Concise enantioselective synthesis of δ,δ -disubstituted δ -valerolactones

Akira Saito,^a Naoya Kumagai,^{a,*} and Masakatsu Shibasaki^{a,b,*}

^aInstitute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

^bJST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

*Corresponding Author. Tel.: +81 3 3441 7779; fax: +81 3 3441 7589.

E-mail address: nkumagai@bikaken.or.jp (N. Kumagai), mshibasa@bikaken.or.jp (M. Shibasaki).

ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

gKeywords:

Keyword_1

Keyword_2

Keyword_3

Keyword_4

Keyword_5

keywords: valerolactone, cyclization, nitrile, silver

ABSTRACT

Efficient access to enantioenriched δ,δ -disubstituted δ -valerolactones is described. A soft Lewis acid/hard Brønsted base cooperative catalyst allowed for direct catalytic asymmetric γ -addition of allyl cyanide to ketones, producing tertiary homoallylic alcohols with a Z-configured α,β -unsaturated nitrile. Electrophilic activation of the nitrile functionality triggered 6-*exo*-dig cyclization, and subsequent N-acylation gave rise to the δ -valerolactone skeleton via C–N bond cleavage.

2009 Elsevier Ltd. All rights reserved.

Introduction

The δ -valerolactone skeleton is a ubiquitous substructure in biologically active natural products.¹ The optically active δ -monosubstituted δ -valerolactone core is readily accessed by the corresponding enantioenriched secondary alcohols through lactonization via δ -hydroxy carboxylic acids or ring-closing metathesis via acryloylated homoallylic alcohols.¹ In contrast, δ,δ -disubstituted δ -valerolactones are less accessible.² Only a limited collection of compounds with a chiral tertiary alcohol unit are present in the chiral pool,³ and enantioselective synthesis of chiral tertiary alcohols is much less explored than that of secondary alcohols.⁴ Moreover, lactonization of carboxylic acid bearing a tertiary alcohol at the δ -position generally requires forcing conditions due to steric hindrance. This steric issue also retards the formation of acryloyl ester for ring-closing metathesis. We recently disclosed a catalytic protocol that allows for enantioselective access to chiral tertiary alcohols bearing a pendant Z-configured α,β -unsaturated nitrile **3**.⁵ We reasoned that this specific transformation is particularly suitable for producing δ,δ -disubstituted δ -valerolactones because; 1) the Z-configuration of olefin is beneficial to cyclization; 2) nitrile is in the carboxylic acid oxidation state and thus the oxidation/reduction process can be avoided; and 3) 1–2 mol% of a designed cooperative catalyst is sufficient to promote the direct addition of allyl cyanide **2** to ketones **1** to afford the requisite cyclization precursors **3** with perfect atom economy. Herein we report a one-pot protocol to convert chiral δ -hydroxy α,β -unsaturated nitriles **3** to δ,δ -disubstituted unsaturated δ -valerolactones.

Scheme 1. Synthetic strategies for δ -substituted δ -valerolactones.

Results and discussion

Enantioselective construction of tetrasubstituted stereogenic centers has been a sustained topic in modern synthetic organic chemistry.⁶ In particular, a catalytic asymmetric transformation that fulfills C–C bond formation with perfect atom economy offers the most productive synthetic protocol.^{7,8} Our research in this field recently revealed that a soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4/(\text{R},\text{R})\text{-Ph-BPE}/\text{Li}(\text{OC}_6\text{H}_4\text{-}p\text{-OMe})$ with hard Lewis acidic bisphosphine oxide additive **5** efficiently promotes the direct addition of allyl cyanide **2** to ketones **1** (Scheme 2).^{5,9} The reaction proceeds through a simple proton transfer between substrates, and γ -addition via a six-membered transition state selectively produces enantioenriched tertiary alcohol **3** bearing a Z-configured olefin. We attempted the intramolecular cyclization of a model compound **3a** to provide δ -valerolactone.¹⁰ The use of mild protic acids resulted in no conversion whereas strong acids induced dehydration of the hydroxyl group, suggesting that chemoselective activation of a nitrile would be a viable strategy. Various soft Lewis acids that could be coordinated by nitrile functionality in an end-on fashion were therefore investigated. In combination with DBU, the addition of AgOTf or $\text{CuOTf}\cdot\text{toluene}_{0.5}$ salts at room temperature rendered rapid disappearance of **3a** within 10 min to give transient cyclic imide **6** as detected by ^1H NMR analysis (Table 1, entries 1,2).¹¹ All attempts to directly convert imide **6** to δ -valerolactone failed, presumably due to an unwanted ring-opening reaction. To eliminate the nitrogen functionality under hydrolytic conditions, appendage of an electron-withdrawing group on the imide nitrogen was examined. In situ acetylation of imide **6** produced the desired δ -valerolactone **4a** in 16% yield after subsequent acidic hydrolysis with 1 M HCl aq. (entry 3). The use of TFAA to generate more electron-withdrawing trifluoroacetylated imide outperformed Ac_2O to furnish **4a** in 32% yield with retention of the enantiopurity (entry 4). The use of sulfonylating reagents was not effective to direct the desired reaction pathway, resulting in complicated reaction mixtures (entries 5, 6). Hydrolysis under milder acidic conditions (1 M AcOH aq.) allowed for the isolation of *N*-mesylated imide **7**, suggesting that sulfonylated imide had enhanced stability to prevent the subsequent liberation of sulfonamide (entry 7). The hydrolytic pathway was dependent on the acidic medium and 1 M AcOH proved to be the best in terms of yield of δ -valerolactone **4a** (76%) and reaction time (10 min) (entries 8–10).¹² The cyclization/trifluoroacetylation/hydrolysis sequence was performed in one-pot without quenching or purification. In contrast to the smooth formation of imide **6** with cationic Cu or Ag salts,¹³ the Ag salts of more intimate ion pairs were not sufficient to induce the initial cyclization. The use of AgNO_3 allowed for the partial formation of imide **6** over an extended period of time and δ -valerolactone **4a** was obtained in moderate yield after subsequent trifluoroacetylation/hydrolysis (entry 11).

Scheme 2. Direct catalytic asymmetric addition of allyl cyanide.

Table 1. Transformation of **3a** to δ,δ -disubstituted δ -valerolactone **4a**.

entry	1. formation of 6 soft Lewis acid	time (min)	2. activation <i>N</i> -acylation (sulfonylation)	3. hydrolysis hydrolytic conditions ^a	yield of 4a (%) ^b	remarks
1	CuOTf^c	10	—	HCl	0	6 was detected
2	AgOTf	10	—	HCl	0	
3	AgOTf	10	Ac_2O	HCl	16	7 (40%)
4	AgOTf	10	TFAA	HCl	32	
5	AgOTf	10	Ti_2O	HCl	0	7 (40%)
6	AgOTf	10	MsCl	HCl	0	
7	AgOTf	10	MsCl	AcOH	0	7 (40%)
8	AgOTf	10	TFAA	H_2SO_4	53	
9	AgOTf	10	TFAA	H_3PO_4	63	7 (40%)
10	AgOTf	10	TFAA	AcOH	76	
11	AgNO_3	60	TFAA	AcOH	46	7 (40%)
12 ^d	AgNO_3	60	TFAA	AcOH	40	
13	AgOAc	180	TFAA	AcOH	0	3a (73%), 8 (16%)
14	Ag_2CO_3	180	TFAA	AcOH	0	
15 ^f	$\text{Ni}(\text{OTf})_2$	180	TFAA	AcOH	0	3a (44%), 8 (39%)
16 ^f	$\text{Fe}(\text{OTf})_3$	180	TFAA	AcOH	18

^a1 M aqueous acid solution (equal volume to the reaction mixture) was added. ^bIsolated yield. ^c $\text{CuOTf}\cdot\text{toluene}_{0.5}$ was used. ^dReaction temperature was 50 °C. ^e0.55 equiv of Ag_2CO_3 (1.1 equiv based on Ag content) was used. ^fReaction temperature was 60 °C.

Increasing the reaction temperature was not beneficial to accelerate the cyclization and **4a** was obtained in even lower yield (entry 12). No indication of the formation of **6** was observed with AgOAc or Ag_2CO_3 and the following reactions afforded trifluoroacetylated substrate **8** and the recovery of **3a** (entries 13, 14). Other cationic transition metal salts were much less effective for inducing the initial cyclization, even at an elevated temperature, and several unidentified byproducts were associated (entries 15, 16).

The scope of the present one-pot protocol for δ,δ -disubstituted δ -valerolactones **4** is summarized in Table 2 with the synthesis of cyclization precursor **3**, produced by a previously reported procedure.^{5b} Ketone **1d** bearing a trifluoromethyl group at the *para* position is a previously unexplored substrate and the corresponding product **3d** was obtained in 80% yield and 98% ee with 1 mol% of catalyst loading (entry 4). Higher catalyst loading (2 mol%) was applied to the reaction using tetralone **1h** to increase the yield, resulting in comparable enantioselectivity (previous report: 1 mol%, 72 h, 53%, 98% ee).^{5b} The obtained *Z*-configured homoallylic tertiary alcohols **3** bearing a nitrile functionality were subjected to the optimized conditions for lactone formation (Table 1, entry 10). Irrespective of the substituents on the aromatic ring, the one-pot protocol produced the corresponding δ,δ -disubstituted δ -valerolactones **4** (entries 1'–5'). Tertiary alcohols **3f** and **3g** derived from ethyl ketone and *n*-propyl ketone, respectively, served as suitable substrates to

afford lactones **4f** and **4g** (entries 6', 7'). An intriguing spiro lactone **4h** was obtained in 74% yield from **3h**

protocol with the use of partially hydrogenated **3i-H₂**, prepared by selective hydrogenation of a styryl group of **3i** over Pd/C in

Table 2. Direct catalytic asymmetric addition of allyl cyanide **2** to ketones **1** to afford cyclization precursors **3** and the subsequent one-pot formation of δ,δ -disubstituted δ -valerolactones **4**.

Reaction scheme: Ketone **1** (R¹, R²) + Allyl cyanide **2** $\xrightarrow[\text{THF, -40 } ^\circ\text{C}]{\begin{smallmatrix} [\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4 \\ (R,R)\text{-Ph-BPE} \\ \text{Li}(\text{OC}_6\text{H}_4\text{-}p\text{-OMe}) \\ \text{x mol\% each} \end{smallmatrix}} \text{Intermediate } \mathbf{3} \xrightarrow[\text{one-pot process}]{\begin{smallmatrix} 1. \text{AgOTf, DBU, rt, 10 min} \\ 2. \text{TFAA, rt, 1 h, THF} \\ 3. \text{AcOH aq., rt, 10 min} \end{smallmatrix}} \delta\text{-valerolactone } \mathbf{4}$

entry	ketone	product	x (mol%)	time (h)	yield ^a (%)	ee ^b (%)	entry	δ -valerolactone	yield ^a (%)	enantiopurity ^b (%)
1			1	40	83	99	1'		76	98
2			1	40	78	98	2'		80	98
3			2	40	67	99	3'		72	99
4			1	40	80	98	4'		78	98
5			1	40	84	99	5'		69	98
6 ^c			1	72	68	94	6'		76	95
7 ^c			1	72	68	96	7'		72	96
8 ^c			2	72	68	99	8'		74	98

^aIsolated yield. ^bDetermined by chiral stationary phase HPLC analysis. ^cLiO^tBu was used instead of Li(OC₆H₄-*p*-OMe).

(entry 8'). All of the δ -valerolactones **4** were obtained in high enantiopurity without loss of enantiopurity.¹⁴

In marked contrast to the reliable formation of enantioenriched δ -valerolactones **4** using benzylic tertiary alcohols **3** as presented in Table 2, homoallylic alcohol **3i** (88% ee) derived from ketone **1i** afforded δ -valerolactone **4i** in a racemic form under identical conditions (Scheme 3a). This undesired racemization was presumably due to the enhanced stability of allylic cation intermediate **9**. Addition of H₂O and recyclization of the resulting acyclic imide **10** led to the formation of racemic δ -valerolactone **4i** (pathway *a*). Our assumption was further supported by the isolation of primary amide **11** that would be formed via imide **10** by hydrolysis of the trifluoroacetimide moiety (pathway *b*). Consistently, performing the one-pot

acetonitrile, afforded δ -valerolactone **4i-H₂** while maintaining the enantiopurity and avoiding undesired ring-opened byproduct **11-H₂** (Scheme 3b). Intriguingly, fully reduced **3i-H₄**, obtained by hydrogenation in AcOEt at room temperature, gave δ -valerolactone in much lower yield,¹⁵ confirming the beneficial and essential effect of *Z*-configured olefin to facilitate the initial cyclization.

Scheme 3. Formation of racemic δ -valerolactone from allylic alcohol **3i** and retention of enantiopurity by selective hydrogenation.

Conclusions

In summary, a one-pot procedure affording enantioenriched δ,δ -disubstituted unsaturated δ -valerolactones was developed. The specific products, *Z*-configured homoallylic tertiary alcohols bearing nitrile functionality derived from the direct addition of allyl cyanide to ketones, were directly converted to the title compounds via a one-pot three-step sequence. Application of the thus-obtained δ,δ -disubstituted δ -valerolactones as deoxygenated sugar units to the development of novel glycosides and their biological evaluation is underway.

Acknowledgments

This work was financially supported by JST, ACT-C, and JSPS KAKENHI Grant Number 25713002. We thank Dr. Yasunari Otsuka at the Institute of Microbial Chemistry for initial experiments at the early stage of this study.

References and notes

- Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225.
- For selected examples for the enantioselective synthesis of δ,δ -disubstituted unsaturated δ -valerolactones: (a) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470. (b) Cefalo, D. R.; Kiely, A. F.; Wuchrer, M.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 3139. (c) Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288. (d) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (e) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440. (f) Shen, L.-T.; Shao, P.-L.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 1943. (g) Mo, J.; Chen, X.; Chi, Y. R. *J. Am. Chem. Soc.* **2012**, *134*, 8810.
- For reviews, see: (a) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dubé, D.; André, C. *Pure Appl. Chem.* **1987**, *59*, 299. (b) Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935. (c) Koskinen, A. M. P. *Pure Appl. Chem.* **2011**, *83*, 435.
- For recent reviews of catalytic asymmetric synthesis of tertiary alcohols, see: (a) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (b) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (c) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647. (d) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (e) Adachi, S.; Harada, T. *Eur. J. Org. Chem.* **2009**, 3661. For a general and efficient protocol for the synthesis of optically active tertiary alcohols from enantioenriched secondary alcohol, see: (f) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778.
- (a) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522.
- For reviews, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363. (d) *Quaternary Stereocenters*, (Eds.: J. Christoffer, A. Baro), Wiley,

- Weinheim, 2005. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (f) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969.
7. Trost, B. M. *Science* **1991**, 254, 1471.
 8. Recent reviews on asymmetric catalysis with particular emphasis on C–C bond-forming reactions with perfect atom economy, see: (a) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, 50, 4760. (b) Matsunaga, S.; Shibasaki, M. *Chem. Commun.* **2014**, 50, 1044.
 9. For recent reviews of cooperative catalysis, see: Lewis acid/Brønsted base: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, 102, 2187. Lewis acid/Lewis base: (b) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (c) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, 41, 655. Lewis acid/Brønsted acid and Lewis acid/Lewis acid: (d) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, 44, 1924. (e) Yamamoto, H.; Futatsugi, K. In *Acid Catalysis in Modern Organic Synthesis* (Eds.: H. Yamamoto, K. Ishihara) Wiley-VCH, Weinheim, 2008.
 10. The intramolecular cyclization of the corresponding secondary alcohol was reported under less efficient reduction/oxidation sequence: Otsuka, Y.; Takada, H.; Yasuda, S.; Kumagai, N.; Shibasaki, M. *Chem. Asian J.* **2013**, 8, 354.
 11. See Supplementary Material.
 12. DBU afforded the best result among amine bases studied under otherwise identical conditions (Et₃N: 67%, pyridine: 59%, DMAP: 65%).
 13. AgOTf (\$136/25g, Sigma-Aldrich) was used throughout the study because of its lower cost compared with CuOTf•toluene_{0.5} (\$275.5/5g, Sigma-Aldrich). The use of Cu(OTf)₂ (\$206.5/25g, Sigma-Aldrich) provided a comparable reaction outcome under otherwise identical conditions. Cu(OTf)₂ can be prepared in large quantities starting from inexpensive Cu salt.
 14. Slight difference of enantiomeric excess of **3** and **4** for some cases was ascribed to rounding off to the closest whole number.
 15. Starting material almost disappeared and several unidentified by-products were observed.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016>

Concise enantioselective synthesis of δ,δ -disubstituted δ -valerolactones

Akira Saito, Naoya Kumagai,* and Masakatsu Shibasaki*

*Institute of Microbial Chemistry (BIKAKEN), Tokyo, Japan*mshibasa@bikaken.or.jp, nkumagai@bikaken.or.jp

1. General	S2
2. Instrumentation	S2
3. Materials	S2
4. Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones	S2-3
4-1. General procedure.	S2-3
4-2. Characterization of a new product.	S3
5. One-Pot Formation of δ,δ -Disubstituted δ -Valerolactones	S3-8
5-1. General procedure for one-pot formation of δ,δ -disubstituted δ -valerolactones.	S3-4
5-2. Hydrogenation of a tertiary alcohol 3i .	S4
5-3. Characterization of the products.	S4-8
6. Characterization of the Transient Imidate 6 .	S8-9
7. NMR Spectra of New Compounds	S10-27

1. General

The direct addition of allyl cyanide and the formation of δ -valerolactone was performed in a flame-dried 20 mL test tube with a Teflon-coated magnetic stirring bar unless otherwise noted. The test tubes were fitted with a 3-way glass stopcock and reactions were run under Ar atmosphere. Air- and moisture-sensitive liquids were transferred via a gas-tight syringe and a stainless-steel needle. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

2. Instrumentation

Infrared (IR) spectra were recorded on a JASCO FT / IR 410 Fourier transform infrared spectrophotometer. NMR was recorded on JEOL ECS-400 and ECA-600 spectrometers. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and referenced to residual protium in the NMR solvent (CDCl_3 ; δ 7.26 ppm). For ^{13}C NMR chemical shifts are reported in the scale relative to NMR solvent (CDCl_3 ; δ 77.0 ppm) as an internal reference. For ^{19}F NMR chemical shifts were reported in the scale relative to TFA (δ -76.50 ppm) as an external reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High resolution mass spectra (ESI TOF (+)) were measured on ThermoFisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (0.46 cm ϕ x 25 cm).

3. Materials

Unless otherwise noted, materials were purchased from commercial suppliers and were used without purification. CH_3CN , AcOEt and THF were purified by passing through a solvent purification system (Glass Contour). (*R,R*)-Ph-BPE, $\text{CuOTf}\cdot\text{toluene}_{0.5}$, $\text{Cu}(\text{OTf})_2$, $\text{Fe}(\text{OTf})_3$, $\text{Ni}(\text{OTf})_2$, and all Ag salts were purchased from Sigma-Aldrich and used as received (opened and handled in a dry box). Ketones were distilled prior to use under standard conditions. Allyl cyanide was purchased from Wako Pure Chemical Co. Ltd. and distilled prior to use. $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ was prepared by following the reported procedures.¹ Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM) purchased from Merck.

4. Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones²

4.1. General procedure.

Preparation of $\text{Li}(\text{OC}_6\text{H}_4\text{-}p\text{-OMe})$ in THF:

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way-stopcock was charged with *p*-methoxyphenol (12.4 mg, 0.1 mmol) in a dry box. Dry THF (1.0 mL) was added via a syringe with a stainless steel needle. To the solution was added *n*-BuLi (62.5 μL , 0.1 mmol, 1.6 M in *n*-hexane) at 0 °C and stirred at the same temperature for 1 h to give a 0.1 M lithium *p*-methoxyphenoxide solution in THF, which was used within 30 min.

Preparation of the catalyst solution:

¹ Kubas, G. J. *Inorg. Synth.* **1979**, Coll. Vol XIX, 90.

² Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, 132, 5522.

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$ (32.7 mg, 0.1 mmol), (*R,R*)-Ph-BPE (50.7 mg, 0.1 mmol), and phosphine oxide **5** (47.8 mg, 0.1 mmol) in dry box. To the flask dry THF (500 μL) was added via a stainless steel needle and a syringe, and the resulting solution was stirred at room temperature for 10 min to give yellow 0.2 M catalyst solution in THF, which was used immediately.

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with dry THF (0.9 mL) was added via a syringe with a stainless-steel needle. Then, allyl cyanide **2** (161 μL , 2.0 mmol), ketone **1** (1.0 mmol) and a premixed solution of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{ClO}_4$, (*R,R*)-Ph-BPE, and phosphine oxide **5** in THF (50 μL , 0.01 mmol, 0.2 M). The test tube was immersed into an electronically-controlled cooling bath at -60°C with 2-propanol as medium. To the solution was added lithium *p*-methoxyphenoxide (0.1 M/THF, 100 μL , 0.01 mmol) and stirring was continued at -40°C for 40 h. The reaction was quenched with sat. aq. NH_4Cl and the biphasic mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 . After evaporation of the solvent under reduced pressure, the crude mixture was purified by silica gel column chromatography to give the desired product.

4.2. Characterization of a new product.

(*S,Z*)-5-Hydroxy-5-(4-(trifluoromethyl)phenyl)hex-2-enenitrile (**3d**)

Pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 1.64 (s, 3H), 2.36 (brs, 1H), 2.86–2.97 (m, 2H), 5.98 (ddd, $J = 1.1, 1.1, 11.1$ Hz, 1H), 6.43 (ddd, $J = 7.6, 7.6, 11.1$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.61 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.3, 45.9, 74.0, 102.1, 115.9, 124.0 (q, $J^{1\text{C-F}} = 270$ Hz), 125.1, 125.3 (q, $J^{3\text{C-F}} = 3.8$ Hz), 129.3 (q, $J^{2\text{C-F}} = 32.4$ Hz), 150.05, 150.15; ^{19}F NMR (376 MHz, CDCl_3) δ -62.3; IR (neat): ν 3465, 2979, 2224, 1620, 1411, 1328, 1166, 1121, 1015, 846 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{13}\text{H}_{12}\text{ONF}_3\text{Na}$ m/z 278.0763 $[\text{M}+\text{Na}]^+$, found 278.0762; $[\alpha]_{\text{D}}^{25}$ 42.8 (c 1.86, CHCl_3 , 98% ee sample); HPLC (CHIRALPAK ID, (ϕ 0.46 cm $\times$ 25 cm)), *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 10.0$ min (minor), 11.4 min (major).

5. One-Pot Formation of δ,δ -Disubstituted δ -Valerolactones

5.1. General procedure for one-pot formation of δ,δ -disubstituted δ -valerolactones.

A flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock was charged with a tertiary alcohol **3** (0.20 mmol) and AgOTf (56.5 mg, 0.22 mmol), then dry THF (2.0 mL) was added via a syringe with a stainless-steel needle. DBU (35.9 μL , 0.24 mmol) was added to the solution at room temperature, and the resulting

mixture was stirred for 10 min at the same temperature. Then, to the mixture was added trifluoroacetic anhydride (62.0 μ L, 0.44 mmol), and stirring was continued for 1 h at the same temperature. Subsequently, to the reaction mixture was added AcOH (1.0 M in H₂O, 2.0 mL) at room temperature, and the resulting mixture was stirred for additional 10 min. The reaction was quenched with sat. aq. NH₄Cl and the biphasic mixture was extracted with AcOEt. The combined organic layers were washed with sat. aq. NaHCO₃ solution and brine, and dried over Na₂SO₄. After evaporation of the solvent under reduced pressure, the crude mixture was purified by silica gel column chromatography to give the desired product.

5.2. Hydrogenation of a tertiary alcohol **3i**.

To a mixture of **3i** (42.7 mg, 0.20 mmol) and Pd/C (10 wt % loading) (10.6 mg, 0.01 mmol) was added CH₃CN (20 mL) under argon atmosphere, and the reaction vessel was cooled to 0 °C. Then, the atmosphere was substituted with H₂, and the reaction mixture was stirred for 20 min at the same temperature. After the mixture was filtered through silica gel pad, the filtrate was concentrated. At the stage of crude mixture, the ratio of **3i**-H₂/**3i**-H₄ = 83/17, based on ¹H NMR analysis. The residue was purified by silica gel column chromatography (hexane/AcOEt = 4/1) to afford **3i**-H₂ (33.6 mg, 78%). The ¹H NMR spectrum of **3i**-H₂ was identical with the reported one.²

5.3. Characterization of the products.

Products **4a**, **4f**, **4h**, **4i**-H₂, and **4i**-H₄ were reported compounds. For those compounds, only HPLC charts and values of optical rotation were attached.

(S)-6-Methyl-6-phenyl-5,6-dihydro-2H-pyran-2-one (**4a**)³

$[\alpha]_D^{25}$ -31.5 (*c* 0.77, CHCl₃, 98% ee sample); HPLC (CHIRALPAK IC, (ϕ 0.46 cm x 25 cm)), *n*-hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, *t*_R = 27.8 min (major), 31.2 min (minor).

(S)-6-Methyl-6-(naphthalen-2-yl)-5,6-dihydro-2H-pyran-2-one (**4b**)

White solid; m.p. 73–76 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.81 (s, 3H), 2.87 (ddd, *J* = 2.3, 3.6, 18.5 Hz, 1H), 3.07 (ddd, *J* = 1.4, 5.2, 18.5 Hz, 1H), 6.02 (ddd, *J* = 1.4, 2.3, 9.8 Hz, 1H), 6.77 (ddd, *J* = 3.6, 5.2, 9.8 Hz, 1H), 7.45–7.53 (m, 3H), 7.79–7.88 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 30.0, 35.3, 83.2, 121.8,

ejeada, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288.

122.5, 123.4, 126.3, 126.5, 127.4, 128.2, 128.4, 132.5, 132.9, 141.1, 143.4, 163.9; IR (neat): ν 3017, 1714, 1381, 1271, 1064, 815, 750 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_2\text{Na}$ m/z 261.0886 $[\text{M}+\text{Na}]^+$, found 261.0885; $[\alpha]_{\text{D}}^{25}$ -61.2 (c 0.73, CHCl_3 , 98% ee sample); HPLC (CHIRALPAK IC, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, t_{R} = 30.8 min (major), 37.4 min (minor).

(S)-6-(2-Fluorophenyl)-6-ethyl-5,6-dihydro-2H-pyran-2-one (4c)

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 1.80 (s, 3H), 2.91 (dddd, J = 0.9, 2.4, 3.7, 18.2 Hz, 1H), 3.10 (ddd, J = 1.5, 5.1, 18.6 Hz, 1H), 5.98 (ddd, J = 1.5, 2.4, 9.8 Hz, 1H), 6.75 (ddd, J = 3.7, 5.1, 9.8 Hz, 1H), 7.03 (ddd, J = 1.3, 8.1, 12.4 Hz, 1H), 7.13 (ddd, J = 1.3, 7.6, 7.6 Hz, 1H), 7.22–7.31 (m, 1H), 7.51 (ddd, J = 1.7, 8.1, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 27.7 (d, $J_{\text{C-F}}$ = 2.9 Hz), 34.3 (d, $J_{\text{C-F}}$ = 6.7 Hz), 81.8 (d, $J_{\text{C-F}}$ = 4.8 Hz), 116.4 (d, $J_{\text{C-F}}$ = 22.9 Hz), 121.0, 124.4 (d, $J_{\text{C-F}}$ = 2.9 Hz), 127.2 (d, $J_{\text{C-F}}$ = 2.9 Hz), 129.5 (d, $J_{\text{C-F}}$ = 8.6 Hz), 130.7 (d, $J_{\text{C-F}}$ = 10.5 Hz), 144.0, 158.6 (d, $J_{\text{C-F}}$ = 245 Hz), 163.7; ^{19}F NMR (376 MHz, CDCl_3) δ -113.4 ; IR (neat): ν 2984, 1715, 1615, 1580, 1488, 1447, 1381, 1256, 1062, 761 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_2\text{FNa}$ m/z 229.0635 $[\text{M}+\text{Na}]^+$, found 229.0638; $[\alpha]_{\text{D}}^{25}$ -107.4 (c 0.96, CHCl_3 , 99% ee sample); HPLC (CHIRALPAK IC-3, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, t_{R} = 18.5 min (major), 20.2 min (minor).

(S)-6-Methyl-6-(4-(trifluoromethyl)phenyl)-5,6-dihydro-2H-pyran-2-one (4d)

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 1.73 (s, 3H), 2.84 (ddd, J = 2.2, 3.8, 18.3 Hz, 1H), 2.95 (ddd, J = 1.6, 4.9, 18.3 Hz, 1H), 6.02 (ddd, J = 1.6, 2.2, 9.8 Hz, 1H), 6.77 (ddd, J = 3.8, 4.9, 9.8 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 29.8, 35.2, 82.7, 121.8, 123.9 (q, $J_{\text{C-F}}$ = 271 Hz), 124.9, 125.6 (q, $J_{\text{C-F}}$ = 3.7 Hz), 129.9 (q, $J_{\text{C-F}}$ = 32.5 Hz), 143.2, 147.9, 163.3; ^{19}F NMR (376 MHz, CDCl_3) δ -62.4 ; IR (neat): ν 2985, 1715, 1620, 1411, 1382, 1327, 1168, 1118, 1066, 845, 816 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{F}_3\text{Na}$ m/z 279.0603 $[\text{M}+\text{Na}]^+$, found 279.0603; $[\alpha]_{\text{D}}^{25}$ -43.9 (c 1.26, CHCl_3 , 98% ee sample); HPLC (CHIRALPAK IA-3, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 95/5, flow rate 0.5 mL/min, detection at 254 nm, t_{R} = 24.2 min (major), 27.2 min (minor).

(S)-6-(3-Methoxyphenyl)-6-methyl-5,6-dihydro-2H-pyran-2-one (4e)

Colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 1.71 (s, 3H), 2.78 (ddd, $J = 2.3, 3.5, 18.4$ Hz, 1H), 2.95 (ddd, $J = 1.4, 5.2, 18.4$ Hz, 1H), 3.80 (s, 3H), 5.99 (ddd, $J = 1.4, 2.3, 9.8$ Hz, 1H), 6.75 (ddd, $J = 3.5, 5.2, 9.8$ Hz, 1H), 6.81 (ddd, $J = 1.0, 2.4, 8.2$ Hz, 1H), 6.91–6.95 (m, 2H), 7.23–7.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 30.1, 35.3, 55.4, 83.0, 110.8, 112.6, 116.7, 121.7, 129.6, 143.5, 145.6, 159.7, 163.9; IR (neat): ν 2979, 1714, 1603, 1584, 1489, 1434, 1381, 1291, 1267, 1235, 1064, 1046, 815, 701 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}$ m/z 241.0835 $[\text{M}+\text{Na}]^+$, found 241.0833; $[\alpha]_{\text{D}}^{25} -33.6$ (c 0.49, CHCl_3 , 98% ee sample); HPLC (CHIRALPAK IC, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 35.9$ min (major), 40.3 min (minor).

(S)-6-Ethyl-6-phenyl-5,6-dihydro-2H-pyran-2-one (4f)³

$[\alpha]_{\text{D}}^{25} -27.0$ (c 1.11, CHCl_3 , 95% ee sample); HPLC (CHIRALPAK IA-3, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-isopropanol = 95/5, flow rate 0.5 mL/min, detection at 254 nm, $t_{\text{R}} = 21.1$ min (minor), 22.4 min (major).

(S)-6-Phenyl-6-propyl-5,6-dihydro-2H-pyran-2-one (4g) **4g**

Pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ 0.83 (dd, $J = 7.3, 7.3$ Hz, 3H), 1.11 (m, 1H), 1.38 (m, 1H), 1.88 (ddd, $J = 4.6, 12.1, 14.0$ Hz, 1H), 2.01 (ddd, $J = 4.7, 12.0, 14.0$ Hz, 1H), 2.83 (ddd, $J = 2.8, 2.8, 18.4$ Hz, 1H), 2.93 (ddd, $J = 1.2, 5.5, 18.4$ Hz, 1H), 5.96 (ddd, $J = 1.1, 2.3, 9.7$ Hz, 1H), 6.71 (ddd, $J = 3.3, 5.6, 9.8$ Hz, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 14.0, 16.7, 33.9, 45.0, 85.6, 121.9, 125.1, 127.4, 128.4, 142.5, 143.5, 164.1; IR (neat): ν 2961, 1718, 1447, 1381, 1253, 1096, 1028, 817, 760, 702 cm^{-1} ; HRMS (ESI+) Anal. calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_2\text{Na}$ m/z 239.1043 $[\text{M}+\text{Na}]^+$, found 239.1044; $[\alpha]_{\text{D}}^{25} -22.7$ (c 0.48, CHCl_3 , 96% ee sample); HPLC (CHIRALPAK IE, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 95/5, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 29.3$ min (minor), 30.7 min (major).

(S)-3,4-Dihydro-2H-spiro[naphthalene-1,2'-pyran]-6'(3'H)-one (4h) **4h**

$[\alpha]_{\text{D}}^{25} -97.9$ (c 0.32, CHCl_3 , 98% ee sample); HPLC (CHIRALPAK ID, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 80/20, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 16.6$ min (major), 18.6 min (minor).

(R)-6-Methyl-6-phenethyl-5,6-dihydro-2H-pyran-2-one (4i-H₂)³ **4i-H₂**

$[\alpha]_{\text{D}}^{25} -47.6$ (c 0.58, CHCl_3 , 88% ee sample); HPLC (CHIRALPAK AD-3, (ϕ 0.46 cm $\times$ 25 cm)), n -hexane/2-propanol = 95/5, flow rate 1.0 mL/min, detection at 254 nm, $t_{\text{R}} = 12.0$ min (minor), 13.4 min (major).

(S)-6-Methyl-6-phenethyltetrahydro-2H-pyran-2-one (4i-H₄)⁴

$[\alpha]_{\text{D}}^{25}$ -18.9 (*c* 0.18, CHCl₃, 88% ee sample); HPLC (CHIRALPAK IC-3, (ϕ 0.46 cm x 25 cm)), *n*-hexane/2-isopropanol = 90/10, flow rate 1.0 mL/min, detection at 254 nm, *t_R* = 46.3 min (major), 62.6 min (minor).

(S)-N-(6-Methyl-6-phenyl-5,6-dihydro-2H-pyran-2-ylidene)methanesulfonamide (7)

Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 1.79 (s, 3H), 2.87 (ddd, *J* = 2.3, 3.6, 18.6 Hz, 1H), 3.07 (ddd, *J* = 1.4, 5.3, 18.6 Hz, 1H), 3.11 (s, 3H), 5.98–6.08 (m, 1H), 6.73–6.81 (m, 1H), 7.25–7.32 (m, 1H), 7.33–7.41 (m, 2H), 7.42–7.50 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 29.8, 34.6, 42.7, 85.3, 122.3, 124.5, 127.9, 128.8, 142.6, 142.9, 161.2; IR (neat): ν 3608, 3535, 3020, 2983, 2935, 1643, 1575, 1497, 1446, 1390, 1308, 1135, 1092, 966, 824, 794, 763 cm⁻¹; HRMS (ESI+) Anal. calcd. for C₁₃H₁₅O₃NNaS *m/z* 288.0665 [M+Na]⁺, found 288.0662;

$[\alpha]_{\text{D}}^{25}$ -197.5 (*c* 0.46, CHCl₃, 99% ee sample).

(S,Z)-5-Cyano-2-phenylpent-4-en-2-yl 2,2,2-trifluoroacetate (8)

Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 2.01 (s, 3H), 3.13–3.27 (m, 2H), 5.47 (ddd, *J* = 1.4, 1.4, 11.0 Hz, 1H), 6.34 (ddd, *J* = 7.6, 7.6, 11.0 Hz, 1H), 7.30–7.45 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 44.4, 87.8, 103.72, 114.2 (q, *J*_{C-F} = 286 Hz), 115.2, 124.3, 128.6, 129.0, 140.5, 147.1, 155.3 (q, *J*_{C-F} = 42 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -75.3; IR (neat): ν 2223, 1785, 1496, 1449, 1367, 1223, 1152, 1097, 1065, 1030, 755, 700 cm⁻¹; HRMS (ESI+) Anal. calcd. for C₁₄H₁₂O₂NF₃Na *m/z* 306.0712 [M+Na]⁺, found 306.0709; $[\alpha]_{\text{D}}^{25}$ 10.7 (*c* 0.54, CHCl₃, 99% ee sample).

(2Z,6E)-5-Hydroxy-5-methyl-7-phenylhepta-2,6-dienamide (11)

Pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 1.43 (s, 3H), 2.77 (dd, *J* = 8.5, 13.5 Hz, 1H), 2.89 (dd, *J* = 8.5, 13.5 Hz, 1H), 3.82 (brs, 1H), 5.99 (brs, 1H), 6.00 (d, *J* = 11.6 Hz, 1H), 6.16 (brs, 1H), 6.18 (ddd, *J* = 8.5, 8.5, 11.6 Hz, 1H), 6.30 (d, *J* = 16.0 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.38 (d, *J* = 7.5 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 28.8, 41.2, 73.3, 125.1, 126.4, 127.3, 127.4, 128.5, 136.2, 136.9, 141.0, 169.2; IR (neat): ν 3454, 3336, 3191, 2972, 1669, 1634, 1601, 1494, 1447, 1336, 1096, 971, 909, 818, 749 cm⁻¹; HRMS (ESI+) Anal. calcd. for C₁₄H₁₇O₂NNa *m/z* 254.1152 [M+Na]⁺, found 254.1150.

6. Characterization of Transient Imidate 6

To an NMR tube, were added **3a** (11.2 mg 0.06 mmol), AgOTf (16.9 mg, 0.066 mmol), DBU (10.8 μ L, 0.072 mmol), and THF-*d*₈ at room temperature. The appearance of new peaks around 6–7 ppm was indicative of the olefinic protons (H_a,H_b) corresponding to the imidate **6** (Chart S1). Two sets of protons were likely due to the presence of *trans* and *cis*

⁴ Gansauer, A.; Bluhm, H.; Pierobon, M. J. *Am. Chem. Soc.* **1998**, *120*, 12849.

geometrical isomers. Correlation between olefinic protons and methylene protons (H_c, H_d) were observed in 1H - 1H cosy spectrum, further supporting the formation of imidate **6**.

(a) 1H NMR (b) 1H - 1H cosy NMR

Chart S1. 1H and 1H - 1H cosy NMR spectra of the mixture of **3a**/AgOTf/DBU in $THF-d_8$.

7. NMR Spectra of New Compounds