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Chiral 2,6-Bis(oxazolinyl)pyridine−Rare Earth Metal Complexes as Catalysts for Highly Enantioselective 1,3-Dipolar Cycloaddition Reactions of 2-Benzopyrylium-4-olates

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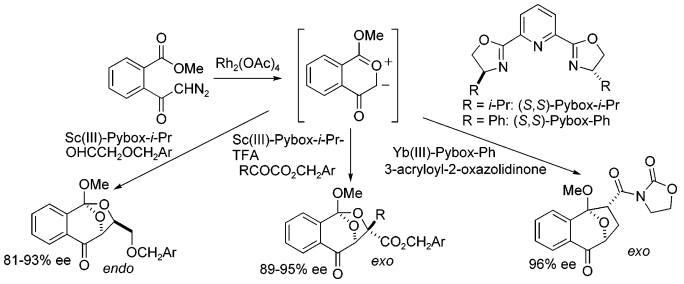

Significant levels of enantioselectivity were obtained in 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olate generated from the $Rh_2(OAc)_4$-catalyzed decomposition of *o*-methoxycarbonyl-α-diazoacetophenone. This reaction utilized chiral 2,6-bis(oxazolinyl)pyridine (Pybox)−rare earth metal triflate complexes as chiral Lewis acid catalysts. The reactions with several benzyloxyacetaldehyde derivatives catalyzed by a Sc(III)−Pybox-*i*-Pr complex (10 mol %) proceeded smoothly to yield *endo*-adducts selectively with high enantioselectivity (up to 93% ee). For the reaction with benzyl pyruvate, the Sc(III)−Pybox-*i*-Pr complex (10 mol %) catalyzed the reaction effectively in the presence of trifluoroacetic acid (10 mol %) to yield an *exo*-adduct with both high diastereo- and enantioselectivity (94% ee). This catalytic system was efficiently applied to the reactions with several other α-keto esters with high *exo*- and enantioselectivities (up to 95% ee). In contrast to the reaction with carbonyl compounds, Yb(III)−Pybox-Ph complex (10 mol %) was found to be effective to obtain high enantioselectivity (96% ee) of diastereoselectively produced *exo*-cycloadduct in the reaction with 3-acryloyl-2-oxazolidinone.

Introduction

The stereoselective synthesis of oxygen heterocycles, especially molecules comprising complex tetrahydrofuran and tetrahydropyran skeletons, has attracted considerable attention in recent years.[1] Among these oxygen heterocycles, medium-sized polycyclic ethers containing epoxy-bridged moieties are recognized as common structural units in naturally occurring biologically important compounds such as brevicomin,[2] frontalin,[2b,3] augastamine,[4] zaragozic acids,[5] didemniserinolipids,[6] and ribasine[7] (Figure 1). The epoxy-bridged tetrahydropyran skeleton is also present in a wide range of natural products, including loukacinols[8] and xanthane epoxide[9]

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(1) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Barlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D. Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6. (d) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.

(2) (a) Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889. (b) Wood, D. L.; Browne, L. E.; Ewing, B., Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pittman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896. For a synthesis using carbonyl ylide cycloadditions, see: (c) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100. (d) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491.

(3) (a) Kinzer, G. W.; Fentiman, A. F.; Page, T. F.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature (London)* **1969**, *221*, 477. (b) Mori, K. *Tetrahedron* **1975**, *31*, 1381. For syntheses and studies, see: (c) Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443. (d) Jarose, S.; Hicks, D. R.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 935. (e) Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1984**, 578. (f) Sato, T.; Kaneko, H.; Yamaguchi, S. *J. Org. Chem.* **1980**, *45*, 3778. (f) Lipkowitz, K. B.; Carter, J. *J. Org. Chem.* **1981**, *46*, 4005.

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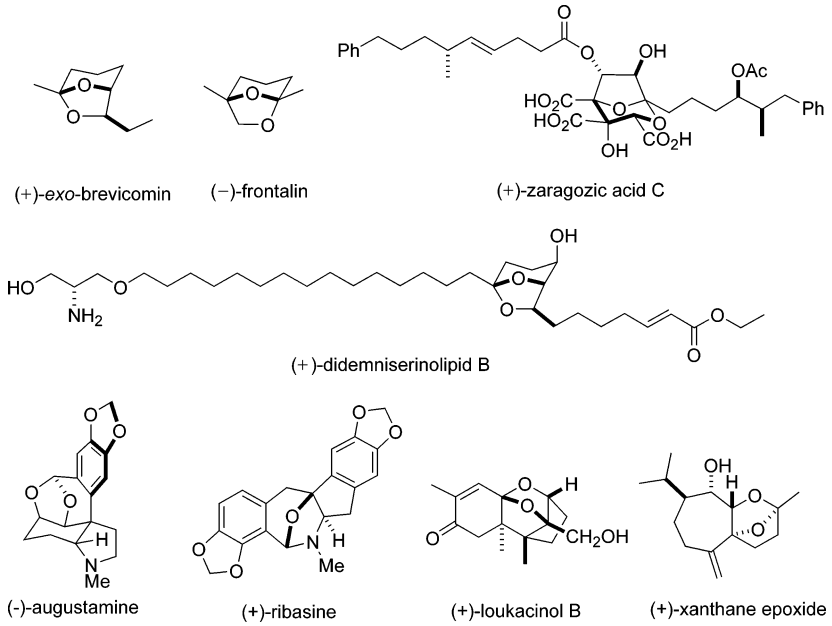
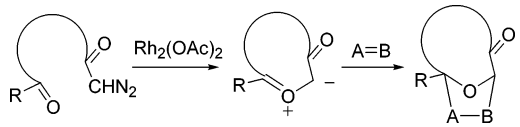


FIGURE 1. Naturally occurring biologically important compounds containing epoxy-bridged moieties.

(Figure 1). As a result of the increasing interest in these bioactive compounds and the well-recognized problems in stereo- and enantioselective construction of those complex polycyclic oxygen heterocycles, the synthesis of such systems is a challenging objective. The intramolecular carbenoid-carbonyl cyclization has been one of the most effective methods for generating carbonyl ylides, since Ibata and co-workers reported the transition-metal-catalyzed decomposition of *o*-alkoxycarbonyl-α-diazoacetophenones in the presence of various dipolarophiles.[10]

SCHEME 1. Tandem Intramolecular Carbenoid-Carbonyl Cyclization-1,3-Dipolar Cycloaddition Methodologies of Carbonyl Ylides



Extensive studies by Padwa and co-workers using a variety of diazocarbonyl substrates revealed that these tandem intramolecular carbenoid-carbonyl cyclization-1,3-dipolar cycloaddition methodologies involving carbonyl ylides are an important tool for constructing the framework of complex molecules containing oxygen heterocycles with a high degree of regio- and stereocontrol (Scheme 1).[11] For example, the tandem cyclization-1,3-dipolar cycloadditions were effectively utilized for the synthesis of epoxy-bridged bicyclic compounds such as brevicomin,[2c,d] as well as zaragozic acid and its skeleton.[5e−k] The epoxy-bridged compounds obtained from the tandem cyclization-1,3-dipolar cycloaddtions were also efficiently utilized as intermediates for the syntheses of biologically important natural products, such as illudins,[12] epoxysorbicillinol,[13] and nemorensine.[14] However, the tandem cyclization-1,3-dipolar cycloadditions could only be applied in the production of racemates or diastereoselective

(4) (a) Ali, A. A.; Kating, H.; Frahm, A. W.; El-Moghazi, A. M.; Ramadan, M. A. *Phytochemistry* **1981**, *20*, 1121. (b) Ali, A. A.; Hambloch, H.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 283. (c) Abd EI Hafiz, M. A.; Ramadan, M. A.; Jung, M. L.; Beck. J. P.; Anton, R. *Planta Med.* **1991**, *57*, 437. For a synthesis, see: (d) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (e) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607.

(5) For reviews, see: (a) Nicolaou, K. C.; Nadin, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1622. (b) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 773. (c) Procopiou, P. A.; Watson, N. S. *Prog. Med. Chem.* **1996**, *33*, 331. (d) Bergstrom, J. D.; Dufresne, C.; Bills, G. F.; Nallin-Omsteas, M.; Byrne, K. *Annu. Rev. Microbiol.* **1995**, *49*, 607. For the skeleton syntheses using carbonyl ylide cycloadditions, see: (e) Hodgson, D. M..; Bailley, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 721. (f) Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432. (g) Villalonga-Barber, C.; Hodgson, D. M. *Abstr. Pap. Am. Chem. Soc.* **2000**, *219*, 778. (h) Hodgson, D. M.; Villalonga-Barber, C. *Tetrahedron Lett.* **2000**, *41*, 5597. (i) Kataoka, O.; Kitagaki, S.; Watanabe, N.; Kobayashi, J.; Nakamura, S.; Shiro, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 2371. (j) Koyoma, H.; Ball, R. G.; Berger, G. D. *Tetrahedron Lett.* **1994**, *35*, 9185. For total synthesis of zaragozic acid C using cycloadditions, see: (k) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5351.

(6) (a) González, N.; Rodríguez, J.; Jiménez, C. *J. Org. Chem.* **1999**, *64*, 5705. (b) Mitchell, S. S.; Rhodes, D.; Bushman, F. D.; Faulkner, D. *J. Org. Chem.* **2000**, *2*, 1605. For a synthesis, see: (a) Kiyota, H.; Dixon, D. J.; Luscombe, C. K.; Hettstedt, S.; Ley, S. V. *Org. Lett.* **2002**, *4*, 3223.

(7) Boente, J. M.; Castedo, L.; Cuadros, R.; Saá, J. M.; Suau, R.; Perales, A.; Martínez-Ripoll, M.; Fayos, J. *Tetrahedron Lett.* **1983**, *24*, 2029. For a synthesis, see: Ollero, L.; Castero, L.; Dominguez, D. *Tetrahedron Lett.* **1998**, *39*, 1413. For a synthetic study using carbonyl ylide cycloadditions, see: Padwa, A.; Precedo, L.; Semones, M. A. *J. Org. Chem.* **1999**, *64*, 4079.

(8) Loukaci, A.; Kayser, O.; Bindsell, K.-U.; Siems, K.; Frevert, J.; Abreu, P. M. *J. Nat. Prod.* **2000**, *63*, 52.

(9) Mahmoud, A. A. *Phytochemistry* **1997**, *45*, 1633.

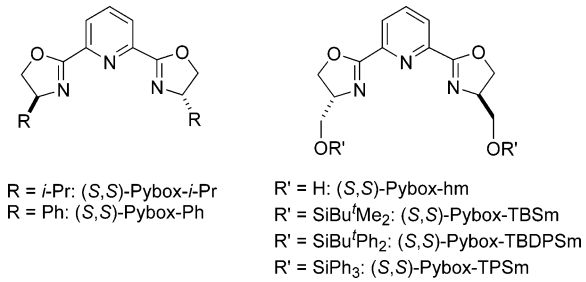
(10) (a) Ueda, K.; Ibata, T.; Takebayashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2779. (b) Ibata, T. *Chem. Lett*. **1976**, 233. (c) Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, *10*, 4475. (d) Ibata, T.; Motoyama, T.; Hamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2298. (e) Ibata, T.; Jitsuhiro, K. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 3582. (f) Ibata, T.; Jitsuhiro, K.; Tsubokura, Y. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 240. (g) Tamura, H.; Ibata, T.; Ogawa, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 926. (h) Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1787. (i) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266.

(11) For reviews, see: (a) MacMills, M. C.; Wright, D. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds,; Jhon Wiley & Sons: Hoboken, 2003; Chapter 4, p 253. (b) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (c) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

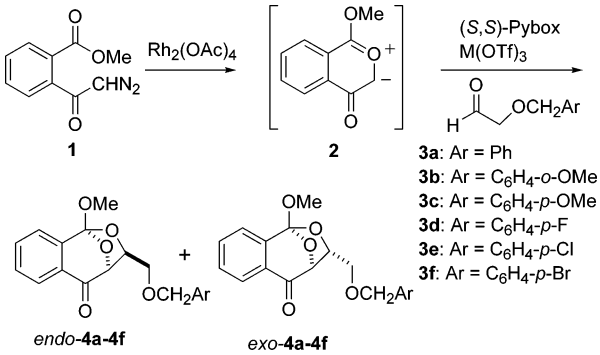
syntheses of chiral compounds. Therefore, the development of an efficient enantioselective version is desirable for the synthesis of medicinally important compounds. Recently, Hodgson[15] and Hashimoto[16] have separately reported enantioselective carbonyl ylide cycloadditions catalyzed by chiral rhodium complexes, in which the chiral rhodium(II)-associated carbonyl ylides were proposed to participate in the transition state. Unfortunately, this method has a number of limitations in terms of its chemical yields, utility with a variety of dipolarophiles, and requirements for specific conditions.

In contrast, prior to our first report in 1998,[17a] the attempt to use Lewis acids in the cycloaddition of carbonyl ylides for enantio-, or even diastereo- or regioselective control had not been reported, probably because of the lability and the Lewis base character of carbonyl ylides. We recently reported that *endo*/*exo* selectivity was controlled by lanthanide triflate in 1,3-dipolar cycloaddition reactions of 2-benzopyrylium-4-olate with *N*-substituted maleimides,[17a,b] aromatic aldehydes,[17c] benzyloxyacetaldehyde,[17c] and 3-acryloyl-2-oxazolidinone.[17d] Asymmetric induction was also observed with moderate enantioselectivity in the reaction of 2-benzopyrylium-4-olate with benzyloxyacetaldehyde using ytterbium tris-(*S*)-1,1′-binaphthyl-2,2′-diyl phosphonate (Yb[(*S*)-BNP]$_3$) as a chiral Lewis acid.[17c] After screening studies of several chiral rare earth metal Lewis acids, including Ln-[(*S*)-BNP]$_3$ derivatives and complexes prepared from a variety of chiral ligands and rare earth metal triflates, we found a number of effective 2,6-bis(oxazolinyl)pyridine[18] (Pybox)-based catalysts. Thus, significant levels of enantioselectivity were obtained in the cycloaddition reaction of 2-benzopyrylium-4-olate with dipolarophiles capable of coordinating in a bidentate fashion, by use of rare earth metal triflate complexes of chiral Pybox ligands as the chiral Lewis acid catalysts.[17e] Details of this investigation including its scope and limitations are reported herein.

CHART 1. Structures of Chiral 2,6-Bis(oxazolinyl)pyridines



SCHEME 2. Asymmetric Cycloaddition Reactions of 2-Benzopyryrium-4-olate with Benzyloxyacetaldehyde Derivatives Catalyzed by (*S*,*S*)-Pybox−Rare Earth Metal Triflate



Results and Discussion

Reactions with Aldehydes. Initially, several chiral Pybox ligands (Chart 1) in combination with Sc(OTf)$_3$ or Yb(OTf)$_3$ were tested as chiral Lewis acid catalysts in the reaction of *o*-methoxycarbonyl-α-diazoacetophenone (**1**), a precursor of 2-benzopyrylium-4-olate **2**, with benzyloxyacetaldehyde (**3a**) (Scheme 2). The chiral Lewis acid catalysts were prepared prior to the reaction by mixing chiral Pybox ligands (10 mol %) with either Sc(OTf)$_3$ or Yb(OTf)$_3$ (10 mol %) in CH_2Cl_2 at room temperature for 2 h. Rh$_2$(OAc)$_4$ and aldehyde **3a** were successively added to the thus prepared catalyst solution. Addition of a solution of diazoacetophenone **1** in CH_2Cl_2 at −10 °C over a period of 1 h afforded a mixture of *exo*- and *endo*-cycloadducts.[19] The ratio of enantiomers is listed in Table 1. Enantioselectivities of *exo*- and *endo*-cycloadducts (*exo*-**4a** and *endo*-**4a**, respectively) were determined by HPLC analysis. In cases in which Yb(OTf)$_3$ was used in combination with chiral Pybox ligands, the *exo*-adduct was obtained with high diastereoselectivity; however, the enantioselectivities of both adducts were low to modest (entries 1−4). The addition of powdered 4 Å molecular sieves (MS 4A) to the reaction mixture in Yb systems, whether before or after preparation of the catalyst, did not significantly affect the diastereo- and enantioselectivities (entries 2 and 3). In contrast, Sc(OTf)$_3$ in combi-

(12) (a) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667. (b) Kinder, F. R.; Bair K. W. *J. Org. Chem.* **1994**, *59*, 6965. (c) Kinder, F. R., Jr.; Wang, R.-M.; Bair, K. W. *Synth. Commun.* **1997**, *27*, 521. (d) McMorris, T. C.; Yu, J.; Hu, Y., Estes, L. A.; Kelner, M. J. *J. Org. Chem.* **1997**, *62*, 3015. (e) McMorris, T. C.; Hu, Y.; Yu, J.; Kelner, M. *J. Chem. Soc., Chem. Commun.* **1997**, 315. (f) McMorris, T. C.; Yu, J. A.; Herman, D. M.; Kelner, M. J.; Dawe, R.; Minamida, A. *J. Labelled Compd. Radiopharm.* **1998**, *41*, 279.

(13) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097.

(14) Hodgson, D. M.; Avery, T. D.; Donohue, A. C. *Org. Lett.* **2001**, *59*, 1157.

(15) (a) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471. (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *J. Chem. Soc., Chem. Commun.* **1999**, 2185.

(16) (a) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (b) Kitagaki, S.; Yasugahira, M., Anada, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron Lett.* **2000**, *41*, 5931.

(17) (a) Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165. (b) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1115. (c) Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Org. Lett.* **2000**, *2*, 3145. (d) Inoue, K.; Suga, H.; Inoue, S.; Sato, H.; Kakehi, A. *Synthesis* **2003**, 1413. (e) A part of the present work has been presented as a preliminary communication: Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836.

(18) For recent examples using rare earth metal triflate−Pybox complexes as chiral Lewis acid, see: (a) Schaus, S. C.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001. (b) Desimoni, G.; Faita, G.; Filippone, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203. (c) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 129095. (d) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375. (e) Evans, D. A.; Wu, J.; Masse, C. E.; MacMillan, D. W. C. *Org. Lett.* **2002**, *4*, 3379. (f) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162. (g) Evans, D. A.; Scheidt, K. A.; Fandrick, H. W.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.

(19) The *endo*-adduct is defined as the product in which the more important substituent is on the opposite side of the epoxy bridge, whereas the *exo*-adduct indicates the product in which the more important substituent is on the same side as the epoxy bridge, as previously defined for *exo*-brevicomin.

TABLE 1. Influence of Pybox Ligands and Metal on Enantio- and Diastereoselectivity in the Pybox-M(OTf)$_3$-Catalyzed Reaction of Diazoacetophenone 1 with Aldehyde 3a[a]

entry	Pybox	M(OTf)$_3$	conditions[b]	MS 4A	yield (%)	*endo*:*exo*	% ee[c] *endo* ( )[d]	% ee[c] *exo* ( )[d]
1	TBSm	Yb(OTf)$_3$	rt, 2 h	no	86	6:94	8 (+)	11 (+)
2	*i*-Pr	Yb(OTf)$_3$	rt, 2 h	no	93	9:91	40 (−)	40 (−)
3	*i*-Pr	Yb(OTf)$_3$	rt, 2 h	yes	92	9:91	35 (−)	36 (−)
4	Ph	Yb(OTf)$_3$	rt, 2 h	yes	quant	14:86	38 (+)	7 (−)
5	hm	Sc(OTf)$_3$	rt, 2 h	no	81	5:95	32 (+)	10 (+)
6	TBSm	Sc(OTf)$_3$	rt, 2 h	no	98	29:71	75 (+)	18 (+)
7	TBSm	Sc(OTf)$_3$	rt, 2 h	yes	50	57:43	77 (+)	9 (+)
8	*i*-Pr	Sc(OTf)$_3$	rt, 1 h	no	85	5:95	1	0
9	*i*-Pr	Sc(OTf)$_3$	rt, 2 h	no	91	55:45	85 (−)	16 (−)
10	*i*-Pr	Sc(OTf)$_3$	rt, 6 h	no	94	76:24	86 (−)	34 (−)
11	*i*-Pr	Sc(OTf)$_3$	reflux, 2 h	no	87	77:23	88 (−)	16 (−)
12	*i*-Pr	Sc(OTf)$_3$	rt, 2 h	yes	96	88:12	91 (−)	18 (−)
13[e]	*i*-Pr	Sc(OTf)$_3$	rt, 2 h	yes	93	85:15	87 (−)	15 (−)
14	Ph	Sc(OTf)$_3$	rt, 2 h	yes	57	86:14	92 (−)	14 (−)

[a] The reaction was carried out at −10 °C by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 h to a suspension of either the Sc or Yb catalyst (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), and **3** (2 equiv) in CH_2Cl_2. [b] The conditions for the preparation of the catalyst. [c] Determined by HPLC analysis (Daicel Chiralpak AS). Absolute configuration of the product was not determined. [d] The sign of the optical rotation. [e] The reaction was carried out at −25 °C.

nation with Pybox ligands showed promising results in terms of enantioselectivity (entries 5, 6, and 9). Although almost no diastereoselectivity was observed in the presence of the catalyst prepared from Pybox-*i*-Pr and Sc(OTf)$_3$ in the absence of MS 4A, the enantiomeric excess of the *endo*-adduct was determined by HPLC analysis to be 85% ee (entry 9). Furthermore, on the basis of investigations of time (entries 8 and 10), temperature (entry 11), and the effect of MS 4A in the preparation of the Sc(III) catalyst (entry 12), the presence of MS 4A during the catalyst preparation was shown to greatly improve the *endo*-selectivity (*endo*:*exo* = 88:12) and increase the level of enantioselectivity (91% ee) of the *endo*-adduct (entry 12). These results probably indicated that stirring less than 6 h at room temperature or even reflux for 2 h in the absence of MS 4A in the preparation of the catalyst was not enough for complete complexation of Sc(OTf)$_3$ and the Pybox ligand, and the use of MS 4A was quite effective in completely preparing the active catalyst. Therefore, high *exo*-selectivity was observed with almost no asymmetric induction in the case of entry 8, and the reversal of the *endo*:*exo* ratio occurred, depending on the stirring time in the preparation of the catalyst (entries 8−10). Although the use of the Sc(III)−(*S*,*S*)-Pybox-TBSm complex prepared in the presence of MS 4A under the same conditions decreased both the diastreo- and enantioselectivities (entry 7), the Sc(III) complex of (*S*,*S*)-Pybox-Ph was similarly effective in preferably yielding the *endo*-isomer, with high enantioselectivity (92% ee) of the *endo*-adduct (entry 14).

Other lanthanide triflates in combination with (*S*,*S*)-Pybox-*i*-Pr were also tested for the chiral catalysts in the reaction of **1** with aldehyde **3a**. For these reactions, the complexes were prepared in the absence of MS 4A, and after preparation of the catalysts, $Rh_2(OAc)_4$ and MS 4A was added before the addition of reactants. In Figure 2, the diastereoselectivity and the enantioselectivities of *exo*- and *endo*-adducts are shown along with the results for Yb(OTf)$_3$ and Sc(OTf)$_3$ with the ionic radius[20] of metals in order of size. Although the enantioselectivities were

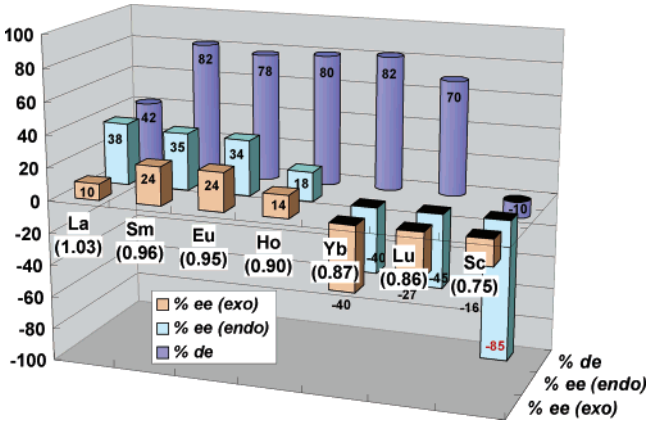


FIGURE 2. Relationship between metal and enantio- and diastereoselectivities in Pybox-*i*-Pr-M(OTf)$_3$-catalyzed reactions of diazoacetophenone **1** with aldehyde **3a**.

modest compared with those of the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr complex, some interesting trends were observed in terms of diastereo- and enantioselectivities (Figure 2). Good *exo*-selectivities were observed for Sm(OTf)$_3$, Eu(OTf)$_3$, Ho(OTf)$_3$, and Yb(OTf)$_3$, in which the ionic radii of each element ranged from 0.96 to 0.87 Å. The sense of asymmetric induction of the *endo*- and *exo*-approaches was switched between Ho and Yb. These results imply that the ionic radius of the lanthanide metal is an important factor in determining the diastereo- and enantioselectivity in the cycloaddition reaction of carbonyl ylide **2** with aldehyde **3a**.

The reactions of diazoacetophenone **1** with several benzyloxyacetaldehyde derivatives **3b**−**3f** were also carried out in the presence of the catalyst (10 mol %) prepared from Sc(OTf)$_3$ and (*S*,*S*)-Pybox-*i*-Pr under optimized conditions (Scheme 2, Table 2). Although substituents on the benzene ring of the arylmethyl group showed minor effects on the diastereoselectivities, all reactions proceeded smoothly with high enantioselectivities (82−93% ee) of the *endo*-adducts (entries 2−6). On the other hand, only modest asymmetric induction (*endo* 3% ee, *exo* 14% ee, *endo*:*exo* = 40:60, 28% yield) was observed in the reaction with benzaldehyde in the presence of the same

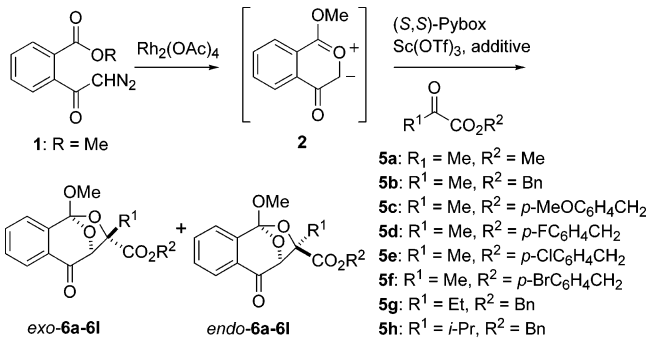
(20) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

TABLE 2. Reactions of Diazoacetophenone 1 with Several Benzyloxacetaldehyde Derivatives 3a−3f Catalyzed by Sc(III)−Pybox-*i*-Pr Complex[a]

entry	aldehyde	Ar	temp (°C)	yield (%)	*endo*:*exo*	% ee[b] *endo*	% ee[b] *exo*
1	**3a**	Ph	−10	96	88:12	91	18
2	**3b**	*o*-MeOC$_6$H$_4$	−10	82	85:15	82	15
3	**3c**	*p*-MeO C$_6$H$_4$	−10	53	91:9	89	12
4	**3d**	*p*-F C$_6$H$_4$	−10	97	82:18	93	22
5	**3e**	*p*-Cl C$_6$H$_4$	−25	84	73:27	86	10
6	**3f**	*p*-Br C$_6$H$_4$	−25	77	67:33	83	5

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 h to a suspension of the Pybox-*i*-Pr-Sc(OTf)$_3$ complex (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), and aldehydes **3a**−**3f** in CH_2Cl_2. [b] Determined by HPLC analysis (Daicel Chiralpak AS or AD). Absolute configuration of the product was not determined.

SCHEME 3. Asymmetric Cycloaddition Reactions of 2-Benzopyrylium-4-olate with α-Keto Ester Derivatives Catalyzed by (*S*,*S*)-Pybox-Sc(OTf)$_3$



Sc(III) catalyst. This result indicates that bidentate coordination of a dipolarophile to a chiral Lewis acid catalyst is important for high enantioselectivity.

Reactions with α-Keto Esters. Based on the above observation, pyruvate was selected as a dipolarophile that can coordinate in a bidentate fashion with Lewis acids. In contrast to the diastereoselectivity of the reaction with benzyloxyacetaldehde derivatives **3a**−**3f**, the Sc(III)−(*S*,*S*)-Pybox catalyzed reactions of diazoacetophenone **1** with methyl and benzyl pyruvate (**5a** and **5b**) showed high *exo*-selectivity.[19] This is attributed to the unfavorable dipolar interactions between the carbonyl groups of ylide **2** and the ester in the *endo*-approach (Scheme 3, Table 3, entries 1−4 and 8). However, the maximum enantiomeric excess of the *exo*-adduct was only 56% ee when (*S*,*S*)-Pybox-TPSm was used as a ligand. After several attempts to increase the enantioselectivity, diastereo- (*exo*:*endo* = 93:7) and enantioselectivies (*exo* 87% ee) were both determined to improve in the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr-catalyzed reaction (85% yield) when benzyl pyruvate was contaminated with pyruvic acid (about 30 mol % determined by ^{1}H NMR (400 MHz) analysis). The influence of the amount of pyruvic acid on diastereo- and enantioselectivities was then investigated (Figure 3). In these experiments, after preparation of the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr catalyst and subsequent addition of $Rh_2(OAc)_4$ and benzyl pyruvate, a 1 mol/L solution of pyruvic acid in CH_2Cl_2 was added prior to the reaction. The enantioselectivity of the *exo*-adduct dramatically increased to over 80% ee in the presence of 10−20 mol % pyruvic acid as an additive (Figure 3, Table 3, entries 14 and 15). The diastereoselectivity and yields also were at a maximum with these amounts of additive. Therefore, several other ketone and acid additives were examined for their influence on the diastereo- and enantioselectivites in the reaction with benzyl pyruvate (entries 9−13, 16−18, and 22). Some ketones and acids increased the enantioselectivity compared with that in the absence of additive. However, trifluoroacetic acid (TFA) (10 mol %) was found to be the most effective additive for both high diastereo- and enantioselectivities (entry 18). Furthermore, decreasing the reaction temperature to −25 °C in the presence of TFA (10 mol %), yielded an *exo*-adduct in the Sc(III)-catalyzed reaction with 94% ee (entry 19). It is important to note that the enantioselectivity of the minor adduct was also high (95% ee) compared with that of minor adduct in the reaction with benzyloxyacetaldehyde. In the Sc(III)-catalyzed reaction with methyl pyruvate, TFA was similarly a more effective additive than pyruvic acid in terms of enantioselectivity of the *exo*-adduct (entries 5−7).

The period at which TFA was added during the preparation of the catalyst was also investigated (Figure 4). Results indicated that addition of TFA just before adding diazo compound **1** (Figure 4, Operation C), after preparation of the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr catalyst and then addition of $Rh_2(OAc)_4$ and benzyl pyruvate showed the best results in terms of diastero- and enantioselectivity (Table 3, entry 18) at −10 °C. However, preparation of Sc(III)−(*S*,*S*)-Pybox-*i*-Pr in the presence of TFA (Operation A, Table 3, entry 20) or addition of TFA before adding $Rh_2(OAc)_4$ and benzyl pyruvate (Operation B, Table 3, entry 21) did not significantly decrease the diastereo- (both *exo*:*endo* = 92:8) and enantioselectivities (84% ee and 81% ee, respectively). Control experiments in which the reactions in the absence of either Sc(OTf)$_3$ or $Rh_2(OAc)_4$ were also conducted. The reaction in the absence of Sc(OTf)$_3$ proceeded smoothly to yield racemic cycloadducts (*exo*:*endo* = 80:20) in 98% yield. On the other hand, the reaction in the absence of $Rh_2(OAc)_4$ did not proceed at all. These results suggest that the Rh(II)−(*S*,*S*)-Pybox-*i*-Pr complex does not catalyze asymmetric induction, whereas the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr-TFA complex serves as an active catalyst for high enantioselectivity of the cycloaddition after the generation of 2-benzopyrylium-4-olate by $Rh_2(OAc)_4$.

In an effort to elucidate the structure of the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr complex containing TFA, the ^{1}H NMR spectrum of the complex was measured. The spectrum of the complex prepared by stirring a mixture of (*S*,*S*)-Pybox-*i*-Pr and Sc(OTf)$_3$ in the presence of MS 4A for 2 h in $CDCl_3$ is shown in Figure 5. Downfield shifts of protons on oxazolines, 4-protons on a pyridine, and isopropyl methine protons compared with those of (*S*,*S*)-Pybox-*i*-Pr suggest that complexation of (*S*,*S*)-Pybox-*i*-Pr and Sc(OTf)$_3$ occurred (Figure 5, (a) and (b)). Addition of $Rh_2(OAc)_4$ to the complex solution did not show any changes in the spectrum (Figure 5, (c)). Contrastingly, addition of TFA (1 equiv, 1 mol/L solution in $CDCl_3$) to the complex solution prepared by the procedure described above showed a downfield shift of methine protons of *i*-Pr and the oxazoline ring as well as a broadening of all

TABLE 3. Reactions of Diazoacetophenone 1 with Pyruvates 5a and 5b Catalyzed by Sc(III)−Pybox Complexes in the Presence of Additives[a]

entry	pyruvate	Pybox	additive (mol %)[b]	yield (%)	*exo*:*endo*	% ee[c] *exo* ( )[d]	% ee[c] *endo* ( )[d]
1	**5a**	TBSm	none	95	96:4	53 (+)	30 (+)
2	**5a**	TBDPSm	none	93	92:8	49 (+)	36 (+)
3	**5a**	TPSm	none	93	95:5	56 (+)	44 (+)
4	**5a**	*i*-Pr	none	84	88:12	46 (−)	26 (−)
5	**5a**	*i*-Pr	$CH_3COCOOH$ (10)	88	96:4	78 (−)	60 (−)
6	**5a**	*i*-Pr	$CH_3COCOOH$ (20)	71	94:6	71 (−)	nd
7	**5a**	*i*-Pr	CF_3COOH (10)	97	96:4	84 (−)	69 (−)
8	**5b**	*i*-Pr	none	82	82:18	11 (−)	2 (−)
9	**5b**	*i*-Pr	CH_3COCH_3 (20)	84	83:17	28 (−)	22 (−)
10	**5b**	*i*-Pr	CH_3COOH (20)	90	87:13	46 (−)	16 (−)
11	**5b**	*i*-Pr	$CH_3COCH_2CH_2COOH$ (20)	86	86:14	49 (−)	21 (−)
12	**5b**	*i*-Pr	$CH_2(COOH)_2$ (20)	85	84:16	28 (−)	10 (−)
13	**5b**	*i*-Pr	$CH_2(COMe)_2$ (20)	64	76:24	3 (−)	4 (+)
14	**5b**	*i*-Pr	$CH_3COCOOH$ (10)	94	93:7	82 (−)	74 (−)
15	**5b**	*i*-Pr	$CH_3COCOOH$ (20)	88	93:7	87 (−)	67 (−)
16	**5b**	*i*-Pr	TfOH (10)	73	81:19	31 (−)	49 (−)
17	**5b**	*i*-Pr	TfOH (20)	75	81:19	36 (−)	55 (−)
18	**5b**	*i*-Pr	CF_3COOH (10)	quant	94:6	90 (−)	88 (−)
19[e]	**5b**	*i*-Pr	CF_3COOH (10)	98	93:7	94 (−)	95 (−)
20	**5b**	*i*-Pr	CF_3COOH (10)[f]	quant	92:8	84 (−)	67 (−)
21	**5b**	*i*-Pr	CF_3COOH (10)[g]	98	92:8	81 (−)	64 (−)
22	**5b**	*i*-Pr	CF_3COOH (20)	quant	92:8	82 (−)	57 (−)

[a] The reaction was carried out at −10 °C by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 h to a suspension of the Sc(III)−Pybox complexes (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), additives, and pyruvates **5a** or **5b** in CH_2Cl_2. [b] Additives were added after an addition of $Rh_2(OAc)_4$ before adding pyruvates. [c] Determined by HPLC analysis (Daicel Chiralpak AS). Absolute configuration of the product was not determined. [d] The sign of the optical rotation. [e] The reaction was carried out at −25 °C. [f] The Sc(III)−Pybox-*i*-Pr catalyst was prepared in the presence of TFA. [g] TFA was added before the addition of $Rh_2(OAc)_4$ and benzyl pyruvate.

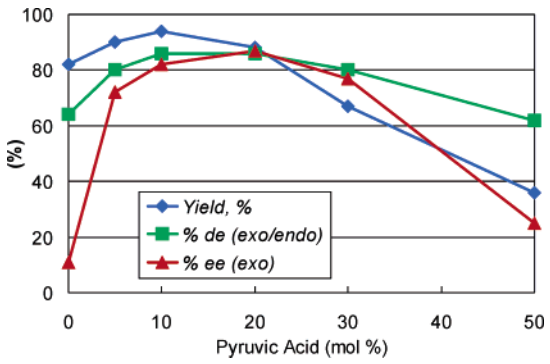


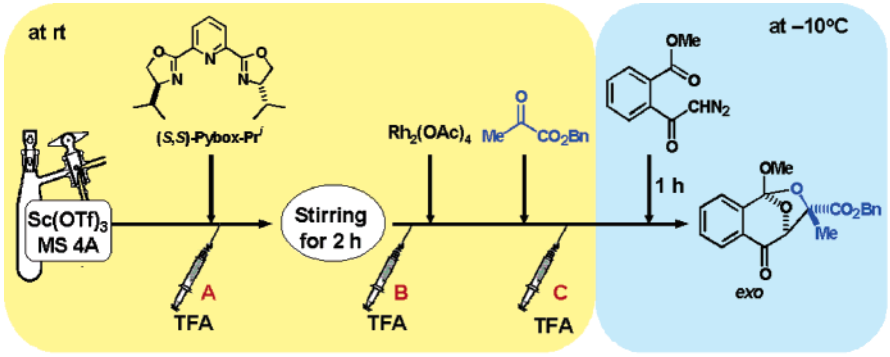
FIGURE 3. Effect of pyruvic acid as an additive in the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr-catalyzed reaction of diazoacetophenone **1** with benzyl pyruvate (**5b**).

signals (Figure 5, (d)). This spectrum was completely different from that obtained for the mixture of (*S*,*S*)-Pybox-*i*-Pr and TFA in $CDCl_3$. These spectra indicate that an active chiral catalyst for the asymmetric cycloaddition reaction of 2-benzopyrylium-4-olate with pyruvates probably is a complex produced from the three components containing (*S*,*S*)-Pybox-*i*-Pr, $Sc(OTf)_3$, and TFA, and $Rh_2(OAc)_4$ acts as a catalyst for decomposition of diazo compound independently from the chiral catalyst. In the three-component complex, TFA may be coordinated to one of the nitrogen atoms on the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr complex or effected in counteranion exchange from a downfield shift of methine protons of *i*-Pr and the oxazoline ring shown in Figure 5, (d).

The Sc(III)−(*S*,*S*)-Pybox-*i*-Pr catalytic system including TFA was applied to the reaction with several pyruvate derivatives and α-keto esters (Table 4, Scheme 3). High levels of diastereo- (*exo*:*endo* = 96:4−97:3) and enantioselectivity (92−94% ee) were observed in the reaction with a number of *p*-substituted benzyl pyruvates. The electronic character of the *p*-substituents however, did not influence the selectivity (entries 3−6). The asymmetric 1,3-dipolar cycloadidtion reactions with several other α-keto esters were also satisfactory in terms of high enantioselectivities of *exo*-cycloadducts (entries 7−11). A reaction of diazo substrate **7** bearing isopropyl ester with benzyl pyruvate proceeded smoothly under similar conditions to give cycloadducts with slightly reduced diastereoselectivity and high enantioselectivity (entry 12, Scheme 4). In the case of the reactions of diazo compound **1** with benzyl glyoxylate (**5l**) and diethyl oxomalonate (**5m**) in the presence of the same catalytic system, the enantioselectivities were low to moderate (entries 13 and 14, Scheme 3).

An absolute configuration of cycloadduct **6f** was also determined by X-ray crystallographic analysis using an anomalous dispersion of bromine atoms. As shown in the crystal structure (Figure 6), the cycloadduct *exo*-**6f** has a (1*S*,5*S*,7*S*) configuration, indicating that the cycloaddition of carbonyl ylide **2** occurred from the *si* face of pyruvate **5f**. Other cycloadducts of α-keto esters were presumed to have the same absolute configurations because the *re* face of α-keto esters must be similarly shielded by the complexation with the chiral Sc(III) catalyst.

Recently, Evans determined the structure of (*S*,*S*)-Pybox-Ph-$Sc(OTf)_3$ complex, as its derived monohydrate, by X-ray crystallography.[22] The metal features a pentagonal bipyramidal geometry with the three triflate ligands bound to the metal center. In the discussion for the stereochemical course of highly enantioselective scandium triflate catalyzed addition and annulation reactions of allenylsilanes with ethyl glyoxylate, two of the triflates in the Pybox−Sc(III) complex are dissociated



entry	addition of TFA	yield, %	*exo*:*endo*	% ee *exo*
1	A	quant	92:8	84
2	B	98	92:8	81
3	C	quant	94:6	90

FIGURE 4. Operation using TFA in the Pybox-*i*-Pr−Sc(III)-catalyzed reaction.

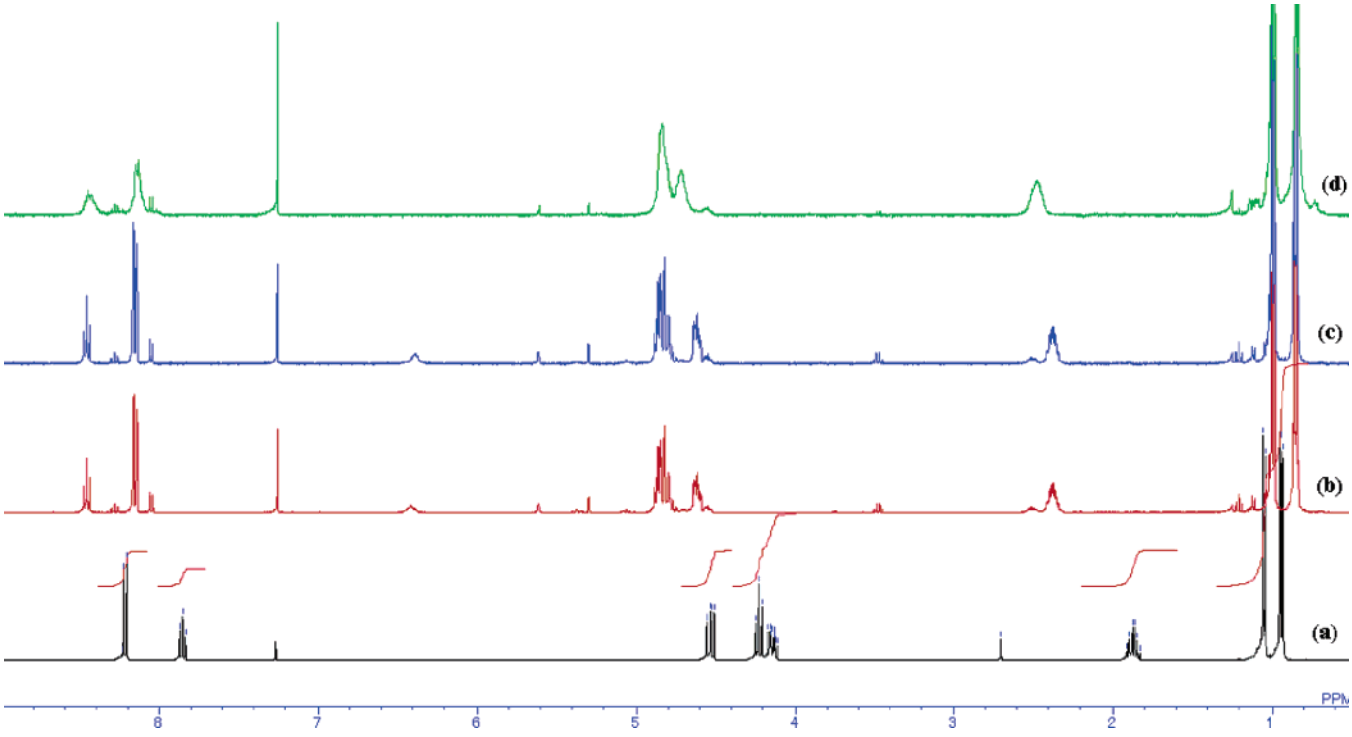


FIGURE 5. ^{1}H NMR spectrum of the Sc(III)−(*S*,*S*)-Pybox-*i*-Pr catalyst including TFA.

from the metal center, an aldehyde functionality is bound in the apical position, and then addition of the allenylsilane from the *re* face is favored as the *si* face is effectively shielded by a phenyl group of the bis(oxazolinyl)pyridine ligand. As mentioned above, in our cases, an attack of 2-benzopyrylium-4-olate occurred from the *si* face of pyruvate **5f** by the determination of the configuration of the cycloadduct shown in Figure 6. Therefore, the sense of asymmetric induction was opposite from that reported for addition and annulation reactions of allenylsilanes with ethyl glyoxylate. Although the issue of the coordination number of the catalyst−substrate complex as well as structure of the complex in the presence of TFA remains unresolved, TFA as an additive or the isopropyl group of the bis(oxazolinyl)-pyridine ligand probably accounted for the reversion of the sense in the asymmetric induction.

Reaction with 3-Acryloyl-2-oxazolidinone. An olefinic dipolarophile capable of coordinating with Lewis

(21) The reaction in the absence of Lewis acid proceeded with *endo*-selectivity both at room temperature (*endo*:*exo* = 71:29) and −25 °C (*endo*:*exo* = 81: 19), see ref 17d.

(22) (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc*. **2001**, *123*, 12095. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.

TABLE 4. Asymmetric Cycloaddition Reactions of Carbonyl Ylide 2 with α-Ketoesters Catalyzed by Sc(III)−Pybox-*i*-Pr-TFA Complex[a]

entry	R	R^1	R^2	yield (%)	*exo*:*endo*	% ee[b] *exo*	% ee[b] *endo*
1	Me	Me	Me	97	96:4	84	69
2	Me	Me	Bn	98	93:7	94	95
3	Me	Me	*p*-$MeOC_6H_4CH_2$	quant	96:4	94	94
4	Me	Me	*p*-$FC_6H_4CH_2$	93	96:4	94	95
5	Me	Me	*p*-$ClC_6H_4CH_2$	95	97:3	92	87
6	Me	Me	*p*-$BrC_6H_4CH_2$	93	96:4	93	88
7	Me	Et	Bn	98	93:7	89	61
8	Me	*i*-Pr	Bn	quant	93:7	95	95
9	Me	*i*-Pr	*p*-$BrC_6H_4CH_2$	98	96:4	95	98
10	Me	Ph	Me	88	68:32	80	45
11	Me	Ph	Bn	95	78:22	89	8
12	*i*-Pr	Me	Bn	77	88:12	93	98
13	Me	H	Bn	77	89:11	27	6
14	Me	CO_2Et	Et	quant		45	

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 h to a suspension of the Sc(III)−Pybox-*i*-Pr complex (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), TFA (10 mol %), and α-ketoesters in CH_2Cl_2. [b] Determined by HPLC (Daicel Chiralpak AS or AD).

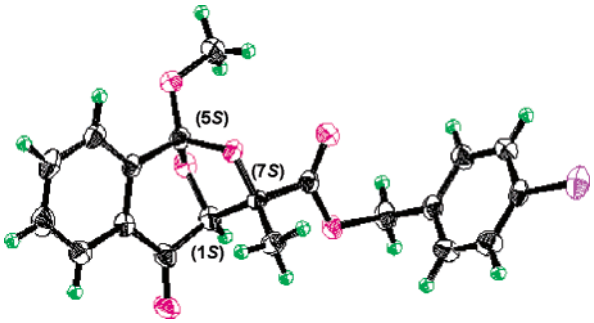
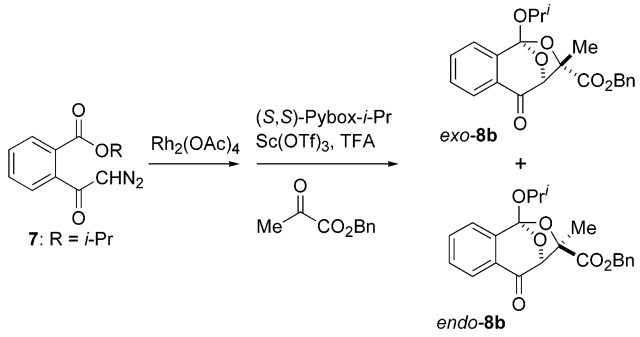


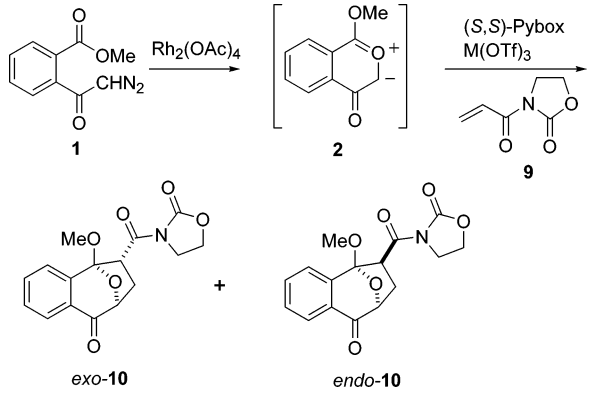
FIGURE 6. Crystal structure of *exo*-**6f**.

SCHEME 4. Asymmetric Reaction of Diazo Compound 7 with Benzyl Pyruvate Catalyzed by (*S*,*S*)-Pybox-Sc(OTf)$_3$-*i*-Pr-TFA



acids in a bidentate fashion, 3-acryloyl-2-oxazolidinone (**9**), was then selected for an asymmetric cycloaddition of 2-benzopyrylium-4-olate. The reaction was carried out similarly using combinations of several chiral Pybox and either $Sc(OTf)_3$ or $Yb(OTf)_3$ as chiral catalysts (Scheme 5, Table 5). Although high *endo*-selectivities in the presence of Sc(III)−Pybox catalysts compared with those using $Sc(OTf)_3$ without ligands (*exo*:*endo* = 60:40)[17d] were noteworthy, near absence to low levels of asymmetric induction were observed using a combination of chiral Pybox with $Sc(OTf)_3$ (entries 1−3). The use of (*S*,*S*)-Pybox-*i*-Pr and (*S*,*S*)-Pybox-TBSm with $Yb(OTf)_3$ as catalysts also showed *endo*-selectivities with low enantioselectivities of both *exo*- and *endo*-cycloadducts (entries 4 and 5). Interestingly, in the reaction with olefin **9**, the

SCHEME 5. Asymmetric Cycloaddition Reactions of 2-Benzopyryrium-4-olate with 3-Acryloyl-2-oxazolidinone (9) Catalyzed by (*S*,*S*)-Pybox-M(OTf)$_3$



combination of (*S*,*S*)-Pybox-Ph and $Yb(OTf)_3$ was found to be promising in terms of enantioselectivity of the *exo*-cycloadduct (entry 6). Further, it is interesting that the enantioselectivity of the *endo*-cycloadduct in this reaction using the Yb(III)−(*S*,*S*)-Pybox-Ph complex as a catalyst was extremely low in contrast to that of the *exo*-cycloadduct. This is thought to be due to the non-Lewis acid catalyzed reaction that proceeded under the reaction conditions in the case in which the *endo*-cycloadduct was formed.[21] To improve the diastereoselectivity of the reaction, lowering the concentration of 2-benzopyrylium-4-olate in the reaction mixture by a slow addition of diazo substrate **1** was investigated (entries 6−8). Increasing the addition time from 1 to 3 h resulted in increasing *exo*-selectivity (70:30) as well as enantioselectivity (91% ee) of the *exo*-adduct. Further optimization of the reaction conditions (lowering the temperature to − 25 °C and slowing the addition to 6 h), improved the diastereoselectivity to *exo*:*endo* = 88:12 and increased the enantioselectivity of the *exo*-cycloadduct to 98% ee (entry 9). However, as shown in entry 10, the use of another lot of $Yb(OTf)_3$ in several runs resulted in a problem in terms of reproducibility of the diastereo- and enantioselectivity. Careful observation of the preparation of the Yb(III)−Pybox-Ph complex in the absence of MS 4A revealed that

TABLE 5. Influence of Pybox Ligands and Metal on Enantio- and Diastereoselectivity in the Pybox-M(OTf)$_3$-Catalyzed Reaction of Diazoacetophenone 1 with 3-Acryloyl-2-oxazolidinone (9)[a]

							% ee[c]	
entry	Pybox	M(OTf)$_3$	temp (°C)	time[b]	yield (%)	*exo*:*endo*	*exo*	*endo*
1	*i*-Pr	Sc(OTf)$_3$	−10	1	65	10:90	1	8
2	TBSm	Sc(OTf)$_3$	−10	1	92	15:85	1	3
3	Ph	Sc(OTf)$_3$	−10	1	86	11:89	14	7
4	*i*-Pr	Yb(OTf)$_3$	−10	1	90	12:88	22	12
5	TBSm	Yb(OTf)$_3$	−10	1	91	23:77	3	1
6	Ph	Yb(OTf)$_3$	−10	1	94	54:46	89	4
7	Ph	Yb(OTf)$_3$	−10	1.5	90	69:31	93	1
8	Ph	Yb(OTf)$_3$	−10	3	97	70:30	91	4
9	Ph	Yb(OTf)$_3$	−25	6	89	88:12	98	4
10[d]	Ph	Yb(OTf)$_3$	−25	6	82−96	46:54−86:14	47−92	<4

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over the period of the time listed in the table to a suspension of either Sc or Yb catalyst (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), and oxazolidinone **9** in CH_2Cl_2. [b] Addition time of diazo compound **1**. [c] Determined by HPLC (Daicel Chiralpak AS). Absolute configuration of the product was not determined. [d] Results of several runs using another lot of Yb(OTf)$_3$.

TABLE 6. Influence of Water in the Preparation of Pybox-Ph-Yb(III) Catalyst on Diastereo- and Enantioselectivity[a]

						% ee[c]	
entry	water (mol %)	conditions[b]	MS 4A	yield (%)	*exo*:*endo*	*exo*	*endo*
1	xH$_2$O[d]	A	yes	88	52:48	21	1
2	xH$_2$O[d]	B	yes	88	61:39	52	3
3[e]	30	C	no	43	33:67	69	5
4[e]	20	D	yes	76	73:27	91	8
5[e]	10	D	yes	98	90:10	92	8
6[e,f]	10	D	yes	51−94	67:33−83:17	90−98	2−10
7[e]	10	E	yes	72	74:26	95	5
8[e,f]	10	E	yes	59−93	73:27−77:23	84−95	5−10

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 6 h to a suspension of the Yb(III)−Pybox-Ph complex (10 mol %), MS 4A, $Rh_2(OAc)_4$ (2 mol %), water, and oxazolidinone **9** in CH_2Cl_2. [b] The conditions for preparation of the Yb(III)−Pybox-Ph complex. Conditions A: The complex was prepared in CH_2Cl_2 in the presence of MS 4A for 2 h. Conditions B: The complex was prepared in CH_2Cl_2 in the absence of MS 4A for 2 h and subsequently stirred with MS 4A for 2 h. Conditions C: The complex was prepared in the absence of MS 4A for 2 h. Conditions D: The complex was prepared in the absence of MS 4A for 1 h and subsequently stirred with MS 4A for 2 h. Conditions E: The complex was prepared in the absence of MS 4A for 1 h and subsequently aged with MS 4A and oxazolidinone **9** for 2 h. [c] Determined by HPLC (Daicel Chiralpak AS). Absolute configuration of the product was not determined. [d] Yb(OTf)$_3$·xH$_2$O was used. [e] Yb(OTf)$_3$ was dried at 200 °C under reduced pressure for over 12 h. [f] Results of many runs under the conditions, expect a representative entry.

Yb(OTf)$_3$ did not always completely dissolve in CH_2Cl_2. When a small amount of water was added to the heterogeneous suspension of Yb(OTf)$_3$ and Pybox-Ph in CH_2Cl_2, the suspension became a clear solution. This indicates that a small amount of moisture may influence the preparation of the complex in CH_2Cl_2 as a result of the hygroscopic properties of Yb(OTf)$_3$. Thus, the addition of water as additive or the use of Yb(OTf)$_3$·xH$_2$O in the preparation of the Yb(III)−Pybox-Ph catalyst was examined (Table 6). In these investigations, Yb(OTf)$_3$ utilized for the reaction was individually dried in a Schlenk tube at 200 °C in vacuo for 12 h. Although the use of the hydrate for the preparation of the catalyst did not show any satisfactory results in terms of diastero- and enantioselectivities, addition of 10−20 mol % water per diazo substrate **1** clearly affected the enantioselectivity. Thus, the cycloaddition reaction catalyzed by the complex (10 mol %) prepared by mixing Yb(OTf)$_3$, (*S*,*S*)-Pybox-Ph, and water (1 equiv per Yb(OTf)$_3$) in CH_2Cl_2 at room temperature for 1 h and subsequently stirred with MS 4A in the absence (Conditions D) or in the presence of 3-acryloyl-2-oxazolidinone (Conditions E) for 2 h showed high enantioselectivity of the *exo*-cycloadduct (entries 5 and 7, 92% and 95% ee, respectively). The reproducibility of this reaction under Conditions D and E, shown in entries 6 and 8, respectively, indicated that the *exo*-adduct can consistently be isolated with enantiomeric excesses over 90%. However, a problem remains in terms of the diastereoselectivity, which ranged from 67:33 to 90:10 in this reaction.

Finally, the complex was prepared in THF, which easily dissolves Yb(OTf)$_3$. Yb(OTf)$_3$ and (*S*,*S*)-Pybox-Ph were mixed in THF for 2 h, the solvent was then removed, and the complex was dried 120 °C in vacuo (<3 mmHg) for 5 h. The reaction was carried out with the above complex in CH_2Cl_2 under conditions similar to those used in entry 9, Table 5. The desired *exo*-cycloadducts were obtained in high yields with high diastereo- (*exo*:*endo* = 82:18) and enantioselectivities (96% ee). From the investigation of a number of runs under these conditions, no problem was observed in terms of reproducibility with respect to the diastereo- (*exo*:*endo* = 80:20−86:14) and enantioselectivity (96−97% ee). Because of good solubility of Yb(OTf)$_3$ in THF, the chiral Yb(III)−Pybox-Ph complex was reproducibly obtained in the THF solution, probably as a complex including THF or H_2O molecules. Therefore, the resulting chiral Yb(III) complex prepared efficiently by this procedure was presumed to operate effectively as a chiral Lewis acid after replacement of solvent to CH_2Cl_2 in the cycloaddition reaction of 2-benzopyrylium-4-olate with oxazolidinone **9** to give the desired cycloadduct with high diastereo- and enantioselectivity.

In conclusion, highly enantioselective cycloaddition reactions of 2-benzopyrylium-4-olate catalyzed by chiral

Pybox−rare earth metal triflate complexes were successfully achieved. In the reaction with benzyloxyacetaldehyde and its derivatives, the complex (10 mol %) prepared from (*S*,*S*)-Pybox-*i*-Pr and $Sc(OTf)_3$ was effective in obtaining high *endo*-selectivity and enantioselectivity, whereas TFA (10 mol %) was required as additive to obtain high enantioselectivity and high *exo*-selectivity in cycloadditions with α-keto esters catalyzed by the same complex. On the other hand, the complex prepared by the combination of (*S*,*S*)-Pybox-Ph and $Yb(OTf)_3$ was determined to be an efficient catalyst for the enantioselective cycloaddition with 3-acryloyl-2-oxazolidinone with high *exo*-selectivity and enantioselectivity. Further studies to extend this enantioselective cycloaddition methodology for other carbonyl ylides generated from diazo compounds are currently underway.

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Supporting Information Available: Details of experimental procedures, spectroscopic data of the reaction products, and X-ray structure in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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