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

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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.

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 of 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).

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 $[Cu(CH_3CN)_4]ClO_4$/(*R*,*R*)-Ph-BPE/$Li(OC_6H_4$-*p*-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

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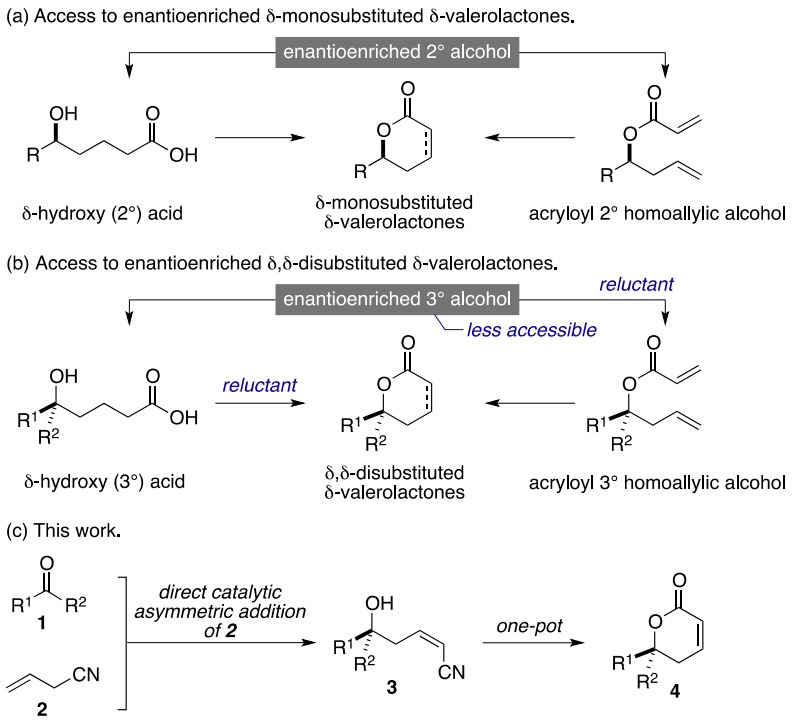
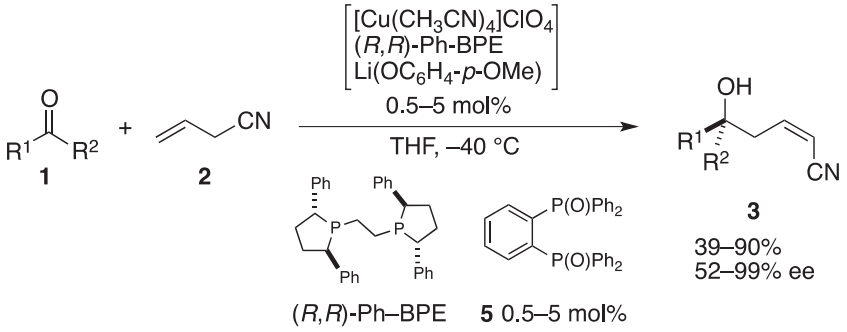
0040-4039/



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



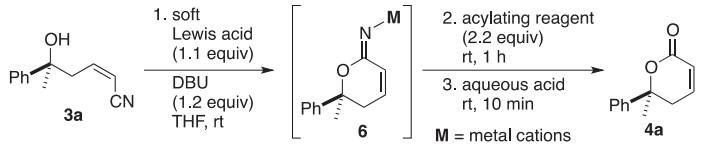
Scheme 2. Direct catalytic asymmetric addition of allyl cyanide.

$CuOTf{\cdot}toluene_{0.5}$ salts at room temperature rendered the rapid disappearance of **3a** within 10 min to give transient cyclic imidate **6** as detected by ^1H NMR analysis (Table 1, entries 1, 2).[11] All attempts to directly convert imidate **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 imidate **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 imidate 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 imidate **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 imidate **6** over an extended period of time and δ-valerolactone **4a** was obtained in moderate yield after subsequent trifluoroacetylation/hydrolysis (entry 11).

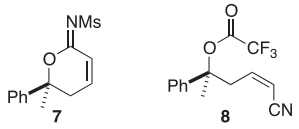
Increasing the reaction temperature was not beneficial to accelerate the cyclization and **4a** was obtained in even lower yield (entry 12). No indication of the formation of **6** was observed with AgOAc or Ag_2CO_3 and the following reactions afforded trifluoroacetylated substrate **8** and the recovery 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

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

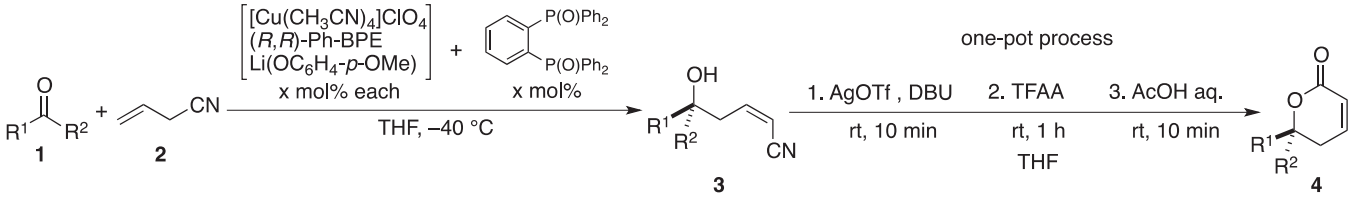


Entry	1. Formation of **6**		2. Activation	3. Hydrolisis	Yield of **4a**[b] (%)	Remarks
	Soft Lewis acid	Time (min)	*N*-Acylation (sulfonylation)	Hydrolytic conditions[a]		
1	CuOTf[c]	10	—	HCl	0	
2	AgOTf	10	—	HCl	0	**6** was detected
3	AgOTf	10	Ac_2O	HCl	16	
4	AgOTf	10	TFAA	HCl	32	
5	AgOTf	10	Tf_2O	HCl	0	
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	
10	AgOTf	10	TFAA	AcOH	76	
11	$AgNO_3$	60	TFAA	AcOH	46	
12[d]	$AgNO_3$	60	TFAA	AcOH	40	
13	AgOAc	180	TFAA	AcOH	0	**3a** (73%), **8** (16%)
14	Ag_2CO_3[e]	180	TFAA	AcOH	0	**3a** (44%), **8** (39%)
15[f]	$Ni(OTf)_2$	180	TFAA	AcOH	0	**3a** (13%), **8** (31%)
16[f]	$Fe(OTf)_3$	180	TFAA	AcOH	18	**3a** (11%), **8** (0%)



[a] 1 M Aqueous acid solution (equal volume to the reaction mixture) was added.
[b] Isolated yield.
[c] CuOTf·toluene$_{0.5}$ was used.
[d] Reaction temperature was 50 °C.
[e] 0.55 equiv of Ag_2CO_3 (1.1 equiv based on Ag content) was used.
[f] Reaction temperature was 60 °C.

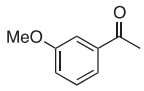
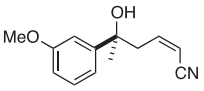
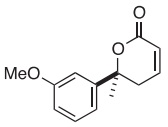
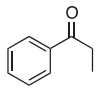
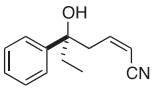
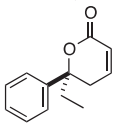
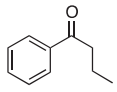
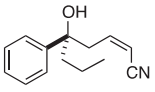
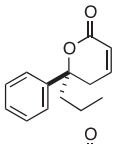
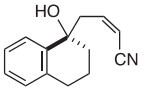
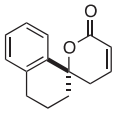
Table 2
Direct catalytic asymmetric addition of allyl cyanide **2** to ketones **1** to afford cyclization precursors **3** and the subsequent one-pot formation of δ,δ-disubstituted δ-valerolactones **4**



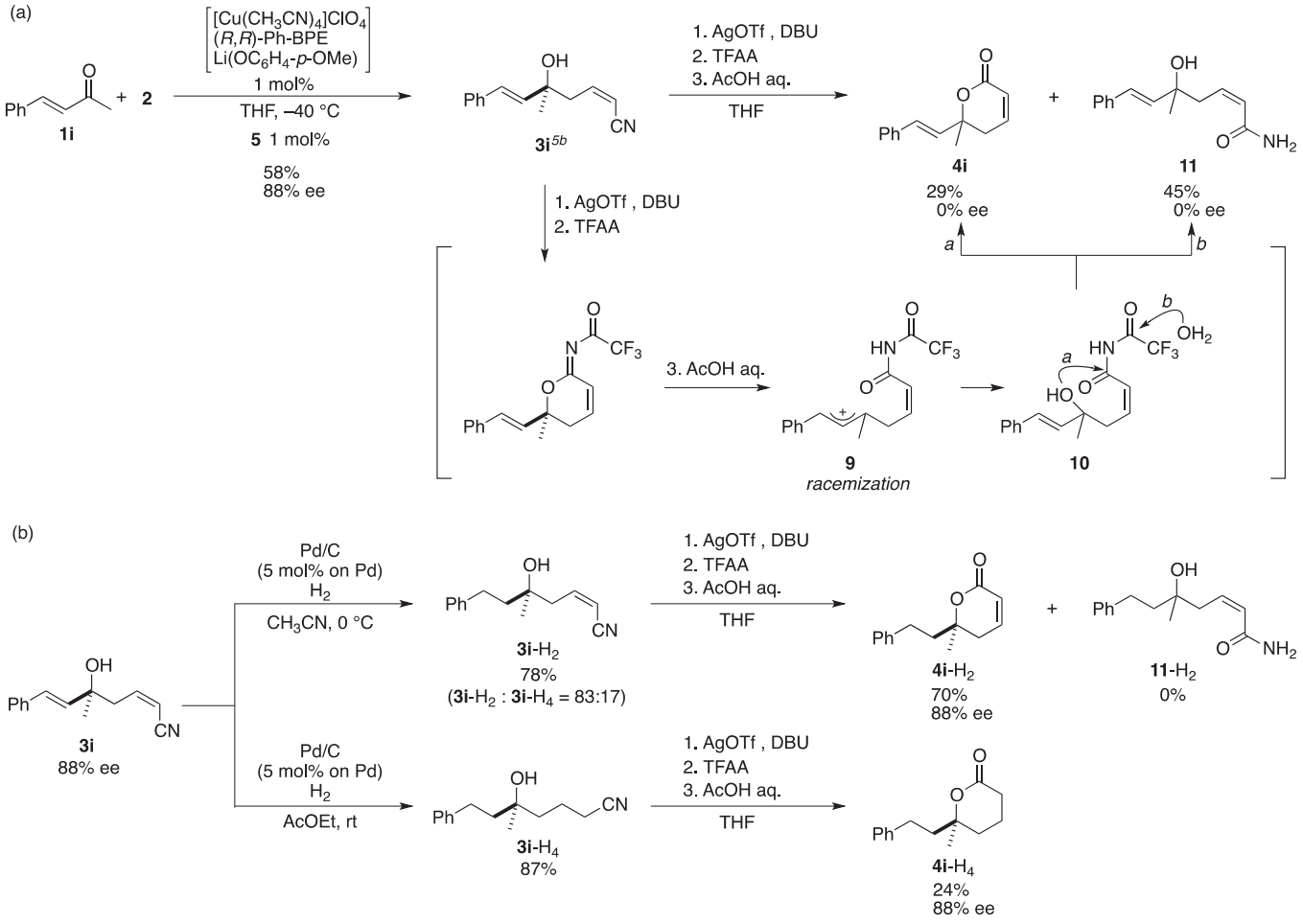
Entry	Ketone	Product	*x* (mol %)	Time (h)	Yield[a] (%)	ee[b] (%)	Entry	δ-Valerolactone	Yield[a] (%)	Enantiopurity[b] (%)
1	**1a**	**3a**[5b]	1	40	83	99	1′	**4a**	76	98
2	**1b**	**3b**[5b]	1	40	78	98	2′	**4b**	80	98
3	**1c**	**3c**[5b]	2	40	67	99	3′	**4c**	72	99
4	**1d**	**3d**	1	40	80	98	4′	**4d**	78	98

(*continued on next page*)

Table 2 (*continued*)

Entry	Ketone	Product	*x* (mol %)	Time (h)	Yield[a] (%)	ee[b] (%)	Entry	δ-Valerolactone	Yield[a] (%)	Enantiopurity[b] (%)
5	 **1e**	 **3e**[5b]	1	40	84	99	5′	 **4e**	69	98
6[c]	 **1f**	 **3f**[5b]	1	72	68	94	6′	 **4f**	76	95
7[c]	 **1g**	 **3g**[5b]	1	72	68	96	7′	 **4g**	72	96
8[c]	 **1h**	 **3h**[5b]	2	72	68	99	8′	 **4h**	74	98

[a] Isolated yield.
[b] Determined by chiral stationary phase HPLC analysis.
[c] LiO^{t}Bu was used instead of Li(OC_6H_4-*p*-OMe).



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

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 spirolactone **4h** was obtained in 74% yield from **3h** (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 H_2O and re-cyclization 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 protocol with the use of partially hydrogenated **3i**-H_2, prepared by selective hydrogenation of a styryl group of **3i** over Pd/C in acetonitrile, afforded δ-valerolactone **4i**-H_2 while maintaining the enantiopurity and avoiding undesired ring-opened byproduct **11**-H_2 (Scheme 3b). Intriguingly, fully reduced **3i**-H_4, 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.

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

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.006.

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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 (Et_3N: 67%, pyridine: 59%, DMAP: 65%).
13. AgOTf ($136/25 g, Sigma-Aldrich) was used throughout the study because of its lower cost compared with CuOTf·$toluene_{0.5}$ ($275.5/5 g, Sigma-Aldrich). The use of $Cu(OTf)_2$ ($206.5/25 g, 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.