ORGANIC LETTERS

2007
Vol. 9, No. 21
4359−4362

Dipole-LUMO/Dipolarophile-HOMO Controlled Asymmetric Cycloadditions of Carbonyl Ylides Catalyzed by Chiral Lewis Acids

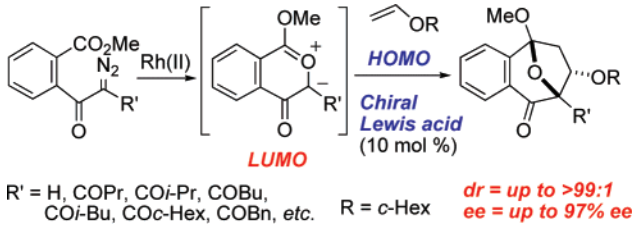
Hiroyuki Suga,*,† Daisuke Ishimoto,† Satoshi Higuchi,† Motoo Ohtsuka,† Tadashi Arikawa,† Teruko Tsuchida,† Akikazu Kakehi,† and Toshihide Baba‡

Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan, and Department of Environmental Chemistry & Engineering, Interdisciplinary Graduate School of Science & Engineering, Tokyo Institute of Technology, G1-14, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan

sugahio@shinshu-u.ac.jp

Received August 8, 2007

ABSTRACT



We have found the first successful example of reverse-electron-demand dipole-LUMO/dipolarophile-HOMO controlled cycloaddition reactions between carbonyl ylides, which were generated from *o*-methoxycarbonyl-α-diazoacetophenone and their acyl derivatives as precursors, and vinyl ether derivatives with high levels of asymmetric induction (97–77% ee) using chiral 2,6-(oxazolinyl)pyridine–Eu(III) or binaphthyldiimine–Ni(II) complexes as chiral Lewis acid catalysts.

Tandem Rh(II)-catalyzed carbonyl ylide formation/1,3-dipolar cycloaddition sequence of α-diazocarbonyl compounds with dipolarophiles has been realized as a powerful and efficient methodology for the synthesis of epoxy-bridged complex polycyclic systems.[1] Recently, this method has been applied toward the syntheses of a variety of biologically important natural products such as brevicomin,[2] zaragozic acids,[3] illudins,[4] epoxysorbicillinol,[5] colchicines,[6] aspidophytine,[7] and polygalolides.[8] Consequently, it has been a challenge to develop the catalytic enantioselective variant of the methodology in the efficient asymmetric synthesis of medicinally important oxygen-containing polycyclic com-

† Shinshu University.
‡ Tokyo Institute of Technology.

(1) For books and reviewes, see: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley and Sons: Hoboken, NJ, 2003.

(2) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.

(3) For representative examples, see: (a) Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432. (b) Nakamura, S.; Hirata, Y.; Kurosaki, T.; Anada, M.; Kataoka, O.; Kitagaki, S.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5351.

(4) (a) Padwa, A.; Sandanayaka, V. P.; Curtis, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 2667. (b) Kinder, F. R., Jr.; Bair, K. W. *J. Org. Chem.* **1994**, *59*, 6965. (c) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem.* **1997**, *62*, 1317.

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

(6) Graening, T.; Friedrichsen, W.; Lex, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1524. (b) Graening, T.; Bette, V.; Neudörfl, J.; Lex, J.; Schmalz, H.-G. *Org. Lett.* **2005**, *7*, 4317.

(7) Mejía-Oneto, J. M.; Padwa, A. *Org. Lett.* **2006**, *8*, 3275.

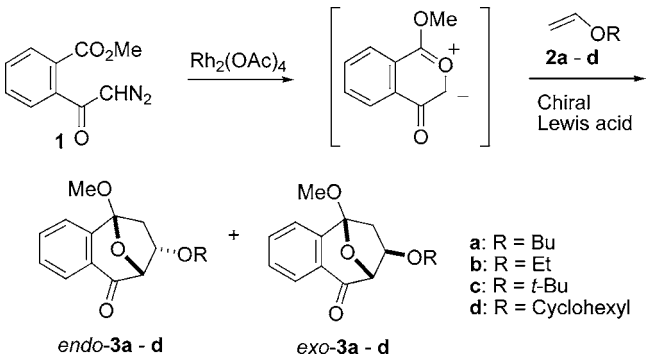
(8) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532.

10.1021/ol701936b CCC: $37.00
Published on Web 09/20/2007

pounds. Hodgson[9] and Hashimoto[10] have independently developed a highly enantioselective chiral Rh(II)-catalyzed procedure that features a chiral Rh(II)-associated carbonyl ylide in the transition state. In contrast, we have developed a conceptually different approach that involves the enantioselective dipole-HOMO/dipolarophile-LUMO controlled cycloadditions of 2-benzopyrylium-4-olate with electron-deficient carbonyl and olefinic dipolarophiles in the presence of rare earth metal complexes of chiral 2,6-(oxazolinyl)-pyridine (Pybox) as the chiral Lewis acid catalyst.[11] In this paper, we report the first successful examples of reverse-electron-demand dipole-LUMO/dipolarophile-HOMO controlled cycloadditions between 2-benzopyrylium-4-olates and vinyl ether derivatives, which were activated by chiral Lewis acids with high levels of asymmetric induction.

Initially, we examined the reaction of *o*-methoxycarbonyl-α-diazoacetophenone (**1**) with butyl vinyl ether (**2a**) in the presence of achiral Lewis acids. The reaction was carried out by adding a solution of acetophenone **1** to olefin **2a** (2 equiv) over a period of 1 h in the presence of $Rh_2(OAc)_4$ (2 mol %) in CH_2Cl_2 at room temperature (Scheme 1). In

Scheme 1. Reaction of Diazoacetophenone **1** with Olefin **2a**



comparison to the uncatalyzed reaction (8% yield, endo/exo = 87:13), the reactions in the presence of $Yb(OTf)_3$ or $Tm(OTf)_3$ (10 mol %) resulted in higher diastereoselectivities (both endo/exo = 94:6)[12] and yields (50% and 75%, respectively). On the basis of these encouraging results, complexes of chiral Pybox ligands (Figure 1) and $Yb(OTf)_3$

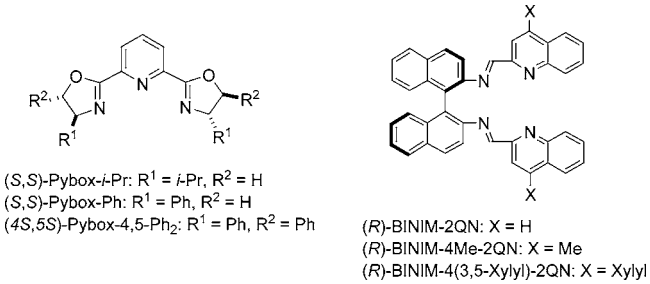


Figure 1. Structures of ligands.

were investigated as chiral Lewis acid catalysts (Table 1). Among the three chiral Pybox ligands, (4*S*,5*S*)-Pybox-Ph_2 showed moderate enantioselectivity and yield for the endo

Table 1. Reactions of Diazoacetophenone **1** with Olefins **2a**−**d** Catalyzed by Chiral Pybox−Lanthanoid Triflate Complexes[a]

entry	R	ligand	M	*T* (°C)	yield (%)	dr[b]	ee[c] (%)
1	Bu	Pybox-*i*-Pr	Yb	rt	44	83:17	4
2	Bu	Pybox-Ph	Yb	rt	48	84:16	2
3	Bu	Pybox-Ph_2	Yb	rt	57	75:25	62
4	Bu	Pybox-Ph_2	Yb	reflux	80	75:25	67
5	Bu	Pybox-Ph_2	Eu	reflux	94	81:19	81
6	Bu	Pybox-Ph_2	Gd	reflux	quant	81:19	85
7	Bu	Pybox-Ph_2	Ho	reflux	89	79:21	85
8	Bu	Pybox-Ph_2	Eu	0	20	86:14	8
9	Bu	Pybox-Ph_2	Eu	25	48	77:23	36
10	Bu	Pybox-Ph_2	Eu	30	78	81:19	76
11	Et	Pybox-Ph_2	Eu	reflux	92	83:17	83
12	*t*-Bu	Pybox-Ph_2	Eu	reflux	91	87:13	88
13	Cy[d]	Pybox-Ph_2	Eu	reflux	quant	88:12	95
14	Cy[d]	Pybox-Ph_2	Gd	reflux	93	88:12	94
15	Cy[d]	Pybox-Ph_2	Ho	reflux	99	88:12	96

[a] The reaction was carried out by adding a solution of **1** in CH_2Cl_2 to a suspension of **2a**−**d**, $Rh_2(OAc)_4$ (2 mol %), MS 4 Å, and Pybox-$M(OTf)_3$ complexes (10 mol %) over a period of 1 h. [b] Endo/exo determined by ^1H NMR. [c] Enantiomeric excess of endo adduct determined by chiral HPLC. [d] Cyclohexyl.

cycloadduct (entry 3), which were improved (yield 80%) by refluxing in CH_2Cl_2 (entry 4). The effects of the ionic radius of lanthanoid metals on the enantio- and diastereoselectivity were investigated using (4*S*,5*S*)-Pybox-Ph_2 as the ligand and refluxing in CH_2Cl_2; promising results were obtained for $Eu(OTf)_3$, $Gd(OTf)_3$, and $Ho(OTf)_3$ in terms of enantioselectivity (entries 5−7) (see the Supporting Information for additional details). It is noteworthy that the reaction temperature dramatically influenced the yields and enantioselectivities for the (4*S*,5*S*)-Pybox-Ph_2-Eu(III)-catalyzed reactions (entries 5, 8−10). Accordingly, the low yield and enantioselectivity for the reaction at 0 °C were drastically improved by raising the reaction temperature. In regard to the R group on the vinyl ether, a series of reactions in the presence of the (4*S*,5*S*)-Pybox-Ph_2-Eu(III) catalyst under reflux in CH_2Cl_2 revealed that a bulky substituent such as

(9) (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. (c) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465. (d) Hodgson, D. M.; Labande, A. H.; Glen, R.; Redgrave, A. J. *Tetrahedron*: *Asymmetry* **2003**, *14*, 921. (e) 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.

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

(11) (a) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836. (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47. (c) Suga, H.; Suzuki, T.; Inoue, K.; Kakehi, A. *Tetrahedron* **2006**, *62*, 9218.

(12) The endo adduct is defined as the product in which the more important substituent is on the opposite side of the epoxy bridge.

t-Bu and cyclohexyl yielded higher diastereo- and enantioselectivities (entries 11−13)−the reaction involving cyclohexyl vinyl ether (**2d**) gave an enantioselectivity of 95% ee (entry 13).[13] Similarly, catalysts involving Gd(III) (entry 14) and Ho(III) (entry 15) exhibited extremely high enantioselectivity in their reactions with cyclohexyl vinyl ether.

To investigate the generality of our methodology on other diazo compounds, the reaction between α,α′-dicarbonyl diazo substrate **4**, which was prepared from diazoacetophenone **1** according to the procedure reported by Padwa,[14] and butyl vinyl ether (**2a**) was carried out (Scheme 2). Although various combinations of the chiral Pybox ligands and lanthanoid triflates as catalysts did not give satisfactory enantioselectivities,[15] our chiral catalyst consisting of Ni(ClO$_4$)$_2$·6H$_2$O and chiral binaphthyldiimine (BINIM) as the ligand,[16] showed promising enantioselectivity with extremely high endo selectivity (Table 2, entries 1−3). As seen for the

Table 2. Reactions of Diazo Compound **4** with Olefin **2a** Catalyzed by (*R*)-BINIM−Ni(II) Complexes[a]

entry	BINIM	*T* (°C)	yield (%)	dr[b]	ee[c] (%)
1	BINIM-2QN	rt	78	>99:1	59
2	BINIM-4(3,5-Xylyl)-2QN	rt	86	>99:1	42
3	BINIM-4Me-2QN	rt	86	>99:1	73
4	BINIM-4Me-2QN	reflux	99	>99:1	92

[a] The reaction was carried out by adding a solution of **4** in CH_2Cl_2 to a suspension of **2a**, $Rh_2(OAc)_4$ (2 mol %), MS 4 Å, and BINIM−Ni(II) complexes (10 mol %) over a period of 1 h. [b] Endo/exo determined by ^{1}H NMR. [c] Enantiomeric excess of endo adduct determined by chiral HPLC.

reactions of **1**, raising the temperature of the reactions of **4** (refluxing at CH_2Cl_2) increased the enantioselectivity−92% ee was achieved using (*R*)-BINIM-4Me-2QN−Ni(II) complex as the Lewis acid (entry 4).[13] The unusual dependence between the selectivity and the reaction temperature can be attributed to the assumed coordination of the chiral Lewis acid to the carbonyl ylide via dissociation of the Rh-associated species to a free carbonyl ylide at higher temperatures. High enantioselectivity was also obtained for the reaction with cyclohexyl vinyl ether (**2d**) under similar conditions (Table 3, entry 1, Scheme 2). Subsequently, the BINIM-4Me-2QN−Ni(II) catalyst was also employed for the reactions of several α,α′-dicarbonyl diazo compounds **5**−**11** with vinyl ether **2d** to give the adducts with good to excellent enantioselectivities (Table 3, entries 2−8).[13] Padwa reported that the carbonyl ylides generated from the α,α′-dicarbonyl diazo compounds by treatment with $Rh_2(OAc)_4$ cyclized to

Table 3. Reactions of Diazo Compounds **4**−**11** with Olefin **2d** Catalyzed by (*R*)-BINIM-4Me-2QN−Ni(II) Complex[a]

entry	R′	substrate	product	yield (%)	ee[b] (%)
1	Pr	**4**	**12d**	96	93
2	*i*-Pr	**5**	**13d**	96	97
3	Bu	**6**	**14d**	87	93
4	*i*-Bu	**7**	**15d**	82	88
5	pentyl	**8**	**16d**	66	84
6	cyclohexyl	**9**	**17d**	78	96
7	$PhCH_2$	**10**	**18d**	85	92
8	$PhCH_2CH_2$	**11**	**19d**	87	77

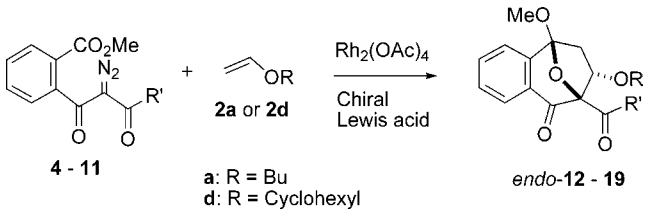
[a] The reaction was carried out by adding a solution of **4**−**11** in CH_2Cl_2 to a suspension of **2d**, $Rh_2(OAc)_4$ (2 mol %), MS 4 Å, and (*R*)-BINIM-4Me-2QN−Ni(II) complex (10 mol %) over a period of 1 h. [b] Enantiomeric excess determined by chiral HPLC.

the corresponding epoxyindanones, which could reproduce the carbonyl ylides by heating.[14] We prepared the corresponding epoxyindanone from diazo compound **7**, and the reaction with vinyl ether **2d** was carried out using (*R*)-BINIM-4Me-2QN−Ni(II) complex (10 mol % with MS 4 Å) under similar conditions in the absence of $Rh_2(OAc)_4$. A long reaction time was needed to complete the reaction under this conditions and the enantiomeric excess of endo adduct was only 9% ee (see the Supporting Information for additional details).

To investigate the scope and limitation with regard to the structure of diazo and olefinic substrates, the reaction using 1-diazo-2,5-hexanedione (**20**) as a carbonyl ylide precursor and the reaction with 2,3-dihydrofuran as a dipolarophile were carried out. Although the enantioselectivity was not excellent as that obtained in the reaction between 2-benzopyrylium-4-olates and cyclohexyl vinyl ether, moderate levels of asymmetric induction were observed in both cases (Scheme 3). Thus, the reaction of 1-diazo-2,5-hexanedione (**20**) with butyl vinyl ether (**2a**) in the presence of (4*S*,5*S*)-Pybox-Ph$_2$-Tm(OTf)$_3$ complex (10 mol %) at 23 °C gave cycloadducts with exo selectivity (exo/endo = 88:12)[17] and 67% ee (exo) in 68% yield.[18] The (4*S*,5*S*)-Pybox-Ph$_2$-Eu(OTf)$_3$-catalyzed reaction of diazoacetophenone **1** with 2,3-dihydrofuran under the same conditions with vinyl ether **2d** gave the endo cycloadduct as a sole product with 59% ee in 98% yield.

Because PM3 calculations indicated that the strongest interaction is between the LUMO of the carbonyl ylide and the HOMO of the vinyl ether on the basis of frontier orbital

Scheme 2. Reactions of Diazo Compounds **4**−**11** with Olefins **2a** or **2d**



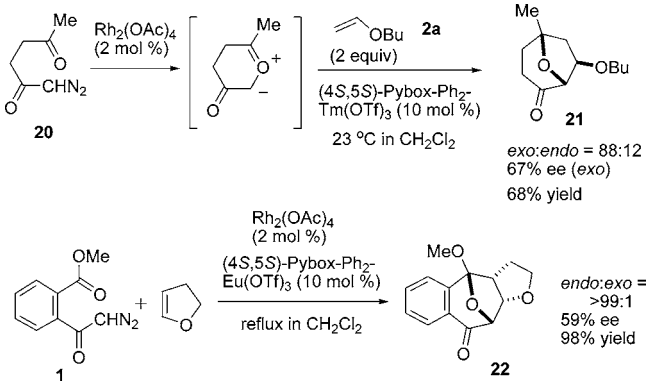
(13) Absolute configuration of the cycloadduct was not determined.

(14) Padwa, A.; Boonsombat, J.; Rashatasakhon, P.; Willis, J. *Org. Lett.* **2005**, *7*, 3725.

(15) (4*S*,5*S*)-Pybox-Ph$_2$-Eu(OTf)$_3$ (10 mol %), CH_2Cl_2, reflux: 89% yield, 44% ee; (4*S*,5*S*)-Pybox-Ph$_2$-Yb(OTf)$_3$ (10 mol %), $CHCl_3$, reflux: 71% yield, 45% ee.

(16) (a) Suga, H.; Kakehi, A.; Mitsuda, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 561. (b) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414. (c) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431. (d) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97.

Scheme 3. Reactions of Other Diazo and Olefinic Substrates



theory (see the Supporting Information), activation of the carbonyl ylide by coordination of chiral Lewis acids to carbonyl oxygen of the ylide (lowering the LUMO level of the carbonyl ylide) and accompanying enantioselctive approach of the vinyl ether from less hindered face of the carbonyl ylide might be a plausible mechanism for this reaction.

In summary, high levels of asymmetric induction were observed for the dipole-LUMO/dipolarophile-HOMO controlled cycloaddition reactions between 2-benzopyrylium-4-olates and vinyl ether derivatives, which were activated by chiral Lewis acids. To the best of our knowledge, this is the first example of such cycloaddition reactions. Studies to expand this methodology with high enantioselectivity to several other diazo substrates and dipolarophiles as well as to prove mechanistic detail are currently underway.

Acknowledgment. This work was supported in part by a Grant-in Aid for Scientific Research (No. 17550097) from the Ministry of Education, Science and Culture, Japan.

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

OL701936B

(17) Although the reason for the switch of the diastereoselectivity in this reaction is not clear at this point, PM3 calculations (heat of formation) of **3d**, **12d**, and **21** show that mostly exo cycloadducts are thermodynamically more stable than endo cycloadducts, and only *endo*-**12d** is slightly more stable (0.81 kcal/mol) than the corresponding exo adduct.

(18) The conditions using other lanthanoid triflates, cyclohexyl vinyl ether, and under reflux in CH_2Cl_2 did not show improved enantioselectivity.