Pergamon

Tetrahedron Letters 43 (2002) 9397–9400

TETRAHEDRON LETTERS

A novel catalytic enantioselective tandem transetherification–intramolecular hetero Diels–Alder reaction of methyl (*E*)-4-methoxy-2-oxo-3-butenoate with δ,ε-unsaturated alcohols

Eiji Wada,[a,*] Hidetaka Koga[b] and Govindaraj Kumaran[a]

[a]*Institute of Advanced Material Study, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*
[b]*Department of Molecular and Material Science, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan*

Received 5 September 2002; revised 7 October 2002; accepted 11 October 2002

Abstract—A novel asymmetric tandem transetherification–intramolecular hetero Diels–Alder reaction of methyl (*E*)-4-methoxy-2-oxo-3-butenoate with δ,ε-unsaturated alcohols has been found to be catalyzed by optically active complexes based on bis(oxazoline) (box) chiral ligands and copper(II) cations. The catalyst derived from the (*S*,*S*)-*tert*-Bu-bis(oxazoline) and $Cu(SbF_6)_2$ in the presence of 5 Å molecular sieves was highly effective to afford corresponding *trans*-fused hydropyranopyran derivatives in good yield (up to 90%) with high enantiomeric excess (up to 98% ee).

The hetero Diels–Alder (HDA) reaction of α,β-unsaturated carbonyl compounds with electron-rich alkenes is a convenient synthetic procedure for the construction of heterocyclic compounds.[1] In recent years an intensive effort has been undertaken toward the development of catalytic enantioselective interemolecular HDA reactions.[2] However, intramolecular HDA reaction is still a relatively unexplored field and only very few reactions have been reported. Examples include the intramolecular hetero Diels–Alder reactions of 1-oxa-1,3-butadienes, which are obtained in situ by a *Knoevenagel* condensation of *N*,*N*-dimethylbarbituric acid and the aromatic aldehydes possessing a dienophile moiety. The cycloaddition of these molecules has been carried out in the presence of an excess of diisopropylideneglucose–titanium complex as chiral catalyst (30–88% ee).[3]

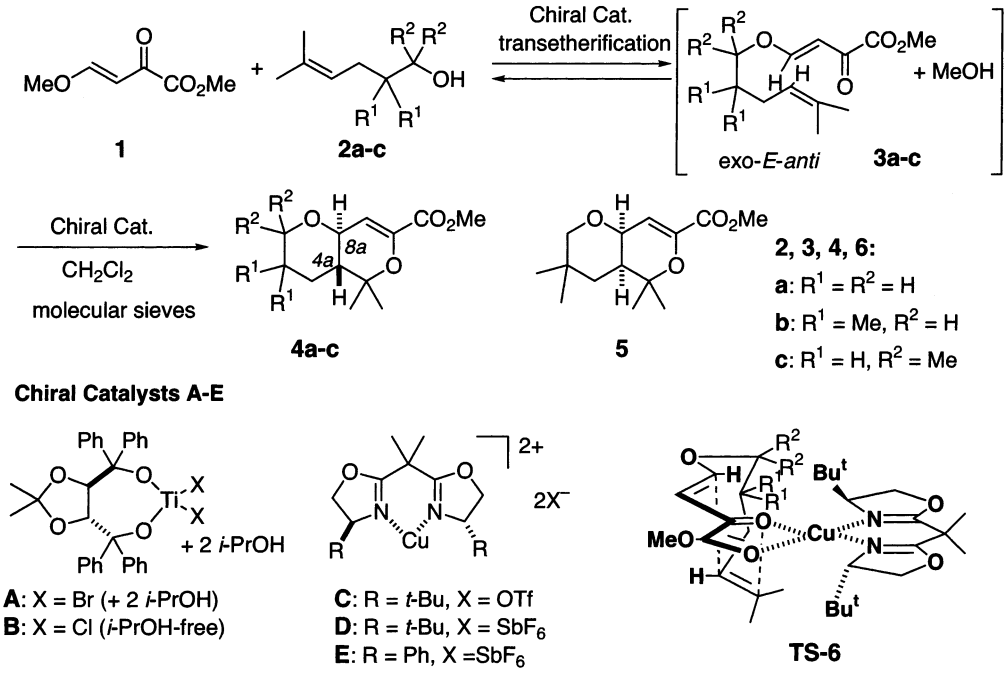
Recently, we have developed a new type of intramolecular HDA reaction of 1-oxa-1,3-butadienes, which are obtained in situ by a transetherification under thermal conditions of β-alkoxy-substituted α,β-unsaturated carbonyl compounds, activated with an additional electron-withdrawing substituent, and δ,ε-unsaturated alcohols.[4] This tandem transetherification–intramolecular HDA reaction proceed stereoselectively to afford *trans*-fused hydropyranopyrans. This new methodology of an intramolecular HDA reaction is useful as an effective synthetic route in the stereoselective preparation of fused heterocycles. Thus, our attention was directed to the development of enantioselective transformation of this new type of tandem reaction process by the use of chiral Lewis acid catalysts.

Here, we present the preliminary results of the enantioselective tandem transetherification–intramolecular HDA reaction by the use of methyl (*E*)-4-methoxy-2-oxo-3-butenoate **1** and primary- and tertiary-δ,ε-unsaturated alcohols **2a**–**c** in the presence of catalytic amounts of chiral Lewis acid catalysts **A**–**E** (Scheme 1). We began our study by examining the enantioselectivity of intramolecular HDA reaction with enone **3a** in order to find a suitable chiral Lewis acid catalysts. The enone **3a** was isolated as the *E*-isomer in 70% yield by the transetherification of enone **1** with 5-methyl-4-hexen-1-ol **2a** (2 equiv.) at 40°C with removal of methanol in vacuo at 40 mm/Hg. The cyclization of **3a** was examined with chiral Lewis acid catalysts such as titanium–TADDOLate and bis(oxazoline)–copper(II) complexes, which are known to be effective catalysts in the enantioselective intermolecular HDA reaction of 1-oxa-1,3-

Keywords: intramolecular hetero Diels–Alder reaction; chiral Lewis acid catalyst; enantioselective reaction; tandem reaction; 1-oxa-1,3-butadiene; transetherification; molecular sieves.

* Corresponding author. Tel.: +81-92-583-7803; fax: +81-92-583-7803; e-mail: wada@cm.kyushu-u.ac.jp

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02320-1



Scheme 1.

butadienes with vinyl ethers.[2] The results are summarized in Table 1.

At first the cyclization of enone **3a** using 10 mol% of titanium–TADDOLate catalysts **A** and **B** was carried out in CH_2Cl_2 in the range of room temperature to −78°C. The corresponding intramolecular HDA adduct **4a** was obtained as a single stereoisomer with 4a,8a-*trans*-configuration ($J_{8a-4a}=9.9$ Hz) in moderate to good yields (41–70%), but enantioselectivity was not observed (entries 1–4).

Next, the cyclization of **3a** was investigated with bis(oxazoline)–Cu(II) complexes as catalysts at room temperature. When (*S*,*S*)-*t*-Bu-Box-CuX_2 **C** (X = OTf) and **D** (X = SbF_6) were used as catalysts, the racemic cycloadduct **4a** was obtained (entries 5 and 6). These results indicate that the formation of racemic **4a** is caused by the action of a strong acid generated from the Lewis acids [$Cu(OTf)_2$ and $Cu(SbF_6)_2$] contaminated with a small amount of water, as it was found that methanesulfonic acid (10 mol%) catalyzes the sequential transformation of enone **1** with alcohol **2a** leading to

Table 1. Asymmetric intramolecular HDA reaction of transetherified enone **3a** with chiral catalysts **A**–**E** leading to hydropyranopyran **4a**[a]

Entry	Catalyst	Additive[b]	Temp. (°C)	Time (h)	Yield (%)[c]	% ee[d]
1	**A**	–	rt	0.5	70	0
2	**A**	–	−25	24	75	0
3	**B**	–	−40	2	72	0
4	**B**	–	−78	86	41	0
5	**C**	–	rt	96	75	0
6	**D**	–	rt	1	82	3
7	**C**	4 Å MS	rt	96	50 (15)	73
8	**C**	5 Å MS	rt	24	83	55
9	**D**	4 Å MS	rt	96	12 (63)	93
10	**D**	5 Å MS	rt	1	63	96
11	**D**	5 Å MS	0	1.5	71	98
12	**D**	5 Å MS	−40	24	81	98
13	**E**	4 Å MS	rt	96	51 (5)	13[e]
14	**E**	5 Å MS	rt	48	51	14[e]

[a] All reactions were performed in the presence of catalysts **A**–**E** (10 mol%) in CH_2Cl_2.
[b] 0.5 g/mmol weight of 4 Å MS and 5 Å were used as additive.
[c] Yields of isolated cycloadduct **4a**. Yields of the recovered **3a** are in parenthesis.
[d] Determined by chiral HPLC analysis (DAICEL CHIRALPAK AD).
[e] The sense of enantioselectivity is reversal.

racemic **4a** (76%) in 15 minutes at room temperature. Therefore, molecular sieves (MS) was used as a dehydration agent to remove this small amount of water existing in the reaction mixture in order to prevent the acid-induced cyclization.[5]

When the cyclization of **3a** was performed with catalyst **C** in the presence of 4 Å MS, it took a long time to obtain **4a** in moderate yield (96 h, 50% and 15% of unchanged **3a**) with good enantioselectivity (73% ee) (entry 7). When 5 Å MS was used as an additive, the same reaction showed complete conversion within 24 h to afford **4a** (83%, 55% ee) (entry 8). By the use of catalyst **D** in the presence of 4 Å MS, the reaction was too slow (96 h, 12 and 63% of unchanged **3a**), but the enantioselectivity was increased (93% ee) (entry 9). Surprisingly, the presence of 5 Å MS forced the reaction to completion within 1 h to afford **4a** with high enantioselectivity (63%, 96% ee) (entry 10). Under the same catalytic conditions, the reaction proceeded smoothly even at lower temperature to afford **4a** with more satisfactory results (71%, 98% ee at 0°C; 81, 98% ee at −40°C) (entries 11 and 12). The reaction catalyzed by (*S*,*S*)-Ph-Box-Cu(SbF_6)$_2$ **E** in the presence of MS also proceeded to afford **4a** having opposite absolute stereochemistry with poor enantioselectivity (13 and 14% ee) (entries 13 and 14).[2b–g] As described above, we fortunately found that (*S*,*S*)-*t*-Bu-Box-Cu(SbF_6)$_2$ **D** in combination with 5 Å MS was highly effective Lewis acid catalyst for both reactivity and enantioselectivity in the intramolecular HDA reaction of **3a.**

The catalytic system using catalyst **D** and MS was applied to the sequential transformation reaction of enone **1** (1.5 equiv.) and alcohols **2a–c** leading to **4a–c**. The results are summarized in Table 2.[7] It again became apparent that the presence of 5 Å MS (0.5 g/mmol) is essential to attain **4a** in high yield with high enantioselectivity in the reaction of **1** with **2a** (76%, 97% ee) using **D** as catalyst (entry 4 versus entries 1, 2, 3, and 5). The reaction with **2b** having a *gem*-dimethyl substituent at C-2 position at room temperature afforded a mixture (**4b**:**5** = 96:4) of *trans*-fused **4b** ($J_{8a–4a}$ = 10.1 Hz) and *cis*-fused **5** ($J_{8a–4a}$ = 6.4 Hz) in 62% combined yield with high enantioselectivity (94% ee) of **4b** (entry 6). When this reaction was carried out at lower temperature, the chemical yields, enantioselectivities of **4b**, and stereoselectivities were improved (90%, 95% ee, **4b**:**5** = 98:2 at 0°C; 83%, 98% ee, **4b**:**5** = >99:<1 at −20°C) (entries 7 and 8). Furthermore, the reaction with bulky tertiary alcohol **2c** proceeded slowly to afford *trans*-fused **4c** ($J_{8a–4a}$ = 9.9 Hz) with high enantioselectivities (92–98% ee) and showed that the chemical yield was dependent on the amount of 5 Å MS added. The chemical yields of **4c** after 96 h are 34, 63, and 74% in the presence of 0.5, 1, and 2 g of 5 Å MS, respectively (entries 9–11). When 5 equiv. of **2c** was used, this reaction proceeded smoothly to afford **4c** (24 h, 69%, 98% ee) (entry 12). In the course of our investigation, MS has been found to act as absorbent of H_2O and/or acid moiety, however, the reason for the novel observation of the significant difference of 4 Å MS and 5 Å in the catalytic activity aid on the chemical yield, catalyst **D** is used, is unclear.[6,8]

The absolute configuration of cycloadducts **4a–c** obtained, when using **C** and **D** as catalyst, is assumed to be 4a*S*,8a*R*, based on the previously proposed model for asymmetric induction of intermolecular HDA with catalyst **C** and **D**.[2b–g] The sense of asymmetric induction can be rationalized by assuming that the vicinal carbonyl functionalities of transetherified enone **3** coordinates to the copper(II) center in bidentate fashion leading to a square-planar intermediate, in which the *re*-face of the reacting enone is available for an intramolecular approach of the *si*-face of alkene with an *exo*-*E*-*anti* conformation (**TS-6** in Scheme 1).

Table 2. Asymmetric tandem transetherification–intramolecular HDA reaction of enone **1** with alcohols **2a–c** leading to hydropyranopyrans **4a–c** by the use of chiral catalyst **D**[a]

Entry	Alcohols **2a–c**	Additive (0.5 g/mmol)	Temp. (°C)	Time (h)	Yield of **4a–c** (%)[b]	% ee[c]
1	**2a**	–	rt	7	**4a** 65	0
2	**2a**	4 Å MS	rt	168	**4a** 22 (40)	92
3	**2a**	5 Å MS[d]	rt	7	**4a** 88	30
4	**2a**	5 Å MS	rt	7	**4a** 76	97
5	**2a**	5 Å MS[d]	rt	7	**4a** 71	97
6	**2b**	5 Å MS	rt	0.5	**4b** 62	94
7	**2b**	5 Å MS	0	2	**4b** 90	95
8	**2b**	5 Å MS	−20	18	**4b** 83	98
9	**2c**	5 Å MS	rt	96	**4c** 34	92
10	**2c**	5 Å MS[d]	rt	96	**4c** 63	98
11	**2c**	5 Å MS[d]	rt	96	**4c** 74	98
12[e]	**2c**	5 Å MS	rt	24	**4c** 69	98

[a] Unless otherwise noted, all reactions were performed with **1** (1.5 equiv.) and **2a–c** using 10 mol% of the chiral Lewis acid catalyst **D** in CH_2Cl_2 in the presence of MS.

[b] Yield of isolated cycloadduct **4a–c**. Yield of transetherified **3a** is in parenthesis. The cycloadduct **4b** was obtained as a mixture with *cis*-fused **5**; **4b**:**5** = 96:4, 98:2, and >99:<1 (entries 6, 7, and 8, respectively).

[c] Determined by chiral HPLC analysis (**4b**: Daicel Chiralcel OD-H, **4c**: Daicel Chiralpak AD).

[d] 5 Å MS: 0.25, 0.75, 1 and 2 g/mmol (entries 3, 5, 10 and 11, respectively).

[e] 5 equiv. of alcohol **2c** was used.

In summary, a new type of catalytic enantioselective tandem transetherification–intramolecular HDA reaction leading to enantiomerically enriched hydropyranopyrans has been achieved successfully by using methyl (*E*)-4-methoxy-2-oxo-3-butenoate and δ,ε-unsaturated alcohols in the presence of (*S*,*S*)-*t*-Bu-Box-$Cu(SbF_6)_2$ **D** (10 mol%) and 5 Å MS. To the best our knowledge, this is the first report of a highly effective asymmetric intramolecular HDA reaction with inverse electron demand by the use of a catalytic amount of chiral Lewis acid. Currently, efforts are under way to probe the scope and limitations of this new enantioselective sequential transformation reaction.

Acknowledgements

Partial financial support by a grant-in-aid for Scientific Research (no. 11640540) from the Japanese Ministry of Education, Science and Culture is acknowledged.

References

1. For example: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651–692; (b) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford; 1991, Vol. 5, pp. 451–512; (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA; 1987, pp. 167–213; (d) Tietze, L. F. *J. Heterocyclic Chem.* **1990**, *27*, 47–69; (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (f) Denmark, S. K. *Chem. Rev.* **1996**, *96*, 137–169; (g) Wada, E.; Pei. W.; Yasuoka, H.; Chin, U. *Tetrahedron* **1996**, *52*, 1205–1220 and references cited therein; (h) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303–2340.
2. (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 1637–1640; (b) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896; (c) Thorhauge, J.; Johansen, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2404–2406; (d) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372–3375; (e) Evans, D. A.; Johnson, J. S.; Burgey, C. S. *Tetrahedron Lett.* **1999**, *40*, 2879–2882; (f) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487–4497; (g) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635–1649.
3. (a) Narasaka, K.; Hayashi, Y.; Shimada, S. *Chem. Lett.* **1988**, 1609–1612; (b) Tietze, L. F.; Saling, P. *Synlett* **1992**, 281–282; (c) Tietze, L. F.; Saling, P. *Chirality* **1993**, *5*, 329–333.
4. (a) Wada, E.; Kumaran, G.; Kanemasa, S. *Tetrahedron Lett.* **2000**, *41*, 73–76; see also (b) Inoue, S.; Asami, M.; Honda, K.; Miyazaki, H. *Chem. Lett.* **1996**, 889–890; (c) Miyazaki, H.; Honda, K.; Inoue, S. *Tetrahedron Lett.* **2000**, *41*, 2643–2646 and references cited therein.
5. Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. *Helv. Chim. Acta* **1992**, *75*, 2171–2209 and references cited therein.
6. Molecular sieves as dehydration reagents, Sen, S. E.; Smith, S. M.; Sullivan, K. A. *Tetrahedron* **1999**, *55*, 12657–12698 and references cited therein.
7. Typical experimental procedure (entry 4 in Table 2): A flask covered with aluminum foil was charged with (*S*,*S*)-bis(*tert*-butyloxazoline) (16.2 mg, 0.055 mmol, weighing in air), $CuCl_2$ (6.7 mg, 0.05 mmol, weighing in air), anhydrous CH_2Cl_2 (3 ml) and the resulting mixture was stirred for 1 h at room temperature. To the solution was added $AgSbF_6$ (34.4 mg, 0.01 mmol, weighing in air) and additionally stirred for 3 h. In a new flask was placed activated 5 Å MS (250 mg) and the blue solution of (*S*,*S*)-*t*-Bu-Box-$Cu(SbF_6)_2$ catalyst **D**, filtered through a membrane filter to remove AgCl, was added. To the resulting suspension was added enone **1** (108 mg, 0.75 mmol) in CH_2Cl_2 (1 ml), followed by alcohol **2a** (57 mg, 0.5 mmol) in CH_2Cl_2 (1 ml) and stirred for 7 h at room temperature under a nitrogen atmosphere. Then the reaction mixture was quenched with sat. $NaHCO_3$ aq., extracted with CH_2Cl_2, dried over $MgSO_4$, and the crude product was subjected to column chromatography on silica gel with EtOAc:hexane (1:4 v/v) to provide *trans*-fused cycloadduct **4a** (85 mg, 76%) as a colorless solid. The enantiomeric excess was determined to be 97% ee by HPLC analysis (Daicel Chiralpak AD). Analytical data for **4a**: mp 84°C; $[\alpha]_D^{25}$ +68.9° ($c=1.00$, EtOAc); IR (KBr): 1720 and 1651 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=1.15$, 1.40 (each 3H, each s, 2×5-Me), 1.25 (1H, m), 1.54 (1H, m), 1.65–1.78 (2H, m), 1.85 (1H, m), 3.51 (1H, dt, $J_{gem}=J_{2ax-3ax}=11.5$ and $J_{2ax-3eq}=3.5$ Hz, H-2ax), 3.75 (1H, dd, $J_{8a-4a}=9.9$ and $J_{8a-8}=2.0$ Hz, H-8a), 3.78 (3H, s, CO_2Me), 4.03 (1H, m, H-2 equiv.), and 5.96 (1H, d, $J_{8-8a}=2.0$ Hz, H-8). ^{13}C NMR ($CDCl_3$) $\delta=19.51$ (5-Me), 24.73 (5-Me), 26.33 (C-3), 26.91 (C-4), 44.86 (C-4a), 52.21 (7-OMe), 68.41 (C-2), 72.67 (C-8a), 80.20 (C-5), 109.51 (C-8), 142.78 (C-7), and 163.46 (7-CO); MS (70 eV) (relative intensity, %) m/z 226 (M^+, 41), 211 (base peak), 167 (54), 151 (36), 149 (23), 125 (47), 97 (47), and 58 (34); Anal. calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%. Found: C, 63.90; H, 8.09%.
8. For the role of 4 Å MS in catalytic asymmetric reactions, see: (a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345; (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812–2820; (c) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639–644; (d) Posner, G. H.; Dai, H.; Bull, D S.; Lee, J.-K.; Eydoux, F.; Ishihara, Y.; Welsh, W.; Pryor, N.; Petr, Jr., S. *J. Org. Chem.* **1996**, *61*, 671–676; (e) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, K. *Chem. Commun.* **1997**, 281–282; (f) Terada, M.; Matsumoto, Y.; Nakamura, Y.; Mikami, *J. Mol. Catal. A* **1998**, *132*, 165–169; (g) Mikami, K.; Terada, M.; Matsumoto, Y.; Tanaka, M.; Nakamura, Y. *Microporous and Mesoporous Mater.* **1998**, *21*, 461–466; (h) Gotherf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 5483–5488; (i) Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721–15730; (j) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 3213–3216; (k) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660–8667; (l) Kodama, H.; Ito, J.; Hori, K.; Ohta, T.; Furukawa, I. *J. Organometallic Chem.* **2000**, *603*, 6–12; (m) Moharram, S. M.; Hirai, Go.; Koyama, K.; Oguri, H.; Hirama, M. *Tetrahedron Lett.* **2000**, *41*, 6669–6673.