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COMMUNICATIONS

Published on Web 11/19/2002

Highly Enantioselective 1,3-Dipolar Cycloaddition Reactions of 2-Benzopyrylium-4-olate Catalyzed by Chiral Lewis Acids

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Received September 24, 2002

Intramolecular carbenoid-carbonyl cyclization of diazocarbonyl compounds catalyzed by rhodium(II) catalysts is one of the most convenient methods for generating carbonyl ylides.[1] Although this procedure has been efficiently applied in the syntheses of biologically active natural products and their skeletons, such as brevicomin,[2] zaragozic acids,[3] epoxysorbicillinol,[4] and illudins,[5] the procedure could only be applied in the production of racemates, and therefore development of an enantioselective version is desirable for the synthesis of medicinally important compounds. Recently, Hodgson[6] and Hashimoto[7] have separately reported on enantioselective carbonyl ylide cycloadditions that were catalyzed by chiral rhodium complexes, in which the chiral rhodium(II)-associated carbonyl ylides were proposed as participating in the transition state. However, this method still has limitations in terms of utility with a variety of dipolarophiles, chemical yields, and requirements for specific conditions. On the other hand, previous to our first report in 1998,[8] the attempt to use Lewis acids in the cycloaddition of carbonyl ylides for controlling enantio-, or even diastereo- or regioselectivity has not been studied, probably due to the lability and the Lewis-basic character of carbonyl ylides. Herein, we report on the first example of significant levels of enantioselectivity obtained in the 1,3-dipolar cycloadditions of 2-benzopyrylium-4-olate with dipolarophiles, which are capable of coordinating in a bidentate fashion, using rare earth metal triflate complexes of chiral 2,6-bis(oxazolinyl)pyridine (Pybox) as the chiral Lewis acid catalyst.[9]

Initially, a mixture of (*S*,*S*)-Pybox-*i*-Pr (see Chart 1) (10 mol %) and $Sc(OTf)_3$ (10 mol %) in CH_2Cl_2 was stirred at room temperature for 2 h. To this catalyst solution were added $Rh_2(OAc)_4$ (2 mol %), powdered 4 Å molecular sieves (MS 4A), and benzyloxyacetaldehyde (**3**). Addition of *o*-methoxycarbonyl-α-diazoacetophenone (**1**) over a period of 1 h at −10 °C (Table 1, entry 1) afforded *endo*- and *exo*-cycloadducts (55:45 ratio) in 91% total yield (Scheme 1). The enantiomeric excesses of the adducts were determined as 85% ee (*endo*) and 16% ee (*exo*) using HPLC analysis. Surprisingly, on the basis of investigations using various conditions in the preparation of the Sc(III) catalysts (Table 1, entries 2−4), the presence of MS 4A during the catalyst preparation was shown to greatly improve *endo*-selectivity (*endo*:*exo* = 88:12)[10] and to increase the level of enantioselectivity (91% ee) of the *endo*-cycloadduct (entry 4).[11] The Sc(III) complex of (*S*,*S*)-Pybox-Ph (see Chart 1) was similarly effective in preferably yielding the *endo*-isomer, with high enantioselectivity of the *endo*-cycloadduct (entry 7). In contrast, the use of $Yb(OTf)_3$ instead of $Sc(OTf)_3$ for the preparation of the catalyst resulted in high *exo*-selectivity with modest enantioselectivity of both adducts (entries 8−10).

Although substituents on the benzene ring of the arylmethyl group showed minor effects on the diastereoselectivities, Sc(III)-catalyzed reactions of benzyloxyacetaldehyde derivatives **4**−**8** (Scheme 1) proceeded smoothly without significant loss of enantioselectivities of the *endo*-cycloadducts (Table 2, entries 2−6). Interestingly, in contrast to aldehydes **3**−**8**, reactions using alkyl pyruvate **9** and **10**, which were catalyzed by Sc(III) complexes, showed high *exo*-selectivity; this can be attributable to unfavorable dipolar interactions between the carbonyl groups of ylide **2** and

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Chart 1

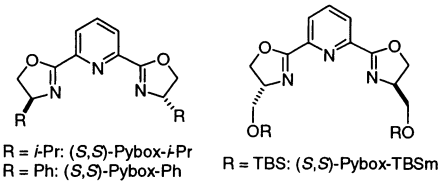
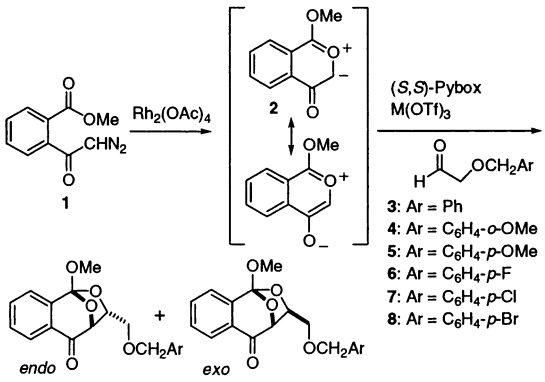


Table 1. Enantioselective Cycloadditions of Carbonyl Ylide **2** with Benzyloxyacetaldehyde (**3**) Catalyzed by (*S*,*S*)-Pybox−Rare Earth Metal Triflate Complexes[a]

					time[b]	yield		% ee[c]	
entry	M	Pybox	MS 4 Å[b]	temp[b]	h	%	*endo*:*exo*	*endo*	*exo*
1	Sc	*i*-Pr	no	rt	2	91	55:45	85	16
2	Sc	*i*-Pr	no	rt	6	94	76:24	86	34
3	Sc	*i*-Pr	no	reflux	2	87	77:23	88	16
4	Sc	*i*-Pr	yes	rt	2	96	88:12	91	18
5[d]	Sc	*i*-Pr	yes	rt	2	93	85:15	87	15
6	Sc	TBSm	no	rt	2	92	71:29	75	18
7	Sc	Ph	yes	rt	2	57	86:14	92	14
8	Yb	*i*-Pr	no	rt	2	99	9:91	40	40
9	Yb	*i*-Pr	yes	rt	2	98	9:91	35	36
10	Yb	Ph	yes	rt	2	quant	14:86	38	7

[a] The reaction was carried out at −10 °C in the presence of the Sc or Yb catalyst (10 mol %) and $Rh_2(OAc)_4$ (2 mol) 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 reaction was carried out at −25 °C.

Scheme 1



10.1021/ja028676c CCC: $22.00

Table 2. Enantioselective Cycloadditions of Carbonyl Ylide **2** with Aldehydes **3**−**8**, Pyruvates **9** and **10** Catalyzed by (*S*,*S*)-Pybox−Sc(OTf)$_3$ Complexes

entry	dipolarophile	additive[a]	temp, °C	yield, %	*endo*:*exo*	% ee[b]
1	**3**	no	−10	96	88:12	91 (*endo*)
2	**4**	no	−10	82	85:15	82 (*endo*)
3	**5**	no	−10	53	91:9	89 (*endo*)
4	**6**	no	−10	97	82:18	93 (*endo*)
5	**7**	no	−25	84	73:27	86 (*endo*)
6	**8**	no	−25	77	67:37	83 (*endo*)
7	**9**	no	−10	84	12:88	45 (*exo*)
8	**9**	yes (10 mol %)[c]	−10	88	4:96	78 (*exo*)
9	**10**	no	−10	82	18:82	11 (*exo*)
10	**10**	yes (20 mol %)[d]	−10	88	7:93	87 (*exo*)

[a] The reaction was carried out in the presence of pyruvic acid. [b] Determined by HPLC analysis. Absolute configuration of the product was not determined. [c] 20 mol %, *endo*:*exo* = 6:94, 72% ee (*exo*). [d] 10 mol %, *endo*:*exo* = 7:93, 82% ee (*exo*).

Scheme 2

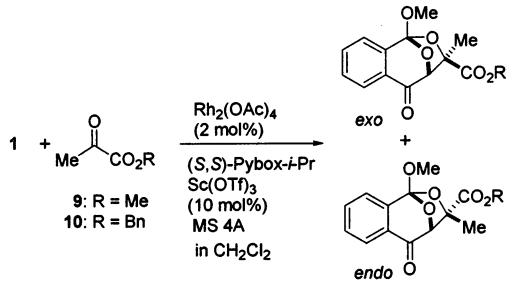
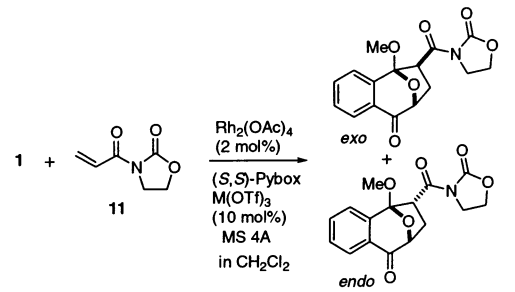


Table 3. Enantioselective Cycloadditions of Carbonyl Ylide **2** with 3-Acryloyl-2-oxazolidinone (**11**) Catalyzed by (*S*,*S*)-Pybox−Rare Earth Metal Triflate Complexes



entry	M	Pybox	temp,°C	time,[a] h	yield,%	*exo*:*endo*[b]	% ee, *exo*[c]
1	Sc	*i*-Pr	−10	1	65	10:90	1 (8)[d]
2	Sc	Ph	−10	1	86	11:89	14 (7)[d]
3	Yb	*i*-Pr	−10	1	90	12:88	22 (13)[d]
4	Yb	Ph	−10	1	94	54:46	89
5	Yb	Ph	−10	3	97	70:30	91
6	Yb	Ph	−25	6	89	88:12	98

[a] Addition time of **1**. [b] Determined by ^{1}H NMR (400 MHz). [c] Determined by HPLC analysis (Daicel Chiralpak AS). Absolute configuration of the product was not determined. [d] % ee of *endo* product.

the ester in the *endo* approach (Scheme 2, Table 2, entries 7−10). In the case of methyl pyruvate (**9**), maximum enantioselectivity was 78% ee, which was observed when the reaction was carried out in the presence of pyruvic acid (10 mol %). Satisfactory results were obtained in terms of enantioselectivity (87% ee) when benzyl pyruvate (**10**) was used in the presence of the additive (entry 10). From examinations using several ketones and carboxylic acids as additives and 5−50 mol % of pyruvic acid, 10−20 mol % of pyruvic acid produced the best results in terms of diastereo- and enantioselectivity. This implies that the complex of Sc(III)−Pybox-*i*-Pr and pyruvic acid is probably an active catalyst for high enantioselectivity in the reaction with pyruvates.

Although the reaction with 3-acryloyl-2-oxazolidinone (**11**) in the presence of (*S*,*S*)-Pybox-*i*-Pr−Sc(OTf)$_3$ complex (10 mol %) proceeded to give cycloadducts with high regio- and *endo*-selectivities (Table 3, entry 1), asymmetric induction was only weakly observed for cycloadducts (*endo*, 8% ee; *exo*, 1% ee). However, in this reaction, we have found that the combination of (*S*,*S*)-Pybox-Ph and Yb(OTf)$_3$ was extremely effective in affording a high level of enantioselectivity. Under Yb(III) complex-catalyzed conditions, the *exo*- and *endo*-cycloadducts were obtained with a ratio of 54:46, with 89% ee of the *exo*-adduct (entry 4). By optimizing the reaction conditions (lowering the temperature to −25 °C, and slowing the addition to 6 h), diastereoselectivity was improved to *exo*:*endo* = 88:12,[12] and the enantioselectivity of *exo*-cycloadduct was increased to 98% ee (entry 6).

In conclusion, we were successful in carrying out highly enantiselective cycloaddition reactions of 2-benzopyrylium-4-olate (**2**) catalyzed by chiral Pybox−rare earth metal triflate complexes. Further studies to extend this enantioselective cycloaddition methodology, not only for other carbonyl ylides but also for other 1,3-dipoles generated from diazo compounds, are currently underway.

Supporting Information Available: Representative experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) We have previously reported that asymmetric induction was observed in a ytterbium tris(*S*)-1,1′-binaphthyl-2,2′-diyl phosphonate-catalyzed cycloaddition of a carbonyl ylide with moderate enantioselectivity (up to 52% ee). See ref 8b.

(10) It is noteworthy that in the presence of Sc(OTf)$_3$ or Yb(OTf)$_3$ (10 mol %) without Pybox ligands, the reactions proceeded with high *exo*-selectivity (*exo*:*endo* = 94:6 or 93:7).

(11) Enantioselectivities in the reaction with benzaldehyde under the same conditions were only 3% ee (*endo*) and 14% ee (*exo*) (28% yield, *endo*:*exo* = 40:60). The reaction with benzyloxyacetaldehyde in the absence of Sc(OTf)$_3$ did not exhibit asymmetric induction. These results indicate that bidentate coordination of a dipolarophile to the catalyst, as a Lewis acid, is important for this reaction.

(12) Although the reason is not clear at this point, only Pybox-Ph-Yb(OTf)$_3$ complex specifically exhibited *exo*-selectivity in contrast to the other complexes (Table 3, entries 1−3, Pybox-TBSm−Yb(OTf)$_3$; *endo*:*exo* = 77:23, Pybox-TBSm−Sc(OTf)$_3$; *endo*:*exo* = 85:15).

JA028676C