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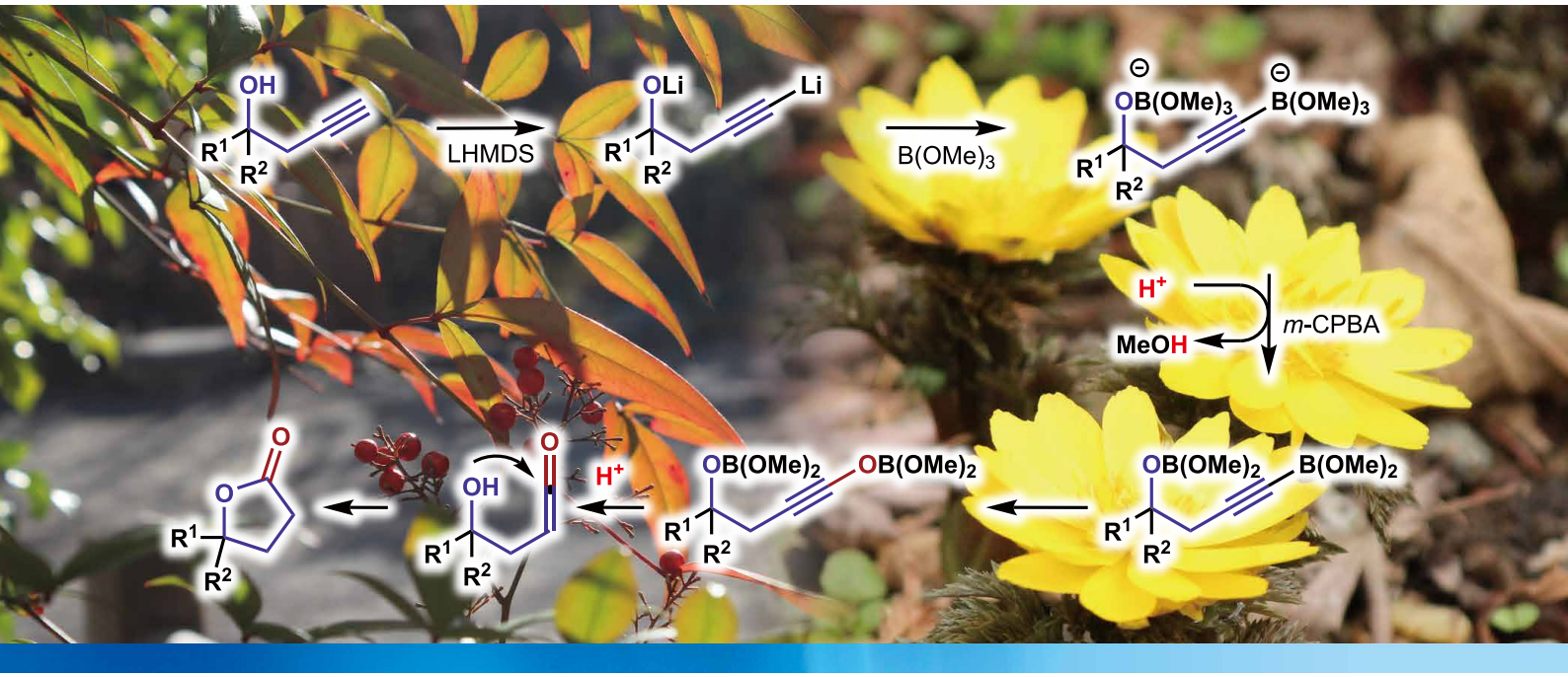

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ISSN 1349-4848 CODEN:TCIMDW

Research Article

One-pot γ-Lactonization of Homopropargyl Alcohol via Intramolecular Ketene Trapping –Its discovery, optimization, and application–

Masaki Ohtawa
School of Pharmacy, Kitasato University

Abstract

In this study, a novel one-pot γ-lactonization reaction of homopropargylic alcohols via deprotonation/boronation/oxidation of terminal alkynes was developed. In this reaction, the oxidation of alkynyl boronates generates ketene intermediates in the system, and the adjacent hydroxy groups are rapidly cyclized to produce good yields of γ-lactones. The results of the substrate scope study revealed that this reaction has a broad substrate generality, and a short synthesis of spironolactone was also achieved by applying this reaction.

Keywords: homopropargyl alcohol, ketene, γ-lactone

Introduction

Synthetic strategies are critical for the total synthesis of natural products, and combining novel reactions (approaches) according to the situation is an important factor. In general, the originally developed novel reactions can be applied to the study of total synthesis; however, it is not surprising to obtain new reactions derived from the synthetic study, including total synthesis. As a case in point, we found a regioselective deprotection reaction[2] of silylene acetals from the synthesis of pyripyropene A derivatives[1] as SOAT2 selective inhibitors, and the γ-lactonization reaction of homopropargylic alcohols in this study was also an extension of the reaction discovered from the study of total synthesis. Herein, we describe the process of discovery, optimization of the reaction conditions, investigation of substrate generality, and application to the synthesis of biologically active compounds.

Discovery of the γ-lactonization of homopropargyl alcohol

Bilobalide (**1**) is a terpene trilactone, a secondary metabolite of *Ginkgo biloba*, which exhibits a characteristic cage-shaped structure with dense functional groups, and is a unique $GABA_A$ receptor antagonist. We started our research to construct an efficient total synthesis pathway that can be applied to the synthesis of various derivatives in the future. **Figure 1** shows a summary of the total synthesis we achieved; for more details, please refer to our original papers.[3-5] First, γ-bromoester **3** was obtained in a one-pot reaction using bromoylide **2**, followed by the addition of β-ketoester **A**. Next, enantiopure cyclopentene **4** was acquired via the catalytic asymmetric Reformatsky reaction with aldehyde **B** in the presence of chiral ligand **C**, followed by an intramolecular stereoselective radical cyclization reaction. Next, stereoselective Mukaiyama hydration was used to stereoselectively introduce a tertiary hydroxy group, followed by stereoselective oxetane acetalization using chiral phosphoric acid catalyst **D** to yield highly functionalized cyclopentane unit **5**. Subsequently, the ethynyl group was stereoselectively introduced as a two-carbon unit via three steps of oxidation/ethynylation/reduction to **6**, followed by lactonization[6] of the homopropargyl alcohol unit (the subject of this study) to **7**. Global deprotection

of the two Bn esters and the oxetane acetal generated 10-des-hydroxybilobalide (**8**). Finally, regio- and diastereoselective introduction of a hydroxy group at the 10-position led to the efficient total synthesis of bilobalide (**1**) in 12 steps.

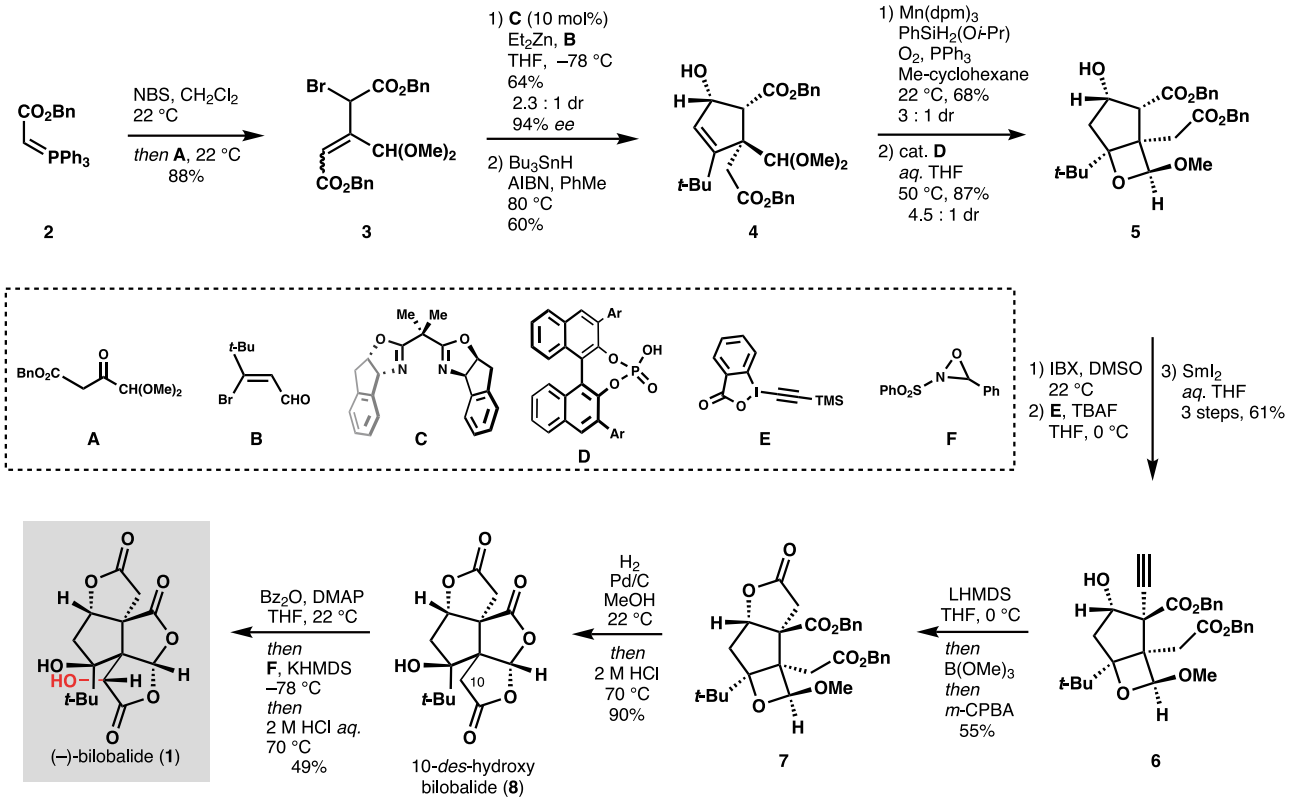
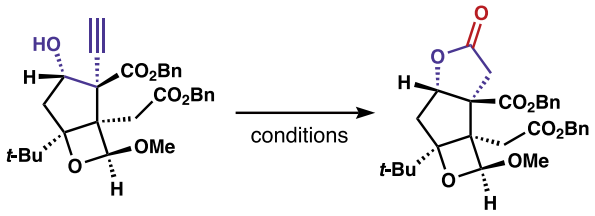


Figure 1. Concise asymmetric synthesis of (–)-bilobalide (**1**).

Figure 2-A shows the examination of the γ-lactonization of homopropargyl alcohol **6**. Sequential γ-lactonization, including hydroboration/oxidation of the generated lactols, was attempted (entries 1 and 2). However, the desired-lactone **7** gave a low yield because of the hindrance around the ethynyl group. The one-pot lactonization of homopropargylic alcohols using Ru[7] or Au[8] catalysts was attempted, but only a trace amount of γ-lactone **7** was obtained or degradation of **6** occurred (entries 3 and 4). However, Julia reported the preparation of the corresponding ynolates via deprotonation of terminal alkynes,[9] followed by oxidation with *t*-BuOOLi and subsequent protonation and intermolecular reaction with EtOH to give ethyl esters (**Figure 2-B**). This method was attempted for **6** as an intramolecular reaction, but functional group conversion did not proceed because of steric hindrance (entry 5). A direct hydroxylation reaction with the pyridine ring, which was used in the total synthesis of atpenin A (**9**) by our group,[10] was utilized as an alternative method for this lactonization. When this method is applied to sp-carbon, the terminal alkyne is oxidized to the corresponding ynolate or ynol, and then ketene is formed to obtain the desired γ-lactone. The condition of the above hydroxylation was attempted for **6**, and the reaction proceeded as expected, giving the desired lactone **7** at 55% (entry 5).

A



6 7

entry	conditions	product
1	1) Cy_2BH *then* $Na_2B_2O_8$ 2) TEMPO PIDA	<10% conversion
2	1) BH_3·THF *then* $Na_2B_2O_8$ 2) TEMPO, PIDA	23%
3	CpRuCl(bpy), PIDA	<5%
4	PPh_3AuNTf_2, *m*-CPBA	decomposition
5	LHMDS, LiOO*t*-Bu	N.R.
6	LHMDS *then* $B(OMe)_3$ *then* *m*-CPBA	55%

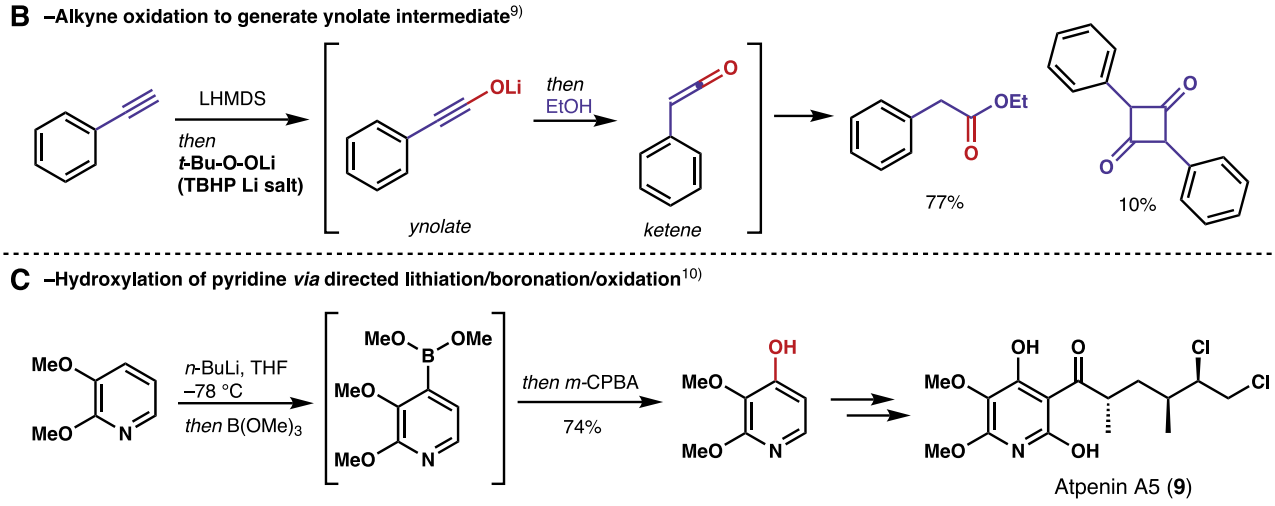
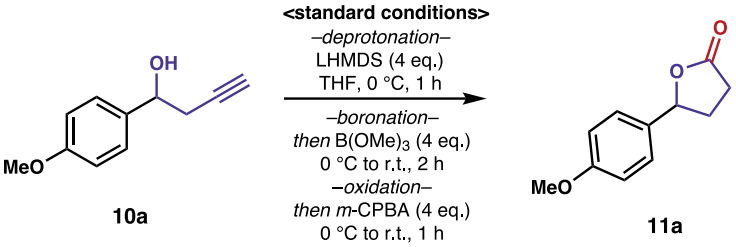


Figure 2. **A**) Attempted γ-lactoniztion of homopropargyl alcohol **6**. **B**) Alkyne oxidation to generate ynolate intermediates reported by Julia. **C**) Hydroxylation of pyridine via directed lithiation/boronation/oxidation.

Fortunately, the oxidation method was novel not only as an alkyne oxidation method but also as a one-pot γ-lactonization of homopropargyl alcohols; therefore, detailed conditions of this reaction were investigated using easily prepared **10a** as a substrate (**Figure 3**). Deprotonation was performed using LHMDS as the base for 1 h at 0 °C, followed by the addition of $B(OMe)_3$ and stirring at room temperature for 2 h. The addition of *m*-CPBA at 0 °C produced the desired lactone **11a** in 79% yield (entry 1), which proved to be the optimal reaction conditions, and this reaction was easily scaled-up (entry 2). Next, the reagents used in the deprotonation/boronatation/oxidation steps were examined; fewer nucleophilic bases and sterically smaller borates were preferred (entries 6 and 7). The oxidation did not proceed when neutral (TBHP, entry 8) or basic (*t*-BuOOLi, entry 9) oxidants were used. Although the reaction proceeded when weakly acidic Triazox[11] was used, the yield was lower than when *m*-CPBA was used (entry 10). Next, the effects of water and *m*-chlorobenzoic acid (*m*-CBA) as stabilizers of *m*-CPBA, which generally included commercially available *m*-CPBA, were investigated. Using anhydrous *m*-CPBA (entry 11) or purified *m*-CPBA (>95% purity) (entry 12), we found that the yields of both reactions decreased, suggesting that *m*-CPBA containing a stabilizer was the most suitable oxidant for this reaction. Finally, the equivalents of reagents for each process were examined and reduced to three equivalents (entries 13 and 14).



entry	variations from standard conditions	result	
		11a	**10a**
1[a]	none	**79%**	13%
2[a]	0 °C, 1 h (*boronation*)	25%	41%
3[a]	0 °C to r.t., 1 h (*boronation*)	52%	44%
4[a]	0 °C to r.t., 3 h (*boronation*)	49%	11%
5[a]	–78 °C to 0 °C, 2 h (ox*idation*)	28%	71%
6[a]	*n*-BuLi instead of LHMDS	21%	66%
7[a]	B(O*i*-Pr)$_3$ instead of B(OMe)$_3$	50%	29%
8	TBHP instead of *m*-CPBA	0%	78%
9[b]	*t*-BuOOLi instead of *m*-CPBA	0%	62%
10[c]	Triazox[11] instead of *m*-CPBA	21%	15%
11[d]	anhydrous *m*-CPBA instead of normal *m*-CPBA	57%	30%
12[e]	purified *m*-CPBA (>95% purity) instead of normal *m*-CPBA	44%	14%
13	3 eq. each reagent	**83%**	12%
14	2.5 eq. each reagent	46%	51%

[a] The purity of *m*-CPBA was >65%, also contained *m*-Cl benzoic acid and H_2O.
[b] *t*-BuOOLi was prepared from TBHP and LHMDS at 0 °C. The conditions of oxidation step was 0 °C to r.t.,18 h.
[c] The conditions of oxidation step was 0 °C to r.t., 18 h.
[d] A prepared CH_2Cl_2 solution of anhydrous *m*-CPBA was used.
[e] Prepared purified *m*-CPBA was used.

Figure 3. Optimization of the reaction conditions.

A plausible mechanism for this reaction is shown in **Figure 4**. First, homopropargylic alcohol **10** is deprotonated by LHMDS to form lithium acetylide **12**, and B(OMe)3 is applied to form borate intermediate **13**. The addition of *m*-CPBA may have facilitated the dissociation of one molecule of MeOH from the borate intermediate as a proton source, thereby giving rise to the boronate intermediate **14**. The resulting boronate intermediate **14** was quickly oxidized by *m*-CPBA to alkynylborate intermediate **15**, which was converted to ketene **16** via protonation. A nearby hydroxy group trapped ketene to give γ-lactone **11**. Although a small amount of homopropargylic alcohol was consistently recovered in this reaction, alkynyl boronates are generally unstable in the presence of proton sources and undergo rapid protonation to give terminal alkynes.[12] Therefore, further improvement in the yield of this lactonization is possible by strictly controlling the equivalent amount and type of proton source used. However, one of the significant advantages of our method is that it can be performed simply by adding inexpensive commercially available reagents in a one-pot reaction. We are currently reserving further consideration of the conditions of this method.

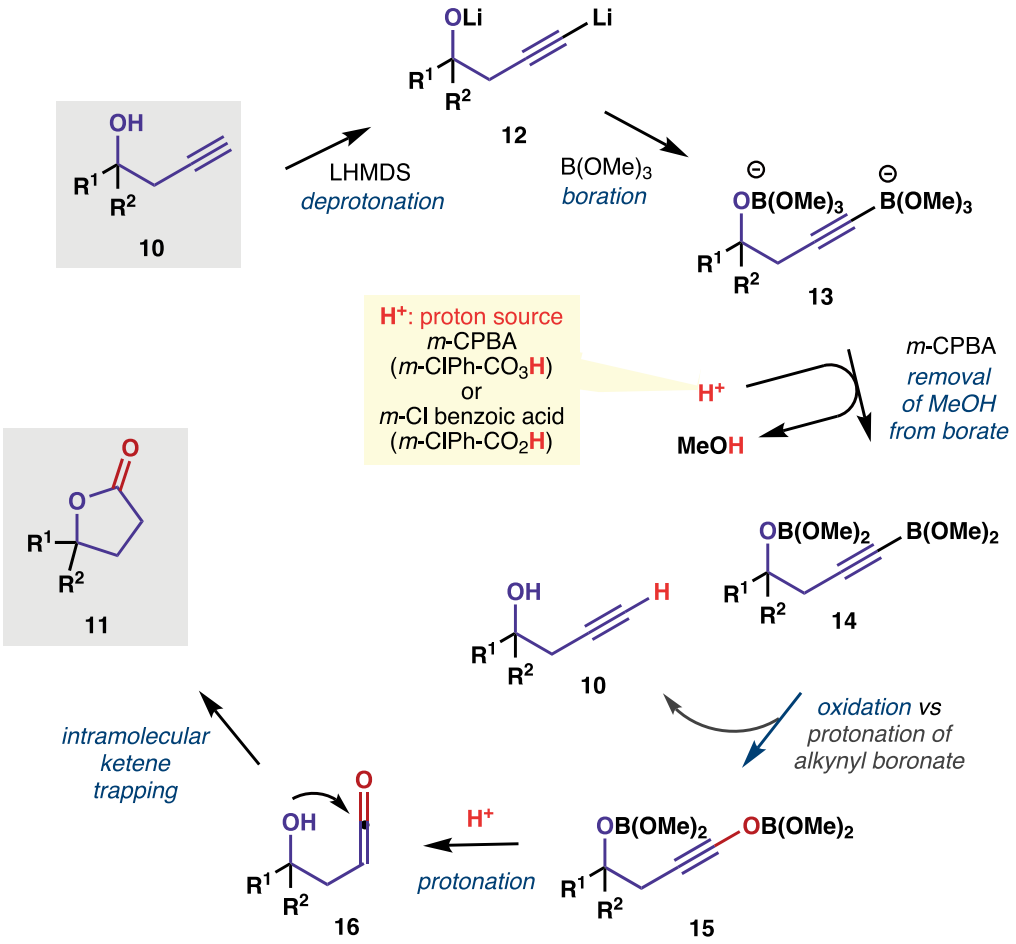


Figure 4. Plausible mechanism.

Subsequent examination of the substrate generality of this reaction revealed that it gave a substantial yield of the corresponding γ-1,2-substituted lactone, except for **11j**, which had an amino group (**Figure 5**). In particular, for lactonization with alkenes such as **11v**, the corresponding γ-lactone was obtained without loss of the substrate alkene, suggesting that this reaction is a useful new reaction for homopropargyl alcohols with wide functional group tolerance.

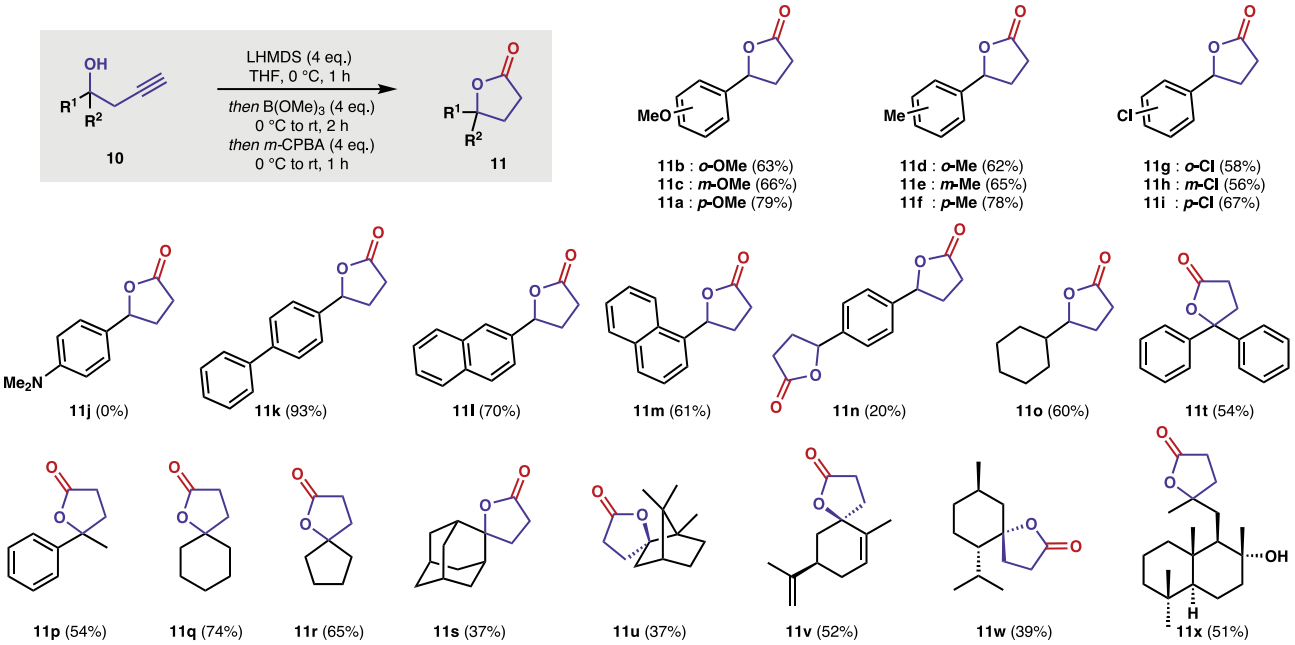


Figure 5. Substrate scope.

The next step was to apply this reaction to the short-step synthesis of spironolactone (**17**) (**Figure 6**). Although it has been semi-synthesized from steroidal compounds by several industrial methods, Ciba-Geigy's process constructed γ-lactone **20** from dehydroepiandrosterone (**18**) in five steps, followed by three steps of FGIs, for a total of eight steps to produce spironolactone (**12**) industrially.[12,13] Therefore, our new lactonization method was applied to their synthesis to improve the synthesis of **17**. Homopropargyl intermediate **19** was obtained in 98% yield from dehydroepiandrosterone (**18**) with *in situ* prepared propargyl Grignard reagent in the presence of mercury (II) chloride. The subsequent lactonization gave γ-lactone **20**, which was Ciba-Geigy's intermediate, in 83% yield in two steps from dehydroepiandrosterone (**18**) without compromising the alkene in the molecule. The γ-lactone **20** was oxidized via Dess–Martin oxidation, followed by the conjugate addition of thioacetic acid to generate spironolactone (**12**). Lactonization enabled the 4–5 step synthesis of spironolactone (**17**) from dehydroepiandrosterone (**18**), and it was shown that this method could be applied to the synthesis of various drugs and natural products containing γ-lactones.

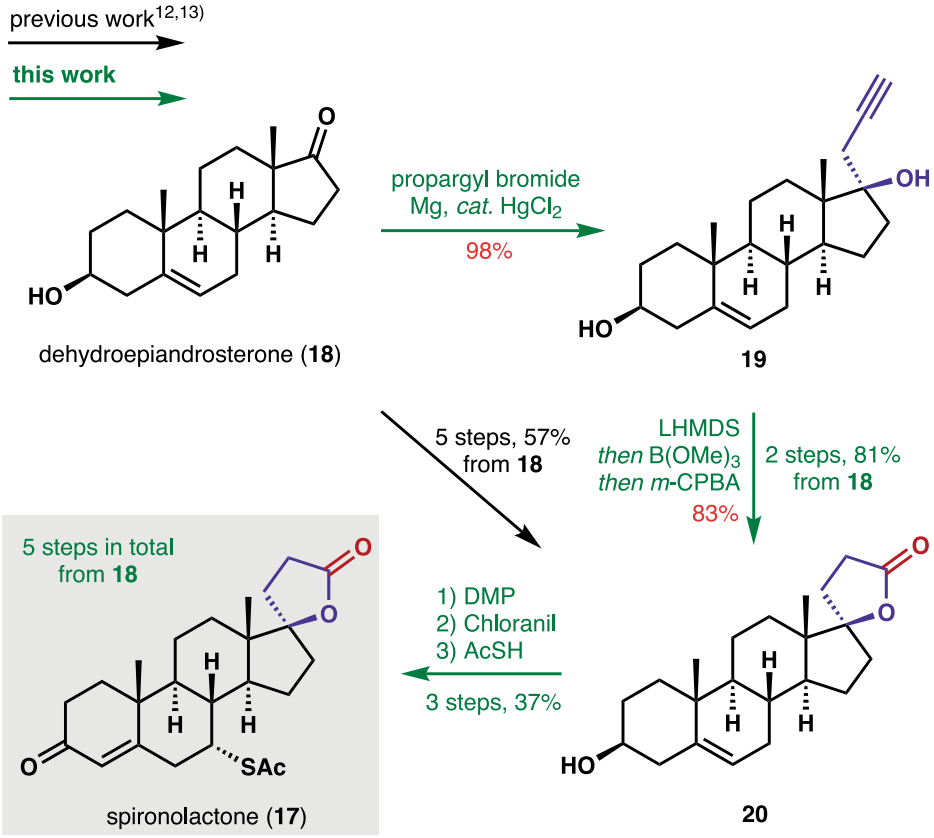


Figure 6. A short synthesis of spironolactone.

Herein, we described a novel lactonization reaction of homopropargylic alcohols. This reaction is a new and versatile oxidation of alkynes that can be performed using only commercially available inexpensive reagents (LHMDS, $B(OMe)_3$, *m*-CPBA), and exhibits high substrate generality and functional group tolerance. Recently, Zhao *et al*. reported intermolecular esterification and amidation of homopropargylic alcohols using a similar method.[14] They produced intermolecular reactions with various nucleophiles by isolating the corresponding alkynyl boronates. However, our new method is beneficial because it is a facile one-pot reaction in which readily available and inexpensive reagents are added sequentially to the reaction system and no isolation of intermediates is required. We are currently investigating the application of this method to lactamization reactions, and hope to present the results in a future paper.

Acknowledgement

I thank Prof. Tohru Nagamitsu (Kitasato University) and Prof. Ryan A. Shenvi (Scripps Research) for their helpful discussions. I also thank Dr. Kenichiro Nagai, Ms. Reiko Seki, and Ms. Noriko Sato (Kitasato University) for their kind NMR and mass spectra measurements. I am grateful to Mr. Daichi Yamane, Ms. Haruna Tanaka, Mr. Akihiro Hirata, Ms. Yumiko Tamura, Mr. Daichi Takakashi, and Mr. Yusuke Takahashi for their assistance.

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Author Information

Masaki Ohtawa

2005, 3	**B.S. Pharm.** School of Pharmacy, Kitasato University
2007, 3	**M.S. Pharm.** Graduate School of Pharmaceutical Sciences, Hokkaido University (Prof. Akira Matsuda)
2007, 4 – 2014, 12	**Assistant Professor** in School of Pharmacy, Kitasato University (Prof. Yoshihiro Harigaya and Prof. Tohru Nagamitsu)
2014, 2	**Ph.D.** Graduate School of Pharmaceutical Sciences, Kitasato University
2015, 1 –	**Lecturer** in School of Pharmacy, Kitasato University (Prof. Tohru Nagamitsu)
2016, 4 – 2018, 3	**Professional Scientific Collaborator** in Scripps Research (USA) (Prof. Ryan A. Shenvi)
2020, 4 –	**Associate Professor** in School of Pharmacy, Kitasato University (Prof. Tohru Nagamitsu)

Related Products

Trimethyl Borate	25mL	100mL	500mL	B0522
Lithium Bis(trimethylsilyl)amide (*ca*. 26% in Tetrahydrofuran, *ca*. 1.3mol/L) (= LHMDS)		100mL	500mL	H0915

Chemistry Chat

My Familiar Compound Family

–1,3-Dicarbonyl Compounds –

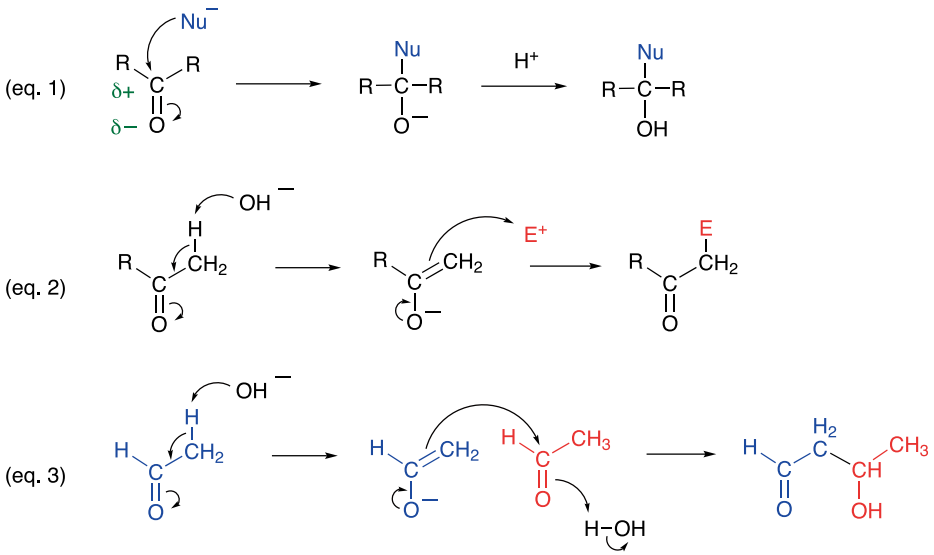
Nagatoshi Nishiwaki

School of Environmental Science and Engineering, Kochi University of Technology

During the course of your research, you are bound to come across one or two compound families that interest you or that you deal with frequently. During my many years in synthetic organic chemistry, I have become quite familiar with a particular compound family. I would like to introduce this family and my new encounters with it in this three-part series. I hope some readers will find useful information contained herein.

Dual Nature

Carbonyl compounds are ubiquitous in research, and their appeal is largely due to their dual nature. The polarized carbon-oxygen double bond makes them excellent electrophiles (**Scheme 1**, eq. 1), while the tautomeric enols and their deprotonated forms, enolates, serve as nucleophiles (eq. 2). Both roles are utilized in the aldol reaction (eq. 3). This duality is what makes this group of compounds so attractive.



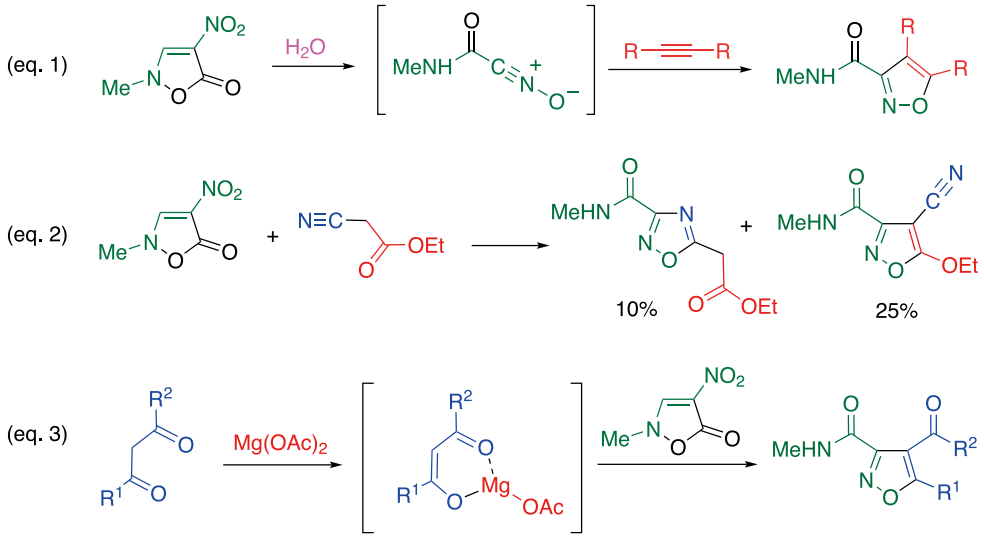
Scheme 1. Reactions of carbonyl compounds with nucleophiles and electrophiles

In the case of 1,3-dicarbonyl compounds (active methylene compounds), the collaboration of the two carbonyl groups results in a variety of new reactivities, such as the formation of highly acidic methylene groups and relatively stable enols. When I was a student, the phrase “active methylene compounds in times of trouble” was often used in the laboratory. This was because when we got stuck while developing reactions, 1,3-dicarbonyl compounds could be used as substrates to get some kind of reaction going, and in some cases, they could bring out new reactivity. On two occasions, 1,3-dicarbonyl compounds have played a leading role in my research.

Dipolarophile

We found that a nitrile oxide with a carbamoyl group is generated simply by treating nitroisoxazolone with water (**Scheme 2**, eq. 1).[1] The cycloaddition reaction proceeds in the presence of alkynes and nitriles to readily construct functionalized isoxazole and oxadiazole frameworks. In this process, we found that when ethyl cyanoacetate was used as a substrate, not only the cycloadduct of the cyano group but also an isoxazole having a cyano group was produced (eq. 2).[2] In an attempt to make this reaction more versatile and practical, I employed various active methylene compounds as dipolarophiles, but no progress was observed. Then, I had the idea that if a chelate complex is formed with a metal ion, it would fix the 1,3-dicarbonyl compound in the enol form. When copper acetate was added, the reaction proceeded as expected, and I was delighted. After trying various metal salts, the best results were obtained when magnesium acetate was used (eq. 3).[3]

Lesson learned: "Even though it is a side reaction, it can grow into a great discovery if you're chasing it."



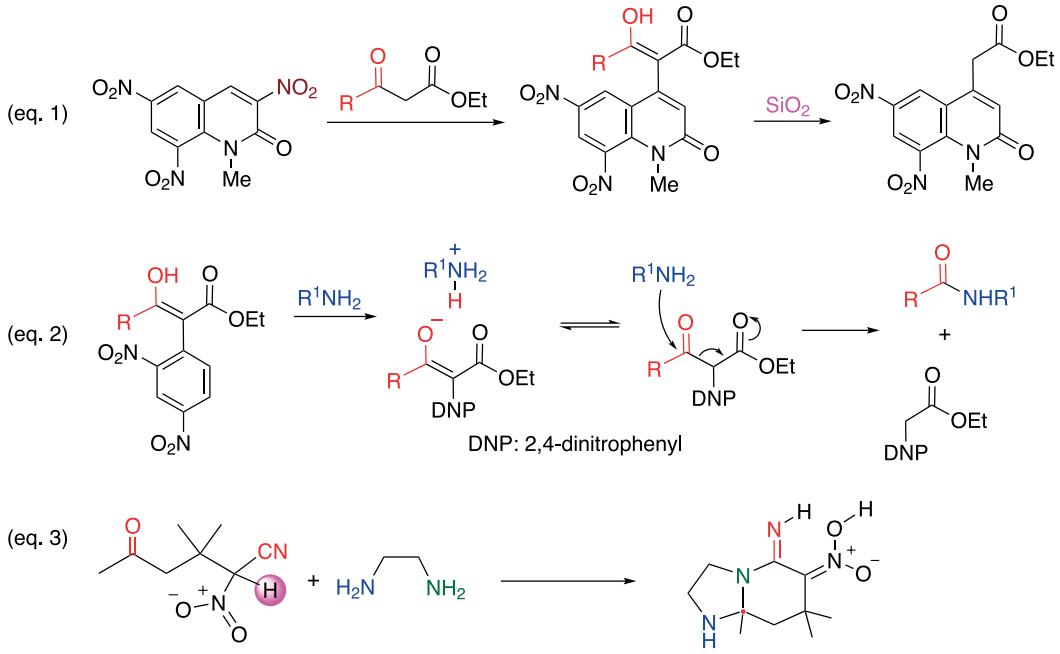
Scheme 2. Generation of a nitrile oxide from nitroisoxazolone and its cycloaddition

Transacylation

Numerous papers on active methylene compounds have been reported and summarized in review articles, giving the impression that the subject has been exhausted. I myself thought that I would never discover new reactivity of active methylene compounds.

To my surprise, then, when a 1,3-dicarbonyl compound was applied to a trinitroquinolone, I found a *cine*-substitution reaction in which substitution proceeded at the 4-position, accompanied by the elimination of the nitro group at the 3-position. When the products were purified by column treatment, deacylation proceeded in the case of a keto ester-substituted product (**Scheme 3**, eq. 1).[4] I considered that the activated acyl group could be utilized in organic synthesis. Indeed, when an α-phenylated keto ester was reacted with an amine, the acyl group was transferred to the amine without any detectable by-products (eq. 2).[5] At the time, when I presented my work at a conference, I could not successfully refute the claim that it was simply a retro-Claisen reaction. However, subsequent studies showed that the bulkiness of the benzene ring is important. The keto form is destabilizing, so it exists in the enol form. As a result, the acidity increases considerably and the reaction proceeds efficiently because the amine is in close proximity to the enol. Subsequently, I named the reaction a "pseudo-intramolecular reaction" and have employed it in the synthesis of diverse skeletons (eq. 3),[6] which continues to this day.

Lesson learned: "Even when you think you have taken all you can get, there are blessings left."



Scheme 3. Transacylation and construction of bicyclic framework using "pseudo-intramolecular reaction"

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Author Information

Professor Nagatoshi Nishiwaki received a Ph.D. in 1991 from Osaka University. He worked in Professor Ariga's group in the Department of Chemistry, Osaka Kyoiku University, as an assistant professor (1991-2000) and associate professor (2001-2008). From 2000 to 2001, he was with Karl Anker Jørgensen's group at Århus (Aarhus) University in Denmark. He worked at the Center for Collaborative Research, Anan National College of Technology as an associate professor from 2008 to 2009. Then, he moved to the School of Environmental Science and Engineering, Kochi University of Technology in 2009, where he has been a professor since 2011. His research interests comprise synthetic organic chemistry using nitro compounds, heterocycles (synthesis, ring transformation, 1,3-dipolar cycloaddition, application as tools in organic synthesis), pseudo-intramolecular reactions.

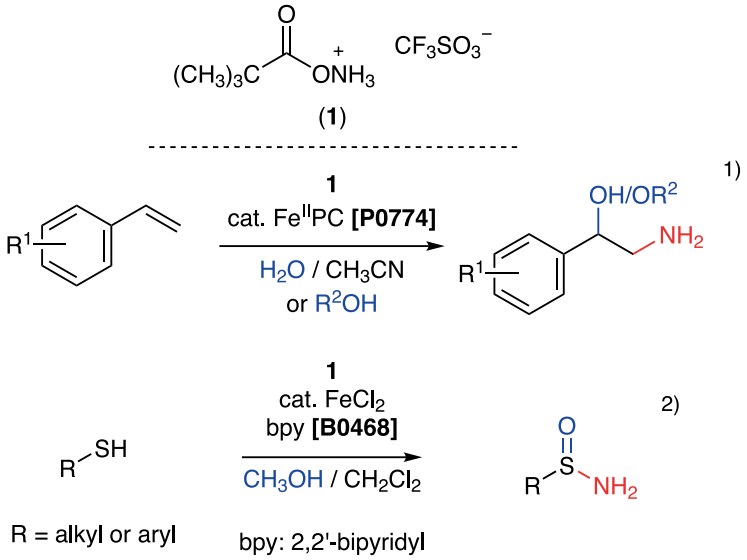
New Products Information

Hydroxyamine Derivative for the Amination of Alkenes and Thiols

O-Pivaloylhydroxyammonium Triflate (1)

Product Number: **P2856**
1g

O-Pivaloylhydroxyammonium triflate (**1**) is reported as an aminating reagent with a unique reactivity. For instance, **1** can regioselectively introduce amino and hydroxy/alkoxy groups to styrene derivatives in high yields by using the iron complex as a catalyst in water or alcohol solvent.[1] In addition, unprotected sulfinamides are obtained in the single-step reaction of thiols and **1** in alcohol solvent.[2]



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Related Products

Iron(II) Phthalocyanine (= Fe^{II}PC)		5g	25g	P0774
2,2'-Bipyridyl (= bpy)	25g	100g	500g	B0468

Guaranteed Analytical Reagents for Oligonucleotides

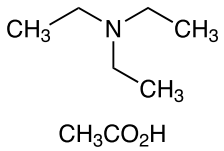
Triethylammonium Acetate (2.0mol/L in Water) (1) — Product Number: **T4022** **100mL**

Triethylamine [for HPLC] (2) — Product Number: **T4021** **50g**

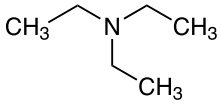
1,1,1,3,3,3-Hexafluoro-2-propanol [for HPLC] (3) — Product Number: **H1793** **100g**

Triethylammonium acetate aqueous solution and triethylamine/1,1,1,3,3,3-hexafluoro-2-propanol (= HFIP) aqueous solution are broadly utilized as the moving phase for the purification/analysis of oligonucleotides.[1] Especially, triethylamine-HFIP buffer improves ESI-MS sensitivity in the detection of oligonucleotide LC-MS analysis.[2]

TCI lines up triethylammonium acetate aqueous solution (**1**), triethylamine (**2**), and HFIP (**3**), which are guaranteed the UV absorptions in the analytical range of oligonucleotides like in the below **Table**. Suitable buffer solutions can be easily prepared by diluting **1** or mixing/diluting the required amounts of **2** and **3**.



(**1**)



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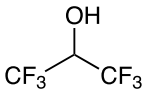

(**3**)

	Specifications		
Absorbance (nm)	**1**	**2**	**3**
210			max. 0.800
220			max. 0.400
230	max. 0.300		max. 0.200
254	max. 0.020	max. 0.200	max. 0.080
270	max. 0.030	max. 0.010	
400	max. 0.030	max. 0.010	max. 0.030

Table. Specifications of absorbance at each wavelength of **1**, **2**, and **3**.

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2) A. Apffel, J. A. Chakel, S. Fischer, K. Lichtenwalter, W. S. Hancock, *Anal. Chem.* **1997**, *69*, 1320.

Imidazolium Salts as Coupling Activators for Oligonucleotide Synthesis

1-Methyl-1*H*-benzimidazol-3-ium Triflate (1) — Product Number: **M3384** — **5g 25g**

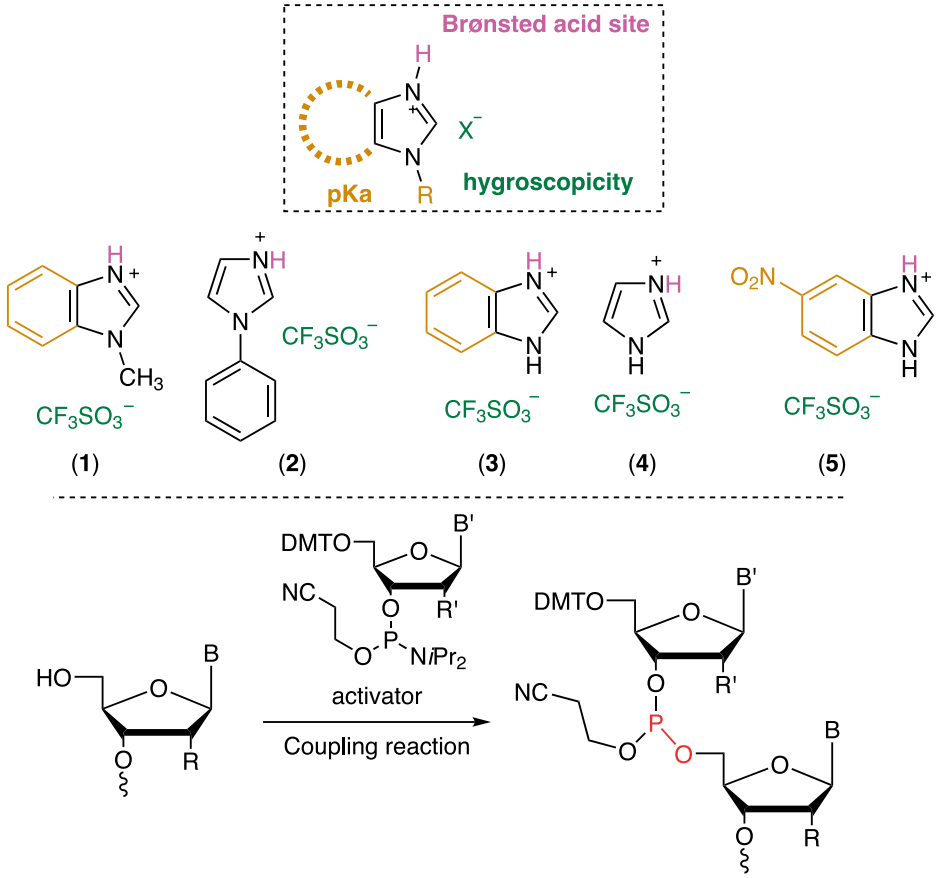
1-Phenyl-1*H*-imidazol-3-ium Triflate (2) — Product Number: **P2822** — **5g 25g**

1*H*-Benzimidazol-3-ium Triflate (3) — Product Number: **B6330** — **1g 10g**

1*H*-Imidazol-3-ium Triflate (4) — Product Number: **I1157** — **1g 10g**

5-Nitro-1*H*-benzimidazol-3-ium Triflate (5) — Product Number: **N1214** — **1g 10g**

In oligonucleotide synthesis, condensation activators are used for coupling reactions of phosphoramidite reagents. TCI offers imidazolium salt type activators (**1**-**5**) as well as tetrazole type activators. Imidazolium salt activators are less acidic than tetrazole type activators, but they are known to show higher coupling efficiency.[1,2] Therefore, the most suitable activator can be selected according to the substrates and targets.



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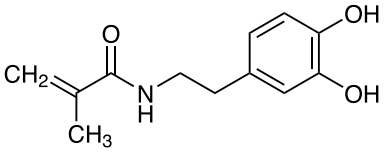
A Monomer Used for Developing Mussel-Inspired Dry/Wet Adhesives

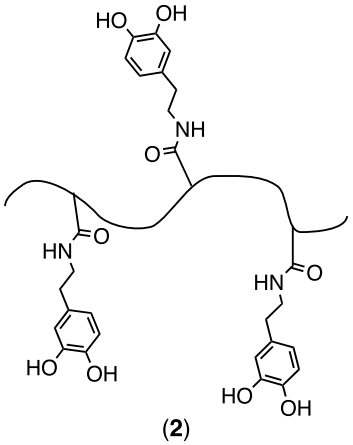
N-(3,4-Dihydroxyphenethyl)methacrylamide (1)

Product Number: **D5907**
1g 5g

Development of catechol-functionalized materials, which are inspired by the mussel's adhesion mechanism using 3,4-dihydroxyphenyl-L-alanine (DOPA) containing proteins, has being a trend in recent years.[1,2] In particular, it is attracting attention to its ability to adhere to wet surfaces as well as dry surfaces, and its ability to modify various surfaces such as polymers, nanocarbons, metals, and metal oxides. *N*-(3,4-Dihydroxyphenethyl)methacrylamide (**1**) is a methacrylamide monomer useful for developing polymer adhesives and surface coating polymers bearing a catechol group (**2**). For example, **1** is applied for developing wound dressing materials[3] and dry/wet adhesives.[4]



(**1**)



(**2**)

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2) Q. Guo, J. Chen, J. Wang, H. Zeng, J. Yu, *Nanoscale* **2020**, *12*, 1307.
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Glycoprotein Capturing Reagents: Lectin-Immobilized Agarose "LecBeads"

rPSL1a-LecBeads [for Siaα(2-6)Gal] (1) Product Number: **R0235** **1vial**

rLSL-N-LecBeads [for Galβ(1-4)GlcNAc, poly LacNAc] (2) Product Number: **R0236** **1vial**

rMOA-LecBeads [for Galα(1-3)Gal] (3) Product Number: **R0237** **1vial**

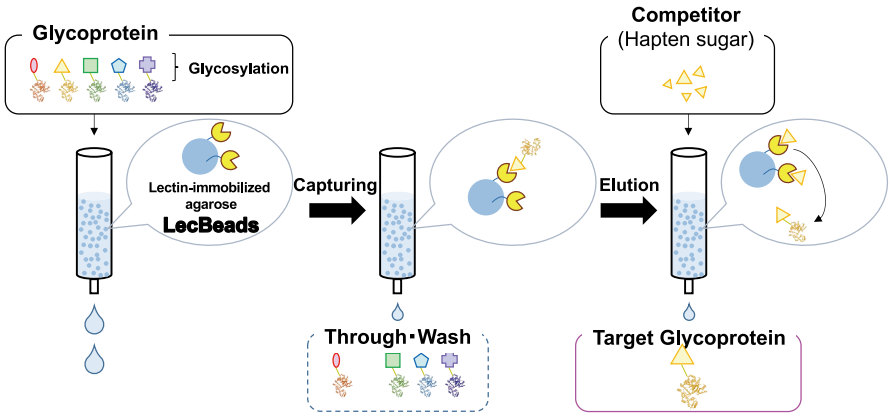
rSRL-LecBeads [for GlcNAcβ(1-2)Man, Galβ(1-3)GalNAc] (4) Product Number: **R0238** **1vial**

rGRFT-LecBeads [for Manα(1-2)Man] (5) Product Number: **R0239** **1vial**

AOL-LecBeads [for Fucα(1-6)/α(1-4)/α(1-3)/α(1-2)] (6) Product Number: **A3331** **1vial**

LecBeads (**1-6**) are lectin-immobilized agarose products developed in a joint effort by National Institute of Advanced Industrial Science and Technology (AIST) and TCI, and they are unique tools for capturing glycoproteins known as the glyco-catch method.[1-3] The LecBeads reagents composed of glycan-binding recombinant lectins immobilized on agarose carrier at high concentration are capable of affinity fractionation of glycoprotein depending on terminal epitopes of glycan structures in addition to convenient elution using inexpensive hapten sugars.

Capturing of glycoprotein by the Glyco-catch method



A wide variety of LecBeads are lined up according to the individual terminal glycan epitopes of glycoconjugates. Please use them for enrichment of glycoproteins/glycopeptides, glycoproteomic analysis, and so on.

Lineup of "LecBeads"

LecBeads	rPSL1a-LecBeads	rLSL-N-LecBeads	rMOA-LecBeads	rSRL-LecBeads	rGRFT-LecBeads	AOL-LecBeads
Glycan-binding specificity (Target epitope)	Siaα(2-6)Gal	Galβ(1-4)GlcNAc, poly LacNAc	Galα(1-3)Gal	GlcNAcβ-(1-2)Man, alβ(1-3)GalNAc	Manα(1-2)Man	Fucα(1-6)/α(1-4)/α(1-3)/α(1-2)]
Carrier	Agarose					
Elution buffer (Hapten sugar)	200 mM lactose	200 mM lactose	400 mM melibiose	200 mM D-GlcNAc	200 mM methyl α-man	200 mM L-fucose
Binding capacity (per 1 ml reagent)	>10 mg of human Transferrin	>12 mg of asialo human Transferrin	>10 mg of Cetuximab	>7.5 mg of agalacto human Transferrin	>6 mg of bovine RNase B	>5 mg of human Lactoferrin

References

1) J. Hirabayashi, Y. Arata, K. Kasai, *Proteomics* **2001**, *1*, 295.
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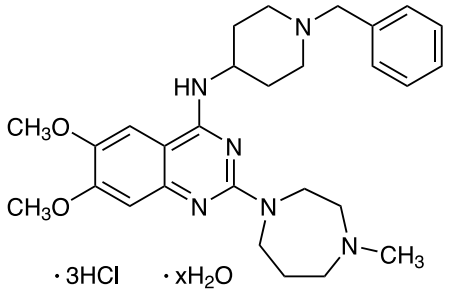
Histone Methyl Transferase (HMTase) Inhibitor

BIX 01294 Trihydrochloride Hydrate (1)

Product Number: **B4211**
25mg



(**1**)

Histone lysine methylation plays important roles in the organization of chromatin domains and the regulation of gene expression. Among histone lysine methyltransferases (HKMTs) in mammals, G9a and G9a like protein (GLP) are the primary enzymes for mono- and dimethylation at Lys 9 of histone H3 (H3K9me1 and H3K9me2, respectively) and exist for the most part as a G9a–GLP heteromeric complex.[1)]

BIX 01294 (**1**) inhibits H3K9 methylation by GLP, G9a HKMTs,[2,3)] and H3K36 methylation by oncoproteins[4)] (**Table**). The inhibition is caused by binding of **1** to the substrate peptide groove of GLP.[3)] **1** can improve the reprogramming efficiency of mouse embryonic fibroblasts or fetal neural progenitor cells to induced pluripotent stem cells without using c-Myc and SOX2.[5,6)]

Table. Inhibition of methylation by **1**

Enzymes	IC_{50} (μM)
H3K9 methylation[3)]	
G9a like protein (GLP)	0.7
G9a	1.9
H3K36 methylation[4)]	
NSD1	112±57
NSD2	41±2
NSD3	95±53

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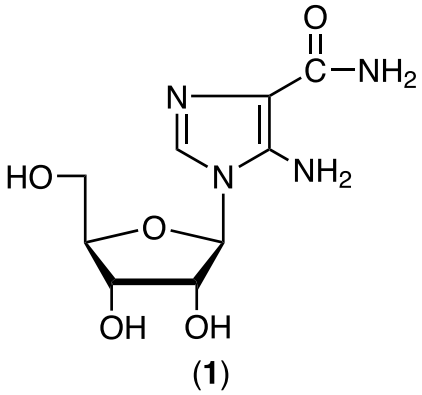
AMP-Activated Protein Kinase (AMPK) Activator

AICAR (1)

Product Number: **A2528**
50mg



(**1**)

5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR, **1**) selectively activates AMP-activated protein kinase (AMPK).[1] Adamo *et al*. reported that **1** induces the expression of Klf2 and Klf4 and activates the pluripotency transcriptional network in mouse embryonic stem cells (mESCs).[2] In mouse embryonic fibroblasts (MEFs), **1** induces Klf4, Klf2, and Myc upregulation. As shown in **Table**, **1** antagonizes retinoic acid induced differentiation in mESCs.

Table. Effects of AICAR on the pluripotency transcriptional network in the presence of high doses of retinoic acid.[2]

Transcription factors	Effects
Nanog	Complete rescue
Oct4	Partial rescue
Klf4	Complete rescue
Klf2	Partial rescue
Sox2	Not rescue

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1) J. M. Corton, J. G. Gillespie, S. A. Hawley, D. G. Hardie, *Eur. J. Biochem*. **1995**, *229*, 558.
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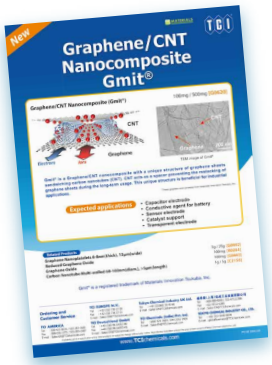

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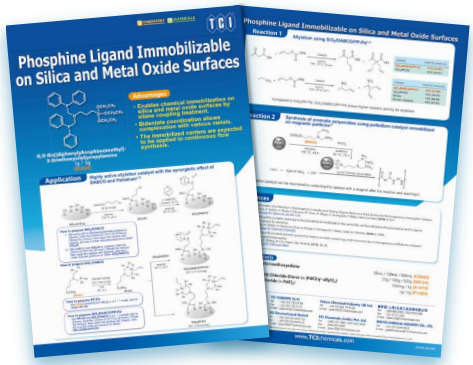

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