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Efficient Two-Step Conversion of α,β-Unsaturated Aldehydes to Optically Active γ-Oxy-α,β-unsaturated Nitriles and Its Application to the Total Synthesis of (+)-Patulolide C

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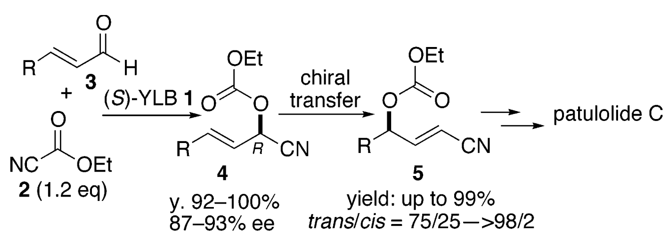
ABSTRACT



An efficient two-step conversion of α,β-unsaturated aldehydes into optically active γ-oxy-α,β-unsaturated nitriles is described. First, catalytic asymmetric cyanation–ethoxycarbonylation using (*S*)-YLi$_3$tris(binaphthoxide) (YLB) afforded chiral allylic cyanohydrin carbonate. Second, a [3,3]-sigmatropic rearrangement proceeded without racemization under thermal conditions to give γ-oxy-α,β-unsaturated nitriles. Lewis acids were also effective for the rearrangement, and the reaction proceeded smoothly under mild conditions. To demonstrate the utility of the conversion, concise catalytic enantioselective total synthesis of (+)-patulolide C was performed.

Optically active cyanohydrins serve as important precursors of many useful organic compounds, and there are various reports of catalytic asymmetric syntheses of cyanohydrins using $(CH_3)_3SiCN$ and/or HCN as a cyanide source.[1] As a part of our ongoing research program on asymmetric cyanation reactions,[2] we recently reported a novel catalytic asymmetric cyanation−ethoxycarbonylation reaction of aldehydes with ethyl cyanoformate (**2**) promoted by a YLi$_3$-tris(binaphthoxide) (YLB, **1**) complex (Figure 1).[3] Ethyl cyanoformate (**2**) serves a combined role as an in situ source of cyanide ions and an ethoxycarbonylating reagent, thus affording atom-economical[4] one-pot access to optically active cyanohydrin carbonates.[5] When utilizing chiral cyanohydrins in the synthesis, transformations of cyanohydrins should be

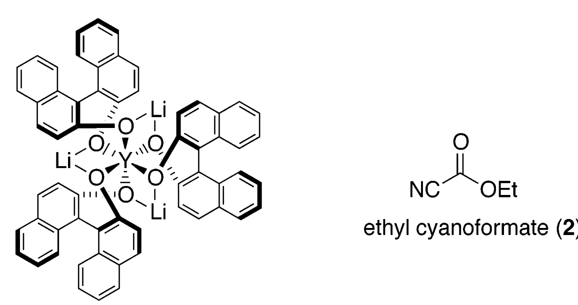


Figure 1. Structure of (*S*)-YLi$_3$tris(binaphthoxide) [(*S*)-YLB: **1**] and ethyl cyanoformate (**2**).

(1) Recent reviews: (a) North, M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 147. (b) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649 and references therein.
(2) Recent reviews: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (b) Gröger, H. *Chem. Eur. J.* **2001**, *7*, 5246. (c) Shibasaki, M.; Kanai, M. *Chem. Pharm. Bull.* **2001**, *49*, 511.
(3) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636.

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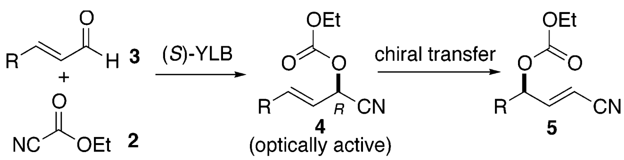
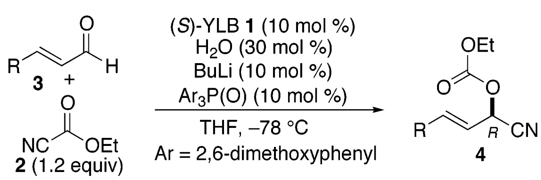
performed under racemization-free conditions. Many racemization-free transformations of trimethylsilyl cyanohydrins and cyanohydrins themselves have been reported;[1] however, transformations from chiral cyanohydrin carbonates have not been adequately investigated, despite their potential as unique chiral building blocks distinct from trimethylsilyl cyanohydrins. Based on a few reports of useful transformations of racemic allylic cyanohydrin carbonates,[6] we investigated a [3,3]-sigmatropic rearrangement of chiral allylic cyanohydrin carbonates. Herein, we report an efficient two-step conversion of α,β-unsaturated aldehydes: catalytic asymmetric cyanation−ethoxycarbonylation reactions of α,β-unsaturated aldehydes **3** (step 1) and a chiral transmission of allylic cyanohydrin carbonate intermediate **4** via the [3,3]-sigmatropic rearrangement (step 2), which provides easy access to optically active γ-oxy-α,β-unsaturated nitriles (Scheme 1). The concise catalytic enantioselective total synthesis of (+)-patulolide C using this method is also described.

Scheme 1. Two-Step Conversion of α,β-Unsaturated Aldehyde into γ-Oxy-α,β-unsaturated Nitrile



As shown in Table 1, chiral allylic cyanohydrin carbonates were efficiently synthesized from α,β-unsaturated aldehydes

Table 1. Catalytic Asymmetric Cyanation−Ethoxycarbonylation of α,β-Unsaturated Aldehydes



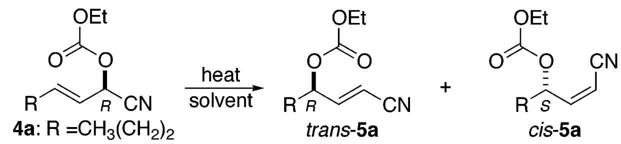
entry	aldehyde (R)	product	time (h)	yield[b] (%)	ee[c] (%)
1[a]	**3a**, $CH_3(CH_2)_2$	**4a**	3	100	92
2	**3b**, Ph $(CH_2)_2$	**4b**	2	96	92
3	**3c**, c-C_6H_{11}	**4c**	3	98	93
4[a]	**3d**, Ph	**4d**	3	100	91

[a] Reported results, see ref 3. [b] Isolated yield. [c] Determined by chiral HPLC and chiral GC analysis.

in one step using 10 mol % of (*S*)-YLB, 30 mol % of H_2O, 10 mol % of BuLi, 10 mol % of $[2,6\text{-}(CH_3O)_2C_6H_3]_3P(O)$, and 1.2 equiv of ethyl cyanoformate.[7] The reaction reached completion within 2−3 h at −78 °C to afford the products in good yield (96−100%) and enantiomeric excess (91−93%), with no 1,4-addition product. Thus, the allylic cyanohydrin carbonates **4** were obtained in one step in a highly atom-economical process.

First, [3,3]-sigmatropic rearrangement of **4a** was examined under thermal conditions. As summarized in Table 2, the

Table 2. [3,3]-Sigmatropic Rearrangement of **4a** under Thermal Conditions



entry	solvent	*T* (°C)	time (h)	yield[b] (%)	trans/cis[b]
1[a]	*o*-xylene	180	36	>95	60/40
2	1,2-dichlorobenzene	180	16	>95	75/25
3	1,2,4-trichlorobenzene	200	5	>95	86/14

[a] Reaction was done using a sealed tube. [b] Yield and trans/cis ratio were determined by NMR analysis.

rearrangement proceeded smoothly to afford thermodynamically favorable α,β-unsaturated nitriles **5a** in quantitative yield as stereochemical mixtures. The trans/cis ratio changed depending on the reaction conditions. Rearrangement in *o*-xylene (180 °C, sealed tube) afforded **5a** in trans/cis = 60/40 after 36 h (entry 1). **5a** was obtained in trans/cis = 75/25 with dichlorobenzene (reflux, 180 °C) after 16 h (entry 2). The reaction proceeded faster in more polar trichlorobenzene (200 °C), and **5a** was obtained in quantitative yield after 5 h. The trans/cis ratio was improved to 86/14. The exposure of isolated pure *cis*-**5a** to the reaction conditions for 6 h (trichlorobenzene, 200 °C) resulted in the recovery of pure *cis*-**5a**, and there was no trans/cis isomerization. The result suggested that the rearrangement is irreversible under the reaction conditions, probably due to the thermodynamic stability of α,β-unsaturated nitrile against allylic cyanohydrin carbonate. The *trans*-**5a** is kinetically favored in the rearrangement. The enantiomeric excess of **4a** (92% ee) and those of *trans*-**5a** (92% ee) and *cis*-**5a** (92% ee) were the same. The absolute configuration at the γ-position of *trans*-**5a** was *R* and that of *cis*-**5a** was *S*.[8] On the basis of the absolute configurations of the products, the proposed transition states to afford the trans adducts (chair) and cis adducts (boat) are shown in Figure 2. Under the optimized conditions, rearrangements of **4a−d** were performed to afford **5a−d** in

(4) Trost, B. M. *Science* **1991**, *254*, 1471.

(5) For other examples of catalytic asymmetric cyanation reaction using cyanoformate, see: (a) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195.(b) Casas, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 197.

(6) Thermal [3,3]-sigmatropic rearrangement (a) Hünig, S.; Reichelt, H. *Chem. Ber.* **1986**, *119*, 1772. Palladium-catalyzed allylic substitution: (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523. (c) Deardorff, D. R.; Taniguchi, C. M.; Tafti, S. A.; Kim, H. Y.; Choi, S.-Y.; Downey, K. J.; Nguyen, T. V. *J. Org. Chem.* **2001**, *66*, 7191 and references therein.

(7) For the optimization of the catalytic asymmetric cyanation-ethoxycarbonylation reaction of aldehydes, see ref 3.

(8) Absolute configuration of *trans*-**5a** and *cis*-**5a** were determined after conversion to a known compound. See the Supporting Information.

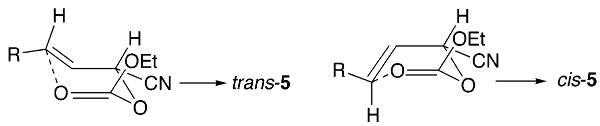
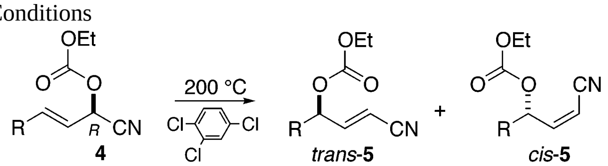


Figure 2. Supposed transition-state model to afford *trans*- and *cis*-**5**.

good isolated yield (93−99%) as summarized in Table 3. In all cases, there was no racemization.

Table 3. [3,3]-Sigmatropic Rearrangement under Thermal Conditions

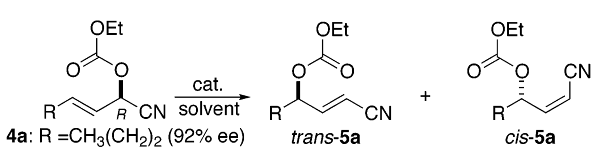


entry	substrate (ee, %)	product	time (h)	yield[a] (%)	ratio[b] trans/cis	ee[c] (%) trans/cis
1	**4a** (92)	**5a**	12	99	86/14	92/92
2	**4b** (91)	**5b**	12	93	76/24	91/91
3	**4c** (93)	**5c**	12	95	77/23	92/93
4	**4d** (91)	**5d**	12	99	75/25	91/90

[a] Isolated yield. [b] Determined by NMR analysis of crude mixture. [c] Determined by chiral GC and HPLC analysis.

There are several excellent examples of cyclization-induced rearrangement of allylic esters and carbamate by Pd(II) catalysis,[9] which led us to examine the Lewis acid-promoted rearrangement of **4a**. As shown in Table 4, the rearrangement proceeded at room temperature using 5 mol % of $PdCl_2(PhCN)_2$ in THF (entry 1, yield 32%).[10] At 50 °C, **5a** was obtained in 90% yield (entry 2). The trans/cis ratio was excellent with Pd catalysis (entry 1, >98/2; entry 2, 96/4); however, partial racemization was observed, and the enantiomeric excess of *trans*-**5a** was decreased to 89% and 86%, depending on the reaction conditions (entries 1 and 2). These results were probably due to the strong affinity of a nitrile moiety to Pd, enabling deprotonation at the α-position of **4** under mild conditions. Slightly lower reactivity of **4a** compared with simple allylic carbonate can also be attributed to the nitrile group. Various hard Lewis acids were also examined to produce a charge-induced concerted rearrangement.[11] As shown in Table 4, $(CH_3)_3SiOTf$ and $Sc(OTf)_3$ were effective for the rearrangement of **4**. The rearrangement proceeded at room temperature in good yield (entries 3−5, yield 76−86%), although stoichiometric amounts of Lewis acids were necessary for good yields. There was no racemization with $(CH_3)_3SiOTf$ in toluene, (entry 3). The trans/cis ratio of **5a** was slightly better than that obtained under thermal conditions (entry 3, 89/11). Both $Sc(OTf)_3$ and $(CH_3)_3SiOTf$ afforded **5a** in good yield in CH_2Cl_2 (entries 4 and 5). Partial racemization, however, occurred in CH_2Cl_2 (entries 3 and 4, 75% ee). Other Lewis acids gave less satisfactory results in terms of reactivity and enantiomeric excess of the product.[12]

Table 4. [3,3]-Sigmatropic Rearrangement Promoted by Lewis Acid



entry	Lewis acid (mol %)	solvent	*T* (°C)	time (h)	yield[a] (%)	trans/cis ratio[b]	ee (%)[c] trans
1	$PdCl_2(PhCN)_2$ (5)	THF	rt	24	32	>98/2	89
2	$PdCl_2(PhCN)_2$ (5)	THF	50	24	90	96/4	86
3	$(CH_3)_3SiOTf$ (100)	toluene	rt	48	82	89/11	92
4	$(CH_3)_3SiOTf$ (100)	CH_2Cl_2	rt	36	74	88/12	75
5	$Sc(OTf)_3$ (100)	CH_2Cl_2	rt	36	86	89/12	75

[a] Isolated yield. [b] Determined by NMR analysis of crude mixture. [c] Determined by chiral GC and HPLC analysis.

The present two-step conversion efficiently afforded optically active γ-oxy-α,β-unsaturated nitriles in good yield and ee, starting from readily available α,β-unsaturated aldehydes. The γ-oxy-α,β-unsaturated nitrile should be a useful chiral building block.

To demonstrate the utility of the present two-step conversion, we examined a catalytic enantioselective total synthesis of (+)-patulolide C. Patulolide C is an antifungal and antibacterial macrolide isolated from the culture broth of the *Penicillium urticae* mutant S11R59.[13] Although several enantioselective approaches have been reported for its syntheses,[14] all of them are rather lengthy, especially the schemes for the enantiocontrolled synthesis of a γ-hydroxy-α,β-unsaturated ester unit. Our catalytic enantioselective approach is summarized in Scheme 2. Starting from aldehyde **3e**, catalytic asymmetric cyanation−ethoxycarbonylation using (*R*)-YLB (**4e**, yield 92%, 87% ee) followed by the rearrangement gave γ-oxy-α,β-unsaturated nitrile **5e** in good yield (yield 99%, trans: 87% ee). After exchange of the protective group, **7** was subjected to a diastereoselective

(9) Review: (a) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 3, 579. (b) Nubbemeyer, U. *Synthesis* **2003**, 961. For leading references, see: (c) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *20*, 321. (d) Oehlschlager, A. C.; Mishra, P.; Dhami, S. *Can. J. Chem.* **1984**, *62*, 791.

(10) $PdCl_2(CH_3CN)_2$ was less reactive.

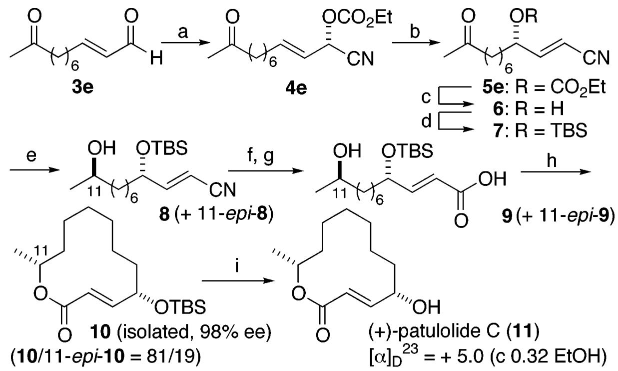
(11) Oxophilic $Eu(fod)_3$ efficiently catalyzes [3,3]-sigmatropic rearrangement of allylic esters at room temperature, although the substrate is limited to allylic alkoxyacetate. (a) Shull, B. K.; Sakai, T.; Koreeda, M. *J. Am. Chem. Soc.* **1996**, *118*, 11690. (b) Dai, W.-M.; Mak, W. L.; Wu, A. *Tetrahedron Lett.* **2000**, *41*, 7101 and references therein.

(12) Only trace **5** was obtained with $Sc(OTf)_3$ in toluene. In toluene, only $(CH_3)_3SiOTf$ was effective for good conversion. Reaction proceeded in CH_2Cl_2 using other Lewis acids such as $TiCl_4$ (yield ca. 60%), $BF_3 \cdot Et_2O$ (yield 19%), $Zn(OTf)_2$ (yield <5%), $Sn(OTf)_2$ (yield <5%), and so on; however, partial racemization occurred.

(13) Rodphaya, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiot.* **1986**, *39*, 629.

(14) (a) Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, 13. (b) Leemhuis, F. M. C.; Thijs, L.; Zwanenburg, B. *J. Org. Chem.* **1993**, *58*, 7170 and references therein. (c) Yang, H.; Kuroda, H.; Miyashita, M.; Irie, H. *Chem. Pharm. Bull.* **1992**, *40*, 1616. (d) Takano, S.; Murakami, T.; Samizu, K.; Ogasawara, K. *Heterocycles* **1994**, *39*, 67.

Scheme 2. Concise Catalytic Enantioselective Total Synthesis of (+)-Patulolide C[a]



[a] (a) (*R*)-YLB (10 mol %), H_2O (30 mol %), BuLi (10 mol %), $[2,6\text{-}(CH_3O)_2C_6H_3]_3P(O)$ (10 mol %), ethyl cyanoformate (1.2 equiv), −78 °C, 5 h, y. 92%, 87% ee; (b) 1,2,4-trichlorobenzene, 190 °C, 6 h, yield 99%; trans/cis = 85/15, trans: 87% ee; (c) K_2CO_3, CH_3OH/H_2O (1/1), rt, 2 h; (d) TBSCl, imidazole, DMF, rt, 8 h, yield 92% (two steps); (e) (*S*)-CBS (30 mol %), catecholborane (2 equiv), toluene, −78 °C, 20 h, yield 95%; (f) DIBAL, toluene, −78 °C, 3 h; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH−H_2O, rt, 5 h, yield 72% (two steps); (h) 2-methyl-6-nitrobenzoic anhydride (1.2 equiv), DMAP, rt, 16 h (slow addition), yield 84%, dr = 81/19 (**10**/11-*epi*-**10**); (i) HF−pyridine, 0 °C, THF, yield 99%.

reduction with (*S*)-CBS (30 mol %) and catecholborane[15] to afford **8** as an inseparable mixture in 95% yield. The enantiomeric excess and diastereomeric ratio (desired/11-*epi*) of the product was determined at a later stage of the synthesis. After conversion of the nitrile to carboxylic acid, macrolactonization of **9** proceeded smoothly with 2-methyl-6-nitrobenzoic anhydride[16] at room temperature to give **10** in 84% yield. The desired diastereomer **10** was isolated from its 11-epimer by silica gel flash column chromatography. The enantiomeric excess of **10** was determined to be 98% at this stage by chiral HPLC analysis. The diastereomeric ratio (**10**/11-*epi*-**10**) was 81/19. These results suggested that statistical asymmetric amplification of the enantiomeric excess was achieved using two catalytic asymmetric reactions.[17] Removal of the TBS group afforded (+)-patulolide C, $[\alpha]^{23}_D = +5.0$ (c 0.32 EtOH) [lit.[12a] $[\alpha]^{25}_D = +5.4$ (c 0.57 EtOH); lit.[12d] $[\alpha]^{30}_D = +5.6$ (c 0.22 EtOH)] from **3e** in nine steps with an overall yield of 33%.

In summary, we developed an efficient two-step conversion of α,β-unsaturated aldehydes to optically active γ-oxy-α,β-unsaturated nitriles. First, catalytic asymmetric cyanation−ethoxycarbonylation afforded allylic cyanohydrin carbonate in good ee (87−93%) and excellent yield (92−100%). Second, [3,3]-sigmatropic rearrangement proceeded smoothly under thermal conditions (yield 93−99%) and/or under Lewis acid-promoted conditions. The utility of the present method was demonstrated by a concise catalytic enantioselective total synthesis of (+)-patulolide C. Further studies to realize the racemization-free rearrangement with catalytic amount of hard Lewis acids as well as other conversions of chiral allylic cyanohydrin carbonates are underway in our group.

Acknowledgment. We acknowledge financial support by RFTF and Grant-in-Aid for Encouragements for Young Scientists (B) (for S.M.) from JSPS.

Supporting Information Available: Experimental procedures, characterization data for new compounds, and determination of the absolute configuration of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Review: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 7, 1986.

(16) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535.

(17) Selectivity in the reduction of **7** with (*S*)-CBS was C11-*R*/*S* = 86/14 (72% ee), which was calculated from dr and ee value of **10**. In the model study using 2-octanone and 30 mol % of (*S*)-CBS, 2-octanol was obtained in 75% ee at −78 °C after 20 h. The calculated ee value for the reduction of **7** (72% ee) matched well with that in the model study. For detailed calculations and discussion of statistical asymmetric amplification, see the Supporting Information. For a recent application of statistical asymmetric amplification in the total synthesis, see: (a) Huo, S.; Negishi, E. *Org. Lett.* **2001**, *3*, 3253 and references therein. For a leading reference, see: (b) Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.