ORGANIC LETTERS

2000
Vol. 2, No. 20
3145−3148

Stereocontrol in Rare Earth Metal Triflate-Catalyzed 1,3-Dipolar Cycloaddition Reaction of 2-Benzopyrylium-4-olate with Aldehydes

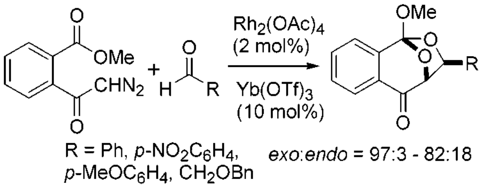
Hiroyuki Suga,*,† Akikazu Kakehi,† Suketaka Ito,† Kei Inoue,† Hajime Ishida,‡ and Toshikazu Ibata‡

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan, and Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan

sugahio@gipwc.shinshu-u.ac.jp

Received July 18, 2000

ABSTRACT



***Exo*-cycloadduct was obtained with high stereoselectivity by the addition of ytterbium triflate ($Yb(OTf)_3$) (10 mol %) in the rhodium(II) acetate ($Rh_2(OAc)_4$)-catalyzed decomposition of *o*-(methoxycarbonyl)-α-diazoacetophenone in the presence of benzaldehyde. In the reaction in the absence of $Yb(OTf)_3$, almost no selectivity was obtained. Stereoselectivity in the reactions with *p*-nitrobenzaldehyde, *p*-anisaldehyde, and benzyloxyacetaldehyde could be also controlled to high *exo* preference by the addition of $Yb(OTf)_3$.**

Intramolecular carbenoid−carbonyl cyclization has represented one of the most effective methods for generating carbonyl ylides[1] since we demonstrated the utility of the method by studying the transition metal-catalyzed decomposition of *o*-(alkoxycarbonyl)-α-diazoacetophenone.[2] For example, Padwa reported the application of this methodology to the synthesis of *exo*- and *endo*-brevicomin by using the $Rh_2(OAc)_4$-catalyzed reaction of 1-diazo-2,5-hexanedione with propionaldehyde after separation of the cycloadducts (Scheme 1).[3] In the case of brevicomin, both *exo* and *endo* isomers are exuded by the female Western Pine Beetle but the *exo* isomer is known to be a key component of the aggregation pheromone of this destructive pest. Control of the stereoselectivity in cycloadditions of carbonyl ylides therefore presents a challenge, with the prospect of applications in the synthesis of agrochemicals and medicinal chemicals.[4]

Recently, we reported the first attempt to control stereoselectivity using Lewis acids in cycloaddition of a carbonyl

---

† Shinshu University.
‡ Osaka University.

[1] (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

[2] (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**, 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.

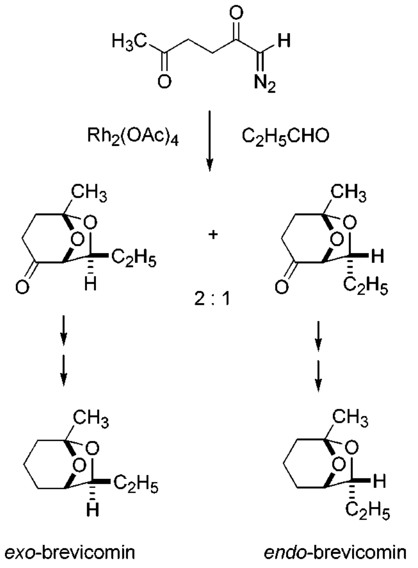
[3] Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.

[4] A few examples of enantioselective cycloadditions of carbonyl ylides using chiral rhodium catalysts have been repored: (a) Kitagawa, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417. (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *J. Chem. Soc., Chem. Commun.* **1999**, 2185 and references therein.

[5] Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165.

10.1021/ol0063454 CCC: $19.00

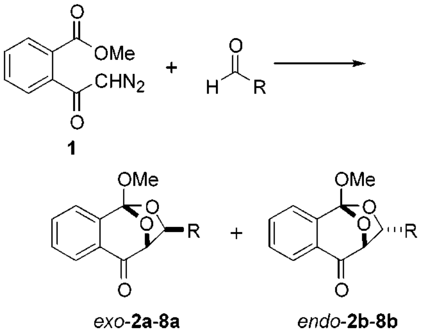
Scheme 1



ylide.[5] That is, the addition of 10 mol % of $Yb(OTf)_3$ was extremely effective in producing cycloadducts with high *endo*-selectivity in the transition metal-catalyzed reaction of *o*-(methoxycarbonyl)-α-diazoacetophenone (**1**) with *N*-substituted maleimides. In this paper, we report that the addition of $Yb(OTf)_3$ resulted in high *exo*-selectivity in the case of the reaction with aromatic aldehydes and benzyloxyacetaldehyde. We also report that the stereoselectivity was greatly influenced by the ionic radii of rare earth elements in the reaction with benzaldehyde.

$Rh_2(OAc)_4$-catalyzed decomposition of diazoacetophenone **1** in the presence of benzaldehyde (2 equiv) in CH_2Cl_2 at room temperature gave cycloadducts as a 1:1 mixture of *exo* and *endo* products (Scheme 2, Table 1, entries 1 and 2).

Scheme 2



Aluminum Lewis acids, aluminum tris(2,6-diphenylphenoxide) (ATPH)[6] and methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[7] were first examined to determine whether stereoselectivity was affected by the hindered structure of the catalysts (entries 3 and 4). Almost no effect was found in terms of stereoselectivity. On the other hand, the addition of $Yb(OTf)_3$ (10 mol %) in the $Rh_2(OAc)_4$-catalyzed reaction of **1** with benzaldehyde in CH_2Cl_2 greatly influenced stereoselectivity to give cycloadducts **2** with high *exo*-selectivity (entry 5). We also found that the use of molecular sieves (MS) increased yield. MS 4A Powder, 4A 1/16, 3A Powder, and 5A Powder were all effective (entries

Table 1. Reaction of Diazoacetophenone **1** with Benzaldehyde[a]

entry	catalyst (mol %)	solvent	MS	yield,[b] %	*exo*:*endo*[b]
1	$Rh_2(OAc)_4$ (2)	CH_2Cl_2		77	51:49
2	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	4A Powder	83	50:50
3	$Rh_2(OAc)_4$ (2) + ATPH (10)	CH_2Cl_2		68	51:49
4	$Rh_2(OAc)_4$ (2) + MDA (10)	CH_2Cl_2		76	54:46
5	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2		76	94:6
6	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	4A Powder	96	90:10
7	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	4A 1/16	86	92:8
8	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	3A Powder	83	88:12
9	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	5A Powder	80	93:7
10	$Rh_2(OAc)_4$ (2) + $Mg(OTf)_3$ (10)	CH_2Cl_2	4A Powder	93	51:49
11	$Rh_2(OAc)_4$ (2) + $Sc(OTf)_3$ (10)	CH_2Cl_2	4A Powder	82	69:31
12	$Rh_2(OAc)_4$ (2) + $Lu(OTf)_3$ (10)	CH_2Cl_2	4A Powder	quant.	89:11
13	$Rh_2(OAc)_4$ (2) + $Tm(OTf)_3$ (10)	CH_2Cl_2	4A Powder	96	87:13
14	$Rh_2(OAc)_4$ (2) + $Ho(OTf)_3$ (10)	CH_2Cl_2	4A Powder	93	83:17
15	$Rh_2(OAc)_4$ (2) + $Eu(OTf)_3$ (10)	CH_2Cl_2	4A Powder	99	73:17
16	$Rh_2(OAc)_4$ (2) + $Sm(OTf)_3$ (10)	CH_2Cl_2	4A Powder	91	70:30
17	$Rh_2(OAc)_4$ (2) + $La(OTf)_3$ (10)	CH_2Cl_2	4A Powder	87	55:45
18	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	$CHCl_3$	4A Powder	79	90:10
19	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	$ClCH_2CH_2Cl$	4A Powder	89	90:10
20	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	C_6H_6	4A Powder	67	79:21
21	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	THF	4A Powder	7	60:40
22	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	diethyl ether	4A Powder	89	97:3

[a] A solution of diazo compound **1** was added to a solution of benzaldehyde in the presence of $Rh_2(OAc)_4$ (2 mol %) and a Lewis acid (10 mol %) at room temperature over a period of 1 h. [b] Determined by HPLC analysis.

Table 2. Reaction of Diazoacetophenone **1** with Other Aldehydes[a]

entry	R	catalyst (mol %)	solvent	products	yield,[b] %	*exo*:*endo*
1	*p*-$MeOC_6H_4$	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**3a**, **3b**	68	46:54
2	*p*-$MeOC_6H_4$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	diethyl ether	**3a**, **3b**	77	87:13
3	*p*-$NO_2C_6H_4$	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**4a**, **4b**	93	25:75
4	*p*-$NO_2C_6H_4$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	diethyl ether	**4a**, **4b**	99	82:18
5	$CH_3CH_2CH_2$	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**5a**, **5b**	82	50:50
6	$CH_3CH_2CH_2$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	**5a**, **5b**	89	45:55
7	$(CH_3)_2CH$	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**6a**, **6b**	77	70:30
8	$(CH_3)_2CH$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	**6a**, **6b**	65	34:66
9	$(CH_3)_2CH$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	diethyl ether	**6a**, **6b**	37	55:45
10	*c*-hexyl	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**7a**, **7b**	83	71:29
11	*c*-hexyl	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	**7a**, **7b**	95	69:31
12	$PhCH_2OCH_2$	$Rh_2(OAc)_4$ (2)	CH_2Cl_2	**8a**, **8b**	96	69:31
13	$PhCH_2OCH_2$	$Rh_2(OAc)_4$ (2) + $Yb(OTf)_3$ (10)	CH_2Cl_2	**8a**, **8b**	97	93:7

[a] A solution of diazo compound **1** was added to a solution of aldehyde in the presence of $Rh_2(OAc)_4$ (2 mol %), $Yb(OTf)_3$ (10 mol %), and MS 4A Powder at room temperature over a period of 1 h. [b] Isolated yield.

6−9). It is also interesting that the stereochemical direction of the cycloaddition was the opposite of that of *N*-substituted maleimides.

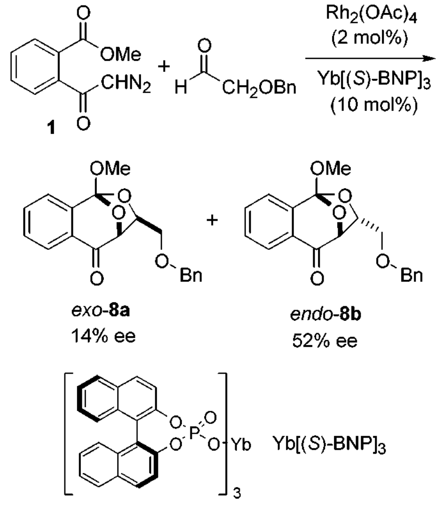
The effect of other metal triflates was also examined (entries 10−17).[8] Interestingly, the metal elements strongly influence the stereoselectivity. Thus, good *exo*-selectivity was obtained when the ionic radii of the lanthanide elements were close to that of ytterbium (entries 12 and 13). Larger or smaller ionic radii resulted in decreasing steroselectivity. The effect of different solvents was also investigated. When the reactions in several solvents were examined (entries 18−22), diethy ether was found to be the best solvent in terms of the highest *exo*-selectivity and high yield (entry 22).

The reactions of diazoacetophenone **1** with *p*-substituted benzaldehydes, aliphatic aldehydes, and benzyloxyacetaldehyde were also carried out in the presence and the absence of $Yb(OTf)_3$ (Scheme 2, Table 2). In the case of *p*-substituted benzaldehydes, the addition of $Yb(OTf)_3$ was also effective in obtaining high *exo*-selectivity which is independent of the electronic character of the *p*-substituent (entries 2 and 4). However, in the reaction with simple aliphatic aldehydes, the addition of $Yb(OTf)_3$ slightly increased the *endo*-cycloadduct or did not affect in terms of stereoselectivity (entries 5−11). On the other hand, in the reaction with benzyloxyacetaldehyde, the addition of $Yb(OTf)_3$ was quite effective in producing cycloadducts with extremely high *exo*-selectivity (entry 13).

Enantioselectivity in the reaction of diazoacetophenone **1** with benzyloxyacetaldehyde using a chiral Lewis acid was investigated. In the presence of 10 mol % of the chiral ytterbium catalyst, which was prepared from (*R*)-2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-BINOL), $Yb(OTf)_3$, and 1,2,6-trimethylpiperidine according to Kobayashi's procedure,[9] the reaction (rt, 1 h in the presence of MS 4A in CH_2Cl_2) proceeded with high *exo*-selectivity (*exo*:*endo* = 91:9) in 97% yield. However, almost no asymmetric induction was observed (*exo*:0% ee, *endo*:2% ee). (*S*)-BINOL-dichlorodiisopropoxytitanium-catalyst (10 mol %, −30 °C, 5 h in the presence of MS 4A in CH_2Cl_2) showed almost no diastereo- (*exo*:*endo* = 68:32) and enantioselective effect (*exo*:3% ee, *endo*:3% ee).

Interestingly, ytterbium tris(*S*)-1,1′-binaphthyl-2,2′-diyl phosphonate (Yb[(*S*)-BNP]$_3$), known to be an effective catalyst for hetero Diels−Alder reaction of Danishefsky's diene,[10] showed moderate enantioselectivity, although almost no diastereoselectivity (*exo*:*endo* = 57:43) was observed (Scheme 3, the absolute configuration of the products was not determined). To the best of our knowledge, this is the

Scheme 3



---

(6) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813 and references therein.

(7) Maruoka, K.; Ito, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588 and references therein.

(8) The ionic radii of each elements are as follows: Mg (0.65), Sc (0.68), Lu (0.84), Yb (0.85), Tm (0.86), Ho (0.89), Eu (0.96), Sm (0.97), La (1.04) (Å).

(9) (a) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Tetrahedron Lett.* **1993**, *34*, 4535. (b) Kobayashi, S.; Ishitani, H.; Araki, M.; Hachiya, I. *Tetrahedron Lett.* **1994**, *35*, 6325. (c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083.

(10) (a) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *New J. Chem.* **1995**, *19*, 707. (b) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79.

first example of asymmetric induction found in the chiral Lewis acid-catalyzed cycloaddition reaction of a carbonyl ylide.

In summary, we have found that addition of 10 mol % of $Yb(OTf)_3$ is quite effective for high *exo*-selectivity in the 1,3-dipolar cycloaddition reaction of 2-benzopyrylium-4-olate with aromatic aldehydes and benzyloxyacetaldehyde. The first example of asymmetric induction in the Yb[(*S*)-BNP]$_3$-catalyzed reaction of 2-benzopyrylium-4-olate with benzyloxyacetaldehyde was also found.

Further investigations to clarify the reaction mechanism and the scope of high *exo*-selectivity as well as to develop asymmetric reactions using the chiral lanthanide catalyst for cycloaddition of carbonyl ylides are now in progress.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

Supporting Information Available: Experimental procedures and characterization for compounds **2a**,**b**−**8a**,**b** and HPLC data for **8a** and **8b** using a chiral column. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0063454