **4a** with **5a** (10 equiv) under the influence of 1 mol % of Rh$_2$(*R*-DDBNP)$_4$ (**3**) in hexane at 25 °C provided cycloadduct **6a** in 41% yield with 61% ee. See ref 13.
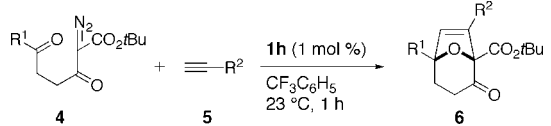
(17) The preferred absolute stereochemistry of cycloadducts was not determined.

(18) Recently, dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-(1-adamantyl)glycinate], Rh$_2$(*S*-TCPTAD)$_4$, was developed by Reddy and Davies: Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013−5016.

profile demonstrated that catalysis with Rh$_2$(*S*-TCPTTL)$_4$ performed exceptionally well over a wide temperature range (entries 9 and 10), which was in stark contrast to that with Rh$_2$(*S*-PTTL)$_4$ (60 °C, 32% yield, 56% ee; 100 °C, 14% yield, 28% ee). Surprisingly, only 15% and 12% drops in enantioselection and product yield, respectively, were observed at 100 °C, suggesting that Rh$_2$(*S*-TCPTTL)$_4$ remains even more strongly associated with the carbonyl ylide than Rh$_2$(*S*-PTTL)$_4$. From frontier molecular orbital (FMO) analysis for the reaction in the absence of a catalyst, the dominant interaction is between the LUMO of the carbonyl ylide derived from **4a** and the HOMO of dipolarophile **5a**, which predicts the regiochemistry exactly as observed.[20] Aside from the stereochemical outcome,[17] these results suggest that cycloaddition would occur on the opposite face of the carbonyl ylide to the catalyst in concert with dissociation of the catalyst as proposed by Hodgson.[4c,13b]

With the superiority of Rh$_2$(*S*-TCPTTL)$_4$ as a catalyst verified, we then investigated the reactions of a range of 2-diazo-3,6-diketoester derivatives and arylacetylene dipolarophiles. The reaction of phenyl-substituted diazodiketoester **4b** with phenylacetylene (**5a**) afforded cycloadduct **6b** in 64% yield with 98% ee (Table 2, entry 1). The reaction

	diazodiketoester		dipolarophile		product	
entry		R^1		R^2		yield[b](%)	ee[c](%)
1[d]	**4b**	C$_6$H$_5$	**5a**	C$_6$H$_5$	**6b**	64	98
2	**4a**	Me	**5b**	4-MeOC$_6$H$_4$	**6c**	80	91
3	**4a**	Me	**5c**	4-MeC$_6$H$_4$	**6d**	77	97
4	**4a**	Me	**5d**	4-BrC$_6$H$_4$	**6e**	70	88
5	**4a**	Me	**5e**	3-MeOC$_6$H$_4$	**6f**	64	92
6	**4a**	Me	**5f**	2-MeOC$_6$H$_4$	**6g**	53	92
7	**4a**	Me	**5g**	EtO	**6h**	93	85
8	**4b**	C$_6$H$_5$	**5g**	EtO	**6i**	85	89
9	**4c**	4-ClC$_6$H$_4$	**5g**	EtO	**6j**	84	88
10	**4d**	4-MeC$_6$H$_4$	**5g**	EtO	**6k**	75	92
11	**4e**	4-MeOC$_6$H$_4$	**5g**	EtO	**6l**	60	94

[a] All reactions were performed on a 0.2 mmol scale with 3 equiv of dipolarophile. [b] Isolated yield. [c] Determined by HPLC. [d] 5 equiv of phenylacetylene (**5a**) was used.

of **4a** with phenylacetylenes bearing methoxy, methyl, and bromo substituents at the *para* position also gave high enantioselectivities (88−97% ee, entries 2−4).[21] A high enantioselectivity (92% ee) was maintained with *m*- or *o*-methoxyphenylacetylenes, though a slight decrease in

(19) The product yields and enantioselectivities obtained with other solvents are as follows: toluene, 73% yield, 95% ee; benzene, 76% yield, 91% ee; hexanes, 63% yield, 90% ee; Et$_2$O, 23% yield, 72% ee; CH$_2$Cl$_2$, 14% yield, 40% ee.

product yield was observed (entries 5 and 6). The reaction of **4a,b** with ethyl ethynyl ether (**5g**) proceeded smoothly to provide cycloadducts **6h,i** in high yields with 85% and 89% ee, respectively (entries 7 and 8). The use of **5g** was found to allow for variation of *para*-substituents in aryl-substituted diazodiketoesters **4c−e** (88−94% ee, entries 9−11). To the best of our knowledge, this is the first example of the use of alkoxyacetylene as a dipolarophile in enantioselective carbonyl ylide cycloaddition reactions.

To expand the scope of this catalytic process, we also examined styrene derivatives as dipolarophiles. Apart from enantiocontrol, *exo*/*endo* diastereocontrol has remained a major challenge in enantioselective carbonyl ylide cycloadditions with styrene dipolarophiles. Thus, we were gratified to find that the reaction of methyl-substituted diazodiketoester **4a** with styrene (**7a**, 3 equiv) produced cycloadduct **8a** in 89% yield with perfect *exo* diastereoselectivity and 97% ee (Table 3, entry 1).[22] Furthermore, the reaction with phenyl-

formation-cycloaddition (entry 2). Aside from complete *exo* diastereoselectivity, the highest enantioselectivity (99% ee) was consistently observed regardless of the nature of *para*-substituents in styrenes (entries 3−6). While an excellent result was also obtained for *m*-methoxystyrene (**7f**) (entry 7), the reaction with *o*-methoxystyrene (**7g**) slightly diminished both the product yield and enantioselectivity (entry 8).

In summary, we have demonstrated that $Rh_2(S\text{-TCPTTL})_4$ is an exceptionally effective catalyst for LUMO-controlled carbonyl ylide cycloadditions of 2-diazo-3,6-diketoester derivatives with arylacetylene, alkoxyacetylene, and styrene dipolarophiles, in which high levels of asymmetric induction (up to 99% ee) as well as perfect *exo* diastereoselectivity for styrenes have been achieved.[23,24] It is also noteworthy that $Rh_2(S\text{-DOSP})_4$, $Rh_2(R\text{-DDBNP})_4$, and $Rh_2(S\text{-TCPTTL})_4$ can complement each other in this type of carbonyl ylide cycloaddition. Further studies on the scope of the reaction as well as mechanistic and stereochemical studies are currently in progress.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Table 3. Enantioselective Intermolecular Cycloaddition of **4a** and **4b** with **7a−g** Catalyzed by $Rh_2(S\text{-TCPTTL})_4$ (**1h**)[a]

	diazodiketoester	dipolarophile		product	
entry	R		Ar	yield[b] (%)	ee[c] (%)
1	**4a** Me	**7a**	C_6H_5 **8a**	89	97
2	**4b** C_6H_5	**7a**	C_6H_5 **8b**	85	99
3	**4b** C_6H_5	**7b**	4-MeOC_6H_4 **8c**	94	99
4	**4b** C_6H_5	**7c**	4-MeC_6H_4 **8d**	90	99
5	**4b** C_6H_5	**7d**	4-BrC_6H_4 **8e**	80	99
6	**4b** C_6H_5	**7e**	$4\text{-CF}_3C_6H_4$ **8f**	73	99
7	**4b** C_6H_5	**7f**	3-MeOC_6H_4 **8g**	88	98
8	**4b** C_6H_5	**7g**	2-MeOC_6H_4 **8h**	75	90

[a] All reactions were performed on a 0.2 mmol scale with 3 equiv of dipolarophile. [b] Isolated yield. [c] Determined by HPLC.

substituted diazodiketoester **4b** exhibited enantioselectivity of 99% ee, which is the highest ever recorded for chiral dirhodium(II) complex-catalyzed tandem carbonyl ylide

(20) For the orbital correlation diagram, see the Supporting Information.
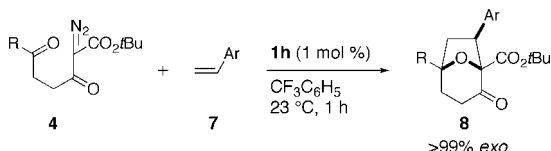
(21) The use of *p*-nitrophenylacetylene as a strongly electron-deficient dipolarophile resulted in 17% yield of cycloadduct with 72% ee.

(22) Hodgson and co-workers reported that the reaction of **4a** with **7a** (10 equiv) under $Rh_2(OAc)_4$ catalysis in CH_2Cl_2 at 20 °C afforded a 2:1 mixture of *exo* and *endo* cycloadducts in 53% yield, while the use of $Rh_2(S\text{-DOSP})_4$ (**2**) in hexane at 20 °C increased *exo* diastereoselectivity (*exo:endo* = 10:1, 73% yield) and provided 61% ee for *exo* cycloadduct **8a**. See ref 13b.

(23) $Rh_2(S\text{-TCPTTL})_4$ was less effective for the reaction of **4a** with DMAD, giving the corresponding cycloadduct in 60% yield with 40% ee.

(24) Very recently, Suga and co-workers have reported highly enantioselective dipole-LUMO/dipolarophile-HOMO controlled cycloadditions between 2-benzopyrylium-4-olates and vinyl ether derivatives using chiral Lewis acid catalysts: Suga, H.; Ishimoto, D.; Higuchi, S.; Ohtsuka, M.; Arikawa, T.; Tsuchida, T.; Kakehi, A.; Baba, T. *Org. Lett.* **2007**, *9*, 4359–4362.