Pot-economical total synthesis of prostaglandins via organocatalyst-mediated asymmetric reactions

Yujiro Hayashi[1]

[1]Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578

E-mail: yujiro.hayashi.b7@tohoku.ac.jp

Yujiro Hayashi

Yujiro Hayashi received PH.D. Degree from The University of Tokyo in 1994. He was appointed as an assistant professor at The University of Tokyo (1987). He moved to Tokyo University of Science as an associate professor (1998), was promoted to full professor (2006), and moved to Tohoku University (2012). Awards: an Incentive Award in Synthetic Organic Chemistry, Japan (1998), SSOCJ Daiichi-Sankyo Award for Medicinal Organic Chemistry (2008), the Chemical Society of Japan Award for Creative Work for 2010, a Novartis Chemistry Lectureship Award (2011/2012), Inoue Prize for Science (2012), The 21th (2021) Green and Sustainable Chemistry Award, Award by the Ministry of Education, Culture, Sports, Science and Technology, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology (2022), and The Ichimura Prize in Science for Excellent Achievement (2023).

Abstract

Prostaglandins are a family of molecules that possess important biological properties, and some of the analogues are used as medicines. Many synthetic methods have been developed for the efficient synthesis of prostaglandins. In this review, we will describe recent advances in the synthesis of prostaglandins and our endeavors in the effective synthesis of prostaglandins. Our group has developed three [3+2] cycloaddition reactions catalyzed by diphenylprolinol silyl ether, affording chiral substituted cyclopentane frameworks with excellent diastereo- and enantioselectivities. By using these cyclopentanes as key intermediates and applying the pot reactions, several prostaglandins were synthesized efficiently in a small number of pots.

Keywords: prostaglandin, organocatalyst, pot economy

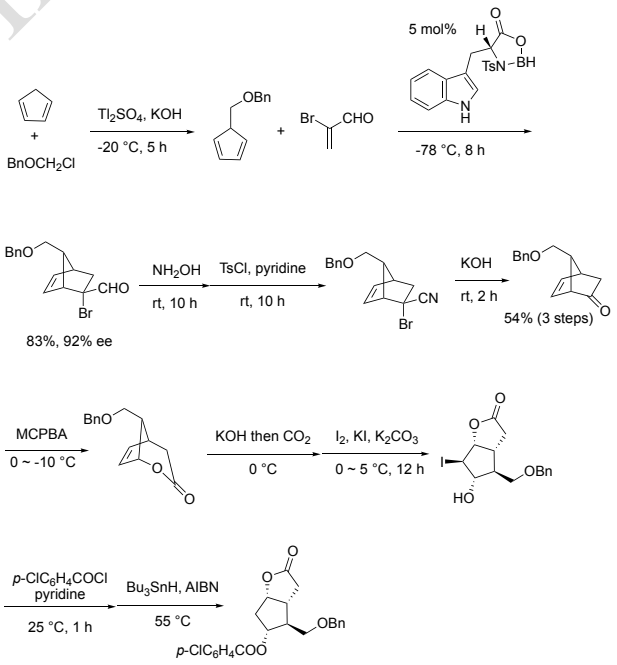
1. Introduction

Prostaglandin was first isolated as a biologically active substance by von Euler from human semen obtained from the prostate gland.[1] Prostaglandin is produced from various tissues as a precursor of arachidonic acid, which is released from phospholipids in the membrane of living tissue cells by the action of phospholipase. Prostaglandin has been attracting attention as a substance that performs a variety of biological activities associated with producing cells in a local hormonal manner. Prostaglandins play a range of important biological roles in the body, such as platelet aggregation inhibition, blood vessel expansion, smooth muscle relaxation and contraction, and cell protection, and these actions are known to be induced at very low prostaglandin doses.[2] With such powerful and useful physiological effects, several natural prostaglandins and analogues have been developed as useful drugs.[3]

2. Previous synthesis

Because prostaglandins are biologically important but difficult to obtain from natural sources, the scientific community has put a great deal of effort and ingenuity into their efficient synthesis.[4] Structurally, prostaglandins have a cyclopentanone skeleton with an α-chain, an ω-chain, and a β-hydroxyketone moiety that is prone to dehydration reactions, making it unstable to acids and bases. Stereoselective synthesis of substituted cyclopentane is one of the key challenges in the synthesis of prostaglandins.

Many masters of organic chemistry such as Woodward,[5] Corey,[6] Stork,[7] Noyori,[8] and Danishefsky[9] reported the synthesis of prostaglandins via their own methodologies. Corey's synthesis via the Corey lactone is a landmark in the synthesis of prostaglandins, which is highly sophisticated and practical. The Corey lactone is synthesized by stereoselective reactions such as Diels–Alder reaction and halo-lactonization reaction. Various prostaglandins have been synthesized from the Corey lactone (Scheme 1).

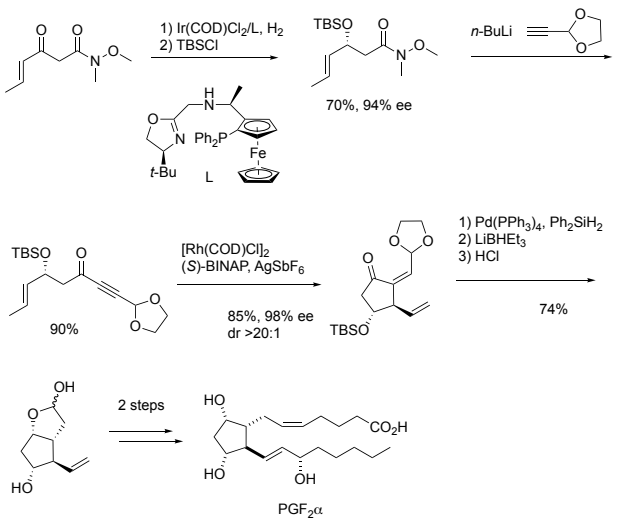


Scheme 1. Corey's synthesis of the Corey lactone

Given the importance of prostaglandin molecules, new methods for the synthesis of prostaglandins have been continuously developed. The syntheses of prostaglandins up to 2017 have been summarized in review articles;[4c] recent advancements in the synthesis of prostaglandins are briefly described below.

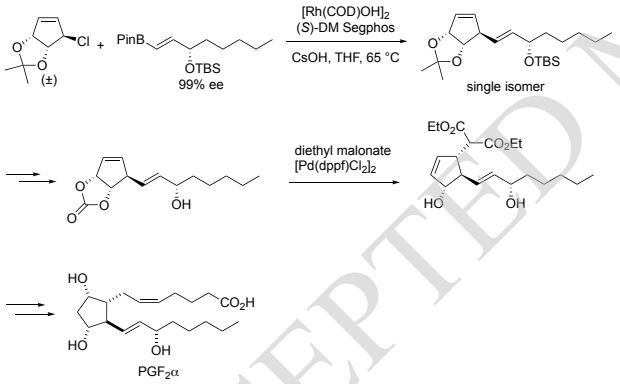
Recently Chen, Zhang, and coworkers used asymmetric reduction of a ketone to generate the required chiral alcohol, and

they developed diastereoselective enyne cycloisomerization for the formation of the chiral cyclopentanone skeleton, from which $PGF_{2\alpha}$ was synthesized (Scheme 2).[10]



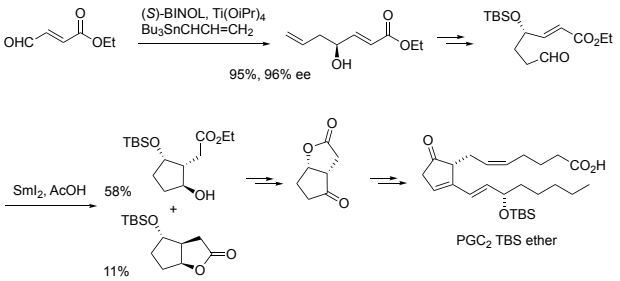
Scheme 2. The synthesis of $PGF_{2\alpha}$ by Chen and Zhang

Fletcher developed a Rh-catalyzed dynamic kinetic asymmetric Suzuki–Miyaura coupling reaction between a racemic bicyclic allyl chloride and alkenyl boronic esters bearing a chiral alcohol to afford a cyclopentene intermediate with three contiguous chiral centers. From this key intermediate, several prostaglandins such as $PGF_{2\alpha}$, bimatoprost and latanoprost were synthesized (Scheme 3).[11]



Scheme 3. Fletcher's synthesis of $PGF_{2\alpha}$

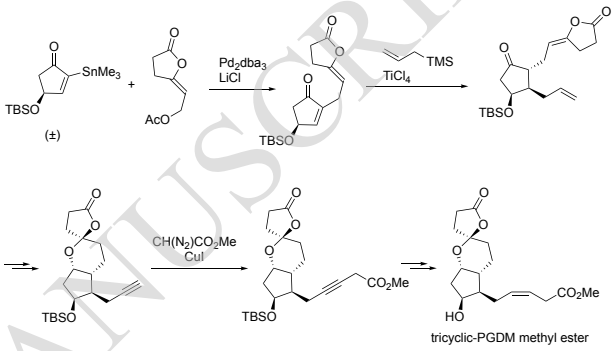
Tang and Chen employed Keck allylation to generate a chiral alcohol. Subsequent intramolecular SmI_2-mediated ketyl-enoate cyclization was a key step for the formation of the functionalized cyclopentane skeleton. From this intermediate, extremely sensitive prostaglandin C_2 TBS ether was prepared (Scheme 4).[12]



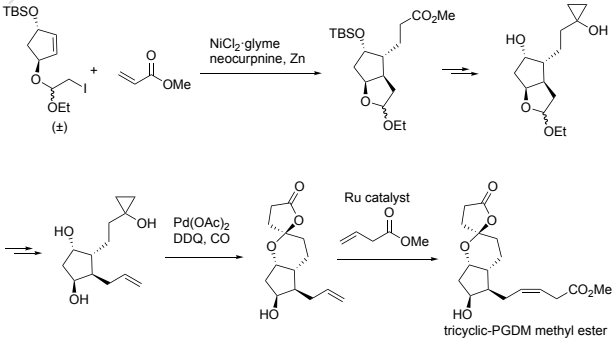
Scheme 4. The synthesis of PGC_2 TBS ether by Tang and Chen

Recently, tricyclic-PGDM, a major human urinary metabolite of prostaglandin D_2, was synthesized by two groups; both syntheses were racemic. Sulikowski employed a known substituted cyclopentenone as a starting material. $TiCl_4$-mediated 1,2-*cis*-selective allylation between the siloxy group and side chain is one of the key reactions. Another key reaction in this approach is Fu's copper-catalyzed C–H insertion of a diazoacetate followed by an alkyne semihydrogenation to introduce the unsaturated side chain (Scheme 5).[13]

Dai used a substituted cyclopentene as a starting material to synthesize the racemic tricyclic-PGDM. Key reactions are a nickel-catalyzed C–C bond formation to afford two continuous stereocenters, a palladium-mediated carbonylative spiro-lactonization for the formation of the core oxaspirolactone, and a *Z*-selective cross-metathesis to introduce the (*Z*)-3-butenoate side chain (Scheme 6).[14]



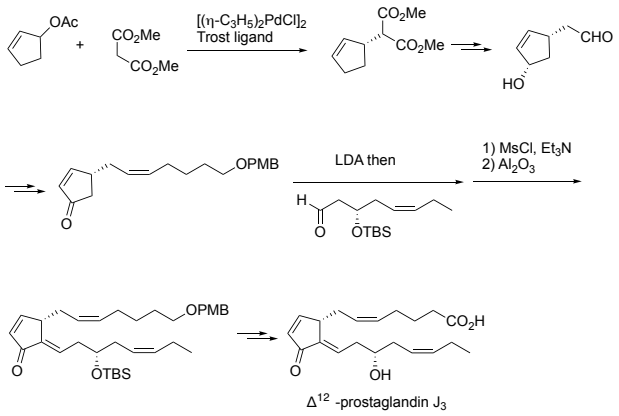
Scheme 5. Sulikowski's synthesis of tricyclic-PGDM



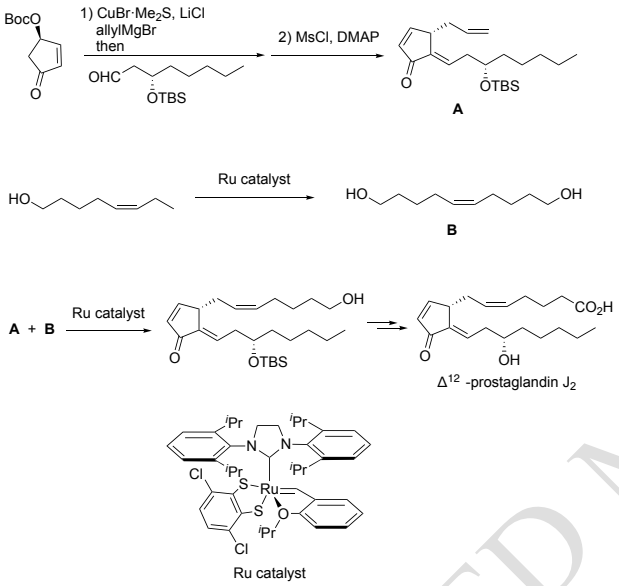
Scheme 6. Dai's synthesis of tricyclic-PGDM

Recently, the Δ^{12}-prostaglandin J family was discovered, the members of which have potent anticancer activity, and several groups have reported their synthesis. Nicolaou synthesized the chiral cyclopentanone moiety using a palladium-catalyzed Tsuji–Trost asymmetric coupling reaction as a key step. The side chain was introduced by an aldol condensation reaction (Scheme 7).[15]

The group of Stoltz and Grubbs synthesized Δ^{12}-prostaglandin J_2 starting from chiral cyclopentenone. One of the key reactions in this approach is the three-component coupling reaction of chiral cyclopentenone, allyl Grignard reagent, and aldehyde. The second key reaction is *Z*-selective homodimerization/cross-methathesis reaction (Scheme 8).[16]

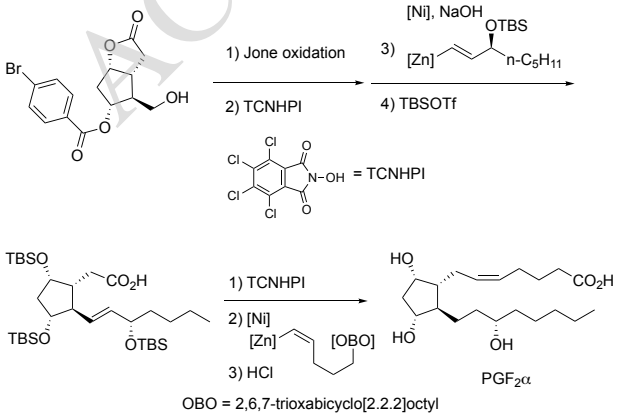


Scheme 7. Nicolaou's synthesis of Δ^{12}-prostaglandin J_3



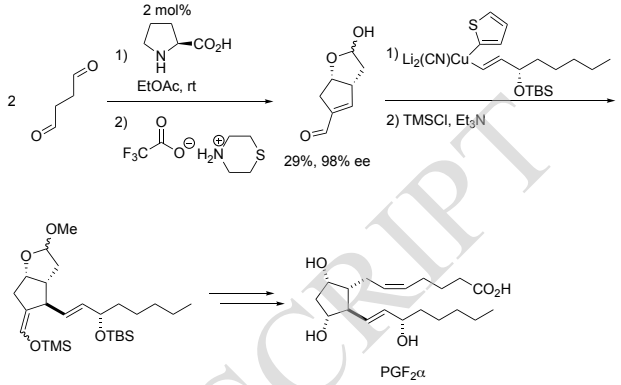
Scheme 8. The synthesis of Δ^{12}-prostaglandin J_2 by Stoltz and Grubbs

A prostaglandin synthesis from the Corey lactone has also been developed. Baran synthesized prostaglandin $F_{2\alpha}$ using a twofold decarboxylative radical coupling reaction with alkenyl zinc reagent. The approach provides a short and efficient synthetic method to access prostaglandin from the Corey lactone (Scheme 9).[17]



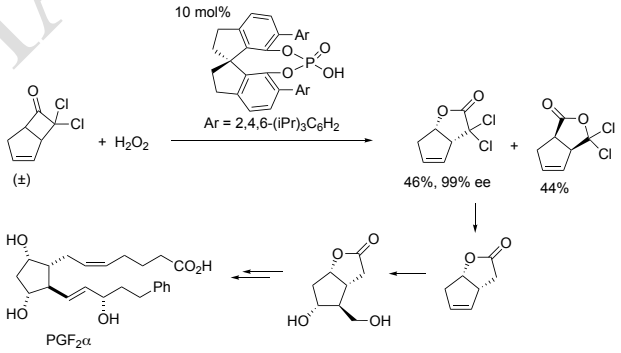
Scheme 9. Baran's synthesis of $PGF_{2\alpha}$ from the Corey lactone

Organocatalysis[18] has developed rapidly since 2000, and organocatalyst-mediated reactions have been successfully employed in the synthesis of prostaglandins. Aggarwal synthesized an almost optically pure bicyclic aldehyde by the aldol reaction of succinaldehyde using proline as an organocatalyst. This bicyclic aldehyde, the yield of which was recently improved,[19e] is a key intermediate from which several prostaglandins were efficiently synthesized (Scheme 10).[19]



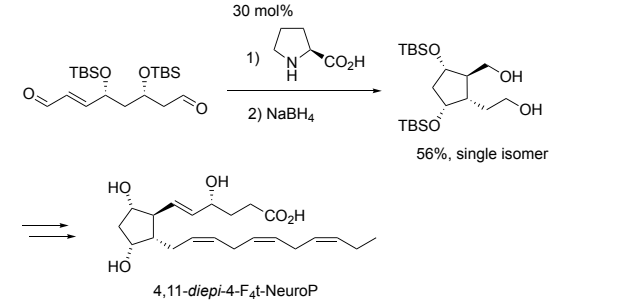
Scheme 10. Aggarwal's synthesis of $PGF_{2\alpha}$

Peng and Chen developed Bayer–Villiger oxidation of a racemic cyclobutanone derivative catalyzed by chiral phosphoric acid to afford a bicyclic lactone with excellent enantioselectivity, from which $PGF_{2\alpha}$ was synthesized (Scheme 11).[20]



Scheme 11. The synthesis of $PGF_{2\alpha}$ by Peng and Chen

Proline-mediated intramolecular diastereoselective Michael reaction of a chiral formyl-enal derivative was used in the synthesis of 4,11-*diepi*-4-F_{4t}-NeuroP by Oger and Galano (Scheme 12).[21]



Scheme 12. The synthesis of 4,11-*diepi*-4-F_{4t}-NeuroP by Oger and Galano

Although many excellent syntheses of prostaglandins have been developed over the decades, it is still necessary to develop more efficient and practical synthetic methods to access prostaglandins.

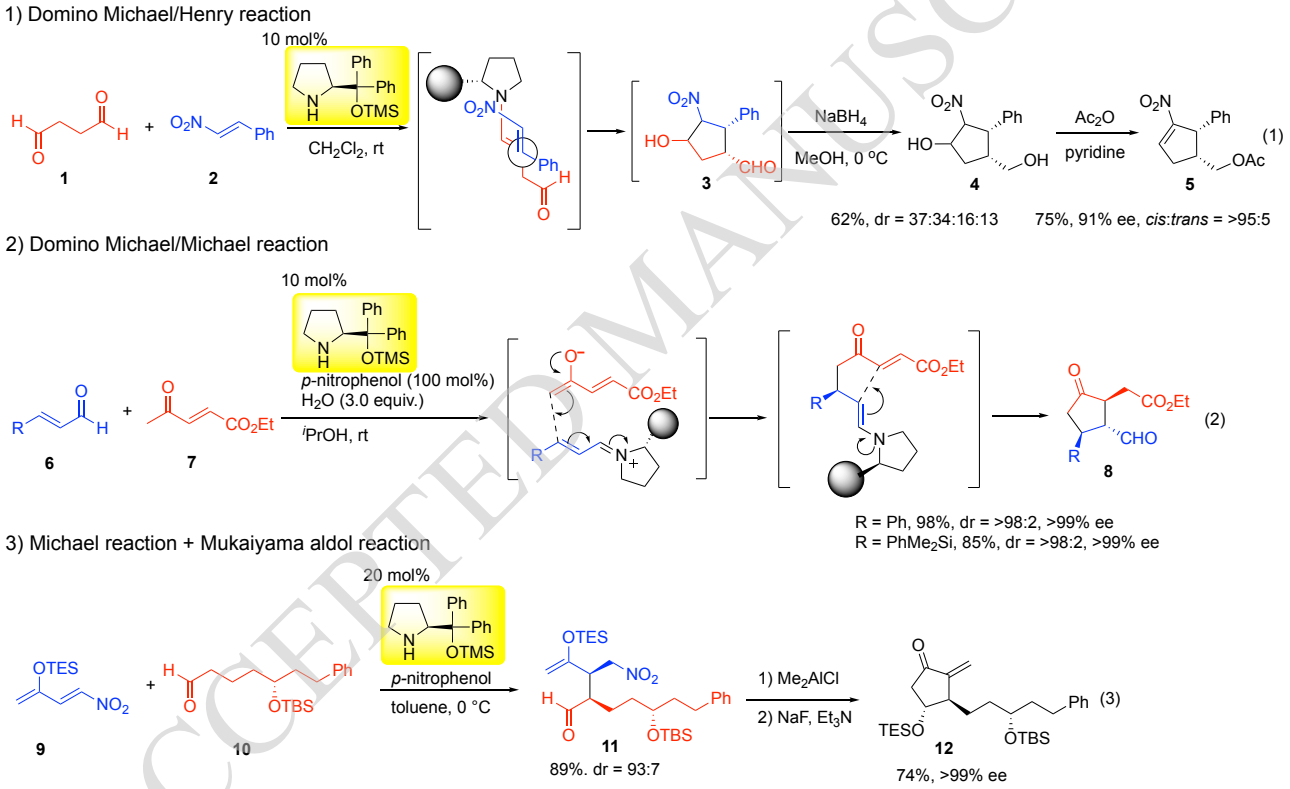
3. One-pot reaction

In the current organic synthesis paradigm, in addition to the selective synthesis of the desired molecules, environmentally friendly synthetic methodologies that produce as little waste as possible are required. A 'one-pot reaction' is a process in which multiple reactions are carried out sequentially in a single reaction vessel. The approach can provide effective methods for making several bonds and generating molecular complexity in a single-pot sequence. Moreover, one-pot operations circumvent several purification steps by using *in situ* quenching events, thereby minimizing chemical waste generation and saving time. Thus, it is considered a green method. Based on this, our group proposed the concept of 'pot economy',[22] and accomplished several total syntheses based on this concept.[23] We also synthesized several prostaglandins in a pot-economical manner, which will be described in this account.

4. [3+2] cycloaddition

For the synthesis of prostaglandins, it is necessary to develop a method to generate a chiral cyclopentane skeleton, which is a key skeletal component of prostaglandins, with suitable substituents at the required position. One of the methods for the formation of a chiral cyclopentane skeleton is an asymmetric [3+2] cycloaddition reaction. In this area, our group developed three organocatalyst-mediated asymmetric [3+2] cycloaddition reactions.

We reported the asymmetric Michael reaction of aldehyde and nitroalkene catalyzed by diphenylprolinol silyl ether.[24, 25] Using succinaldehyde (**1**) as the aldehyde component, domino Michael/Henry reaction proceeded to afford cyclopentane **3**, from which cyclopentene **5** was obtained by reduction and dehydration reaction (Scheme 13, Eq. 1).[26] In this reaction, catalyst reacts with aldehyde **1** to generate enamine. As diphenyltrimethylsilyloxymethyl moiety covers one enantioface of the enamine selectively, excellent enantioselectivity is realized. Compound **5** was obtained with excellent *cis*-selectivity and enantioselectivity.



Scheme 13. Three [3+2] cycloaddition reactions developed by our group

The second [3+2] cycloaddition reaction that we developed was a domino Michael/Michael reaction.[27] We previously reported the asymmetric Michael reaction of ketone and α,β-enal catalyzed by diphenylprolinol silyl ether.[28] Based on this precedent of the Michael reaction of a ketone as the Michael donor, we designed a reagent having methyl ketone and unsaturated ester moieties; namely, ethyl 4-oxo-2-pentenoate (**7**). Catalyst reacts with α,β-unsaturated aldehyde **7** to generate an iminium ion, in which bulky diphenyltrimethylsilyloxymethyl moiety covers one enantioface of the iminium ion selectively, and excellent enantioselectivity is realized in the first Michael reaction. The domino Michael/Michael reaction proceeds to afford the trisubstituted cyclopentanone **8** with excellent diastereo- and enantioselectivities (Eq. 2). The first reaction is a chiral-catalyst-mediated asymmetric Michael reaction, and the second reaction is a chiral-catalyst-mediated diastereoselective, intramolecular Michael reaction. In the second reaction, a kinetic resolution occurred, and nearly optically pure product was obtained.

The third [3+2] cycloaddition reaction is a two-pot process. We employ nitroalkene **9**, bearing a silyl enol ether moiety, in the Michael reaction with aldehyde **10** (Eq. 3). Because the product **11** possesses both silyl enol ether and formyl moieties in the molecule, intramolecular Mukaiyama aldol reaction and elimination of HNO_2 proceeds to afford the substituted cyclopentanone **12** with excellent enantioselectivity.[29]

Through the use of these three reactions as key steps, we

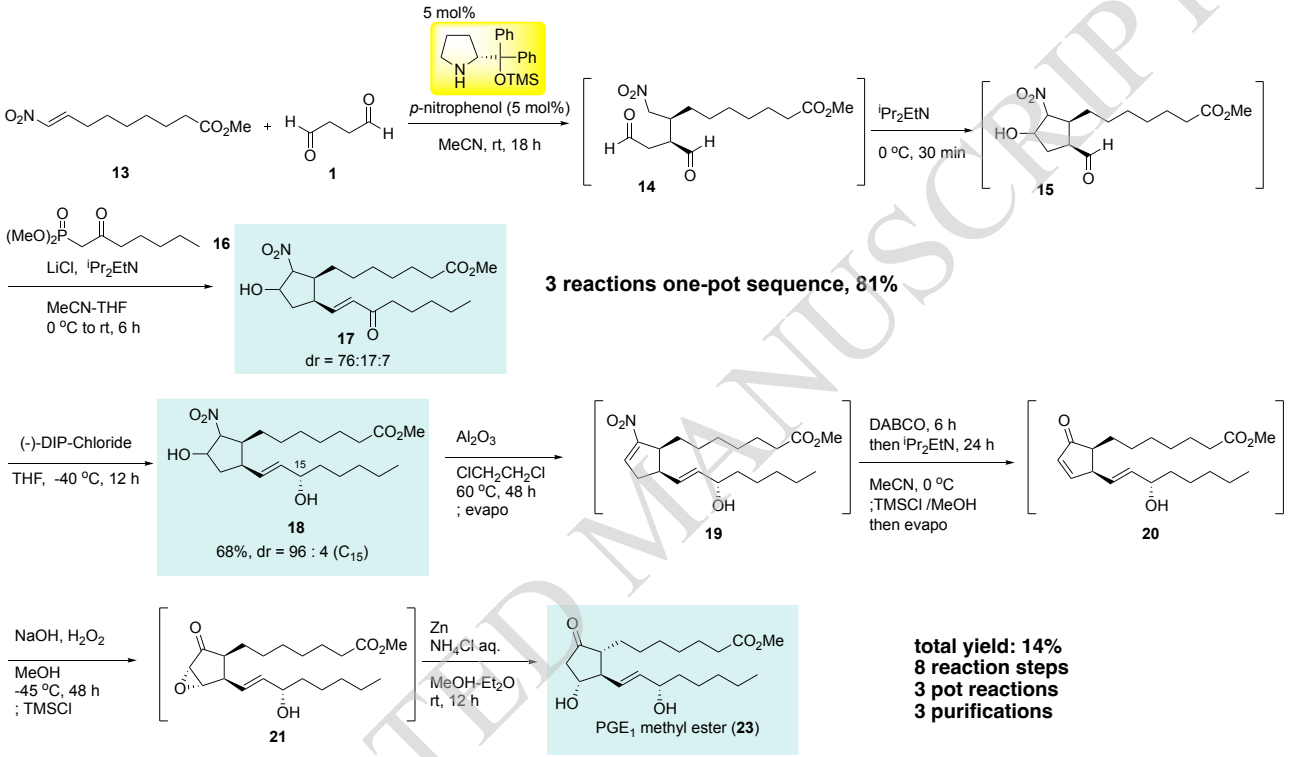
have synthesized several prostaglandins.

5. Synthesis of prostaglandins based on domino Michael/Henry reaction

5..1 Synthesis of prostaglandin E_1 methyl ester

Prostaglandin E_1 was isolated in 1957 and it is anti-inflammatory, antithrombotic, a vasodilator, and stimulates the formation of cyclic adenosine monophosphate, which inhibits phospholipase A_2. It is on the World Health Organization's list of essential medicines.[30]

The synthesis of PGE_1 methyl ester (**23**) was conducted using the asymmetric [3+2] cycloaddition reaction (Eq. 1). The asymmetric [3+2] cycloaddition reaction of succinaldehyde (**1**) and nitroalkene **13**, bearing an ester moiety, proceeded to afford cyclopentane carbaldehyde **15**, which was treated with Horner–Wadsworth–Emmons reagent **16** in the same vessel (Scheme 14). Highly substituted nitrocyclopentane **17**, which possesses all carbons of PGE_1 methyl ester, was obtained in one pot. Reagent-controlled reduction using (–)-diisopinocamphenyl chloroborane (DIP-Cl)[31] afforded allyl alcohol **18**. The transformation from **18** into PGE_1 methyl ester (**23**) needed five reactions, including dehydration, isomerization of the side-arm double bond, oxidative Nef reaction,[32] epoxidation, and reductive opening of the epoxide, all of which were conducted in a single reaction vessel. This approach provides a three-pot synthesis of PGE_1 methyl ester with a total yield of 14%.[33]



Scheme 14. Three-pot synthesis of prostaglandin E_1 methyl ester (**23**)

5.2 Synthesis of beraprost

Toray Industries Inc. developed beraprost (**26**) as a stable, orally active prostacyclin analogue of prostaglandin I_2 (**25**) with vasodilatory, antiplatelet, and cytoprotective effects. A mixture of four isomers (**26a**, **26b**, **26c**, and **26d**) is used as a drug, but **26a** is known to be the most biologically active isomer (Figure 1).[34] Beraprost possesses a tricyclic core and an ω-side chain. We synthesized both key structural units of **26** enantioselectively using organocatalyst-mediated reactions.

Organocatalyst-mediated [3+2] cycloaddition reaction of succinaldehyde (**1**) and nitroalkene **27**, followed by acetalization and dehydration, afforded **29** in one pot (Scheme 15). Oxidative Nef reaction using molecular oxygen, as developed by our group,[32] afforded cyclopentenone **30**, the enantioselectivity of which was found to be excellent (93% ee). Epoxidation, reductive opening of the epoxide, and reduction of the ketone proceeded to afford diol **31**. Intramolecular aromatic substitution reaction (S_NAr), followed by the Suzuki–Miyaura coupling reaction with **33**, provided the tricyclic core **34**.

Chiral phosphonate **41** was prepared through diphenylprolinol silyl ether mediated Michael reaction of nitromethane and crotonaldehyde (**35**), which was developed by our group.[35] The Michael product **36**, with excellent optical purity (90% ee), was converted into phosphonate **41** by Ohira–Bestmann reaction[36] methylation, and Nef reaction, and finally a Claisen-type reaction with diethyl methylphosphonate (**40**).

After conversion of acetal **34** into the aldehyde, it was coupled with **41** to afford enone **42** by Horner–Wadsworth–Emmons reaction. Stereoselective reduction using (–)-DIP-Cl,[31] followed by hydrolysis, afforded beraprost (**26a**).[37] This approach provides a short and efficient synthesis of beraprost.

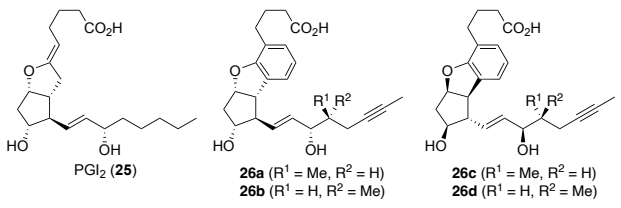
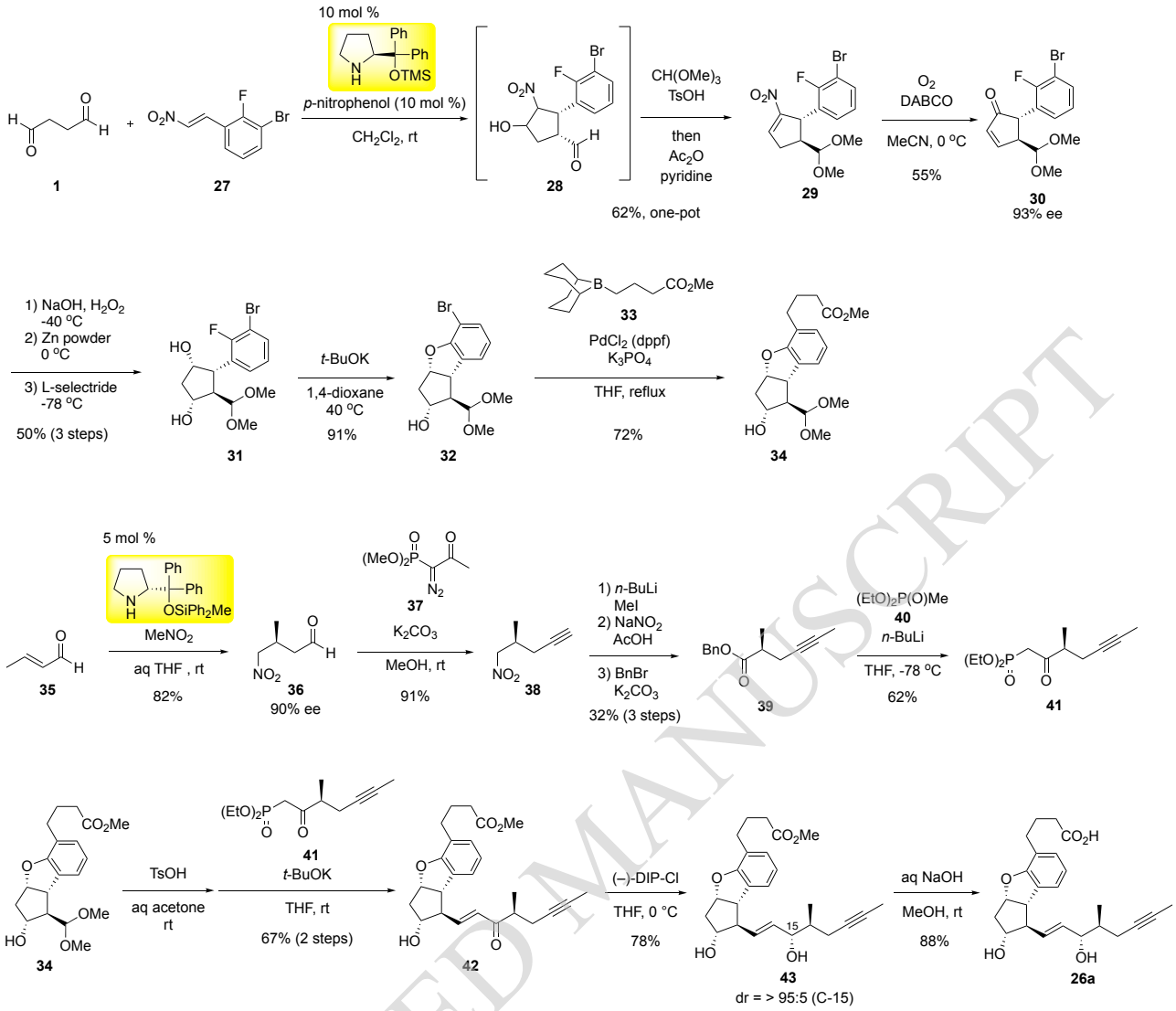


Figure 1. Prostaglandin I_2 and isomers of beraprost



Scheme 15. Total synthesis of beraprost (**26a**)

5.3 Synthesis of latanoprost (The first-generation synthesis)

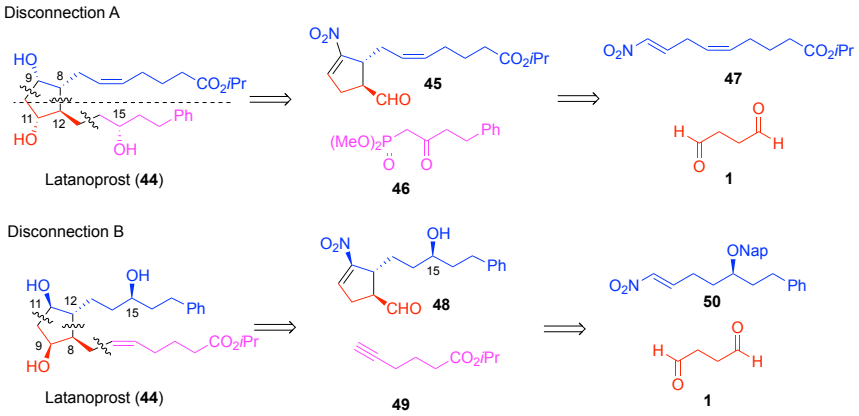
Latanoprost (**44**) is an antiglaucoma, "blockbuster" drug developed by Pfizer.[38] It is an analogue of the prostaglandin $F_{2\alpha}$ and is manufactured via the Corey lactone. As it is an important drug, several synthetic methods have been reported.[19b, 39]

Based on our [3+2] cycloaddition reaction (Eq. 1), two retrosynthetic routes were considered (Scheme 16). Route A is similar to that used for our synthesis of prostaglandin E_1 methyl ester. Latanoprost (**44**) could be synthesized from three parts: succinaldehyde (**1**), **46**, and **47**; however, as we anticipated that there would be a problem with facile isomerization of nitro-1,4-diene **47** into undesired 1,3-diene derivative, we did not take this route.

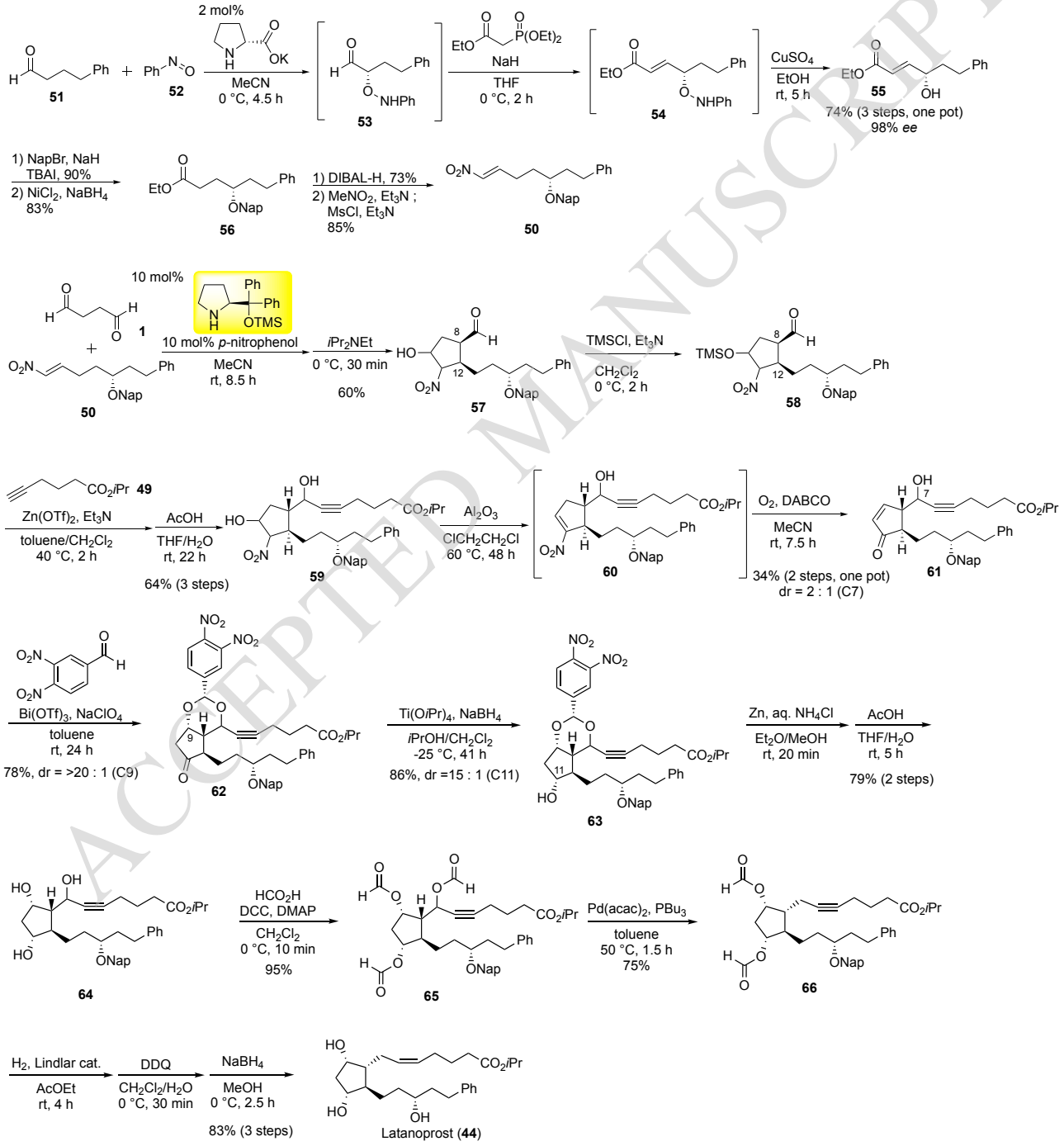
By rotating latanoprost (**44**) around the dotted line shown in Scheme 16, Route B, and focusing on symmetry, latanoprost (**44**) can be divided into an alternative set of three parts: succinaldehyde (**1**), nitroalkene **50**, and alkyne **49**. We synthesized latanoprost by this route.

Chiral nitroalkene **50** was prepared starting from potassium prolinate-mediated α-aminoxylation of aldehyde **51** with nitrosobenzene **52**, in which potassium prolinate was a more reactive catalyst than proline (Scheme 17).[40] The generated **53** was treated with Horner–Wadsworth–Emmons reagent in the same vessel to afford **55** with 98% ee. After protection of the hydroxy group, two reductions, Henry reaction and dehydration reaction, **50** was afforded in good overall yield.

Key [3+2] cycloaddition reaction of succinaldehyde (**1**) and nitroalkene **50** proceeded to afford **57**, in which a *trans* isomer (C8, C12, prostaglandin numbering) was obtained, as the first Michael reaction of aldehyde and nitroalkene proceeds with *syn*-selectivity. Protection of the hydroxy group afforded **58**.



Scheme 16. The retrosynthesis of latanoprost (**44**)



Scheme 17. The first-generation total synthesis of latanoprost (**44**)

When $Zn(OTf)_2$ and Et_3N[41] were added to the reaction mixture, complete isomerization of the α-position of the formyl

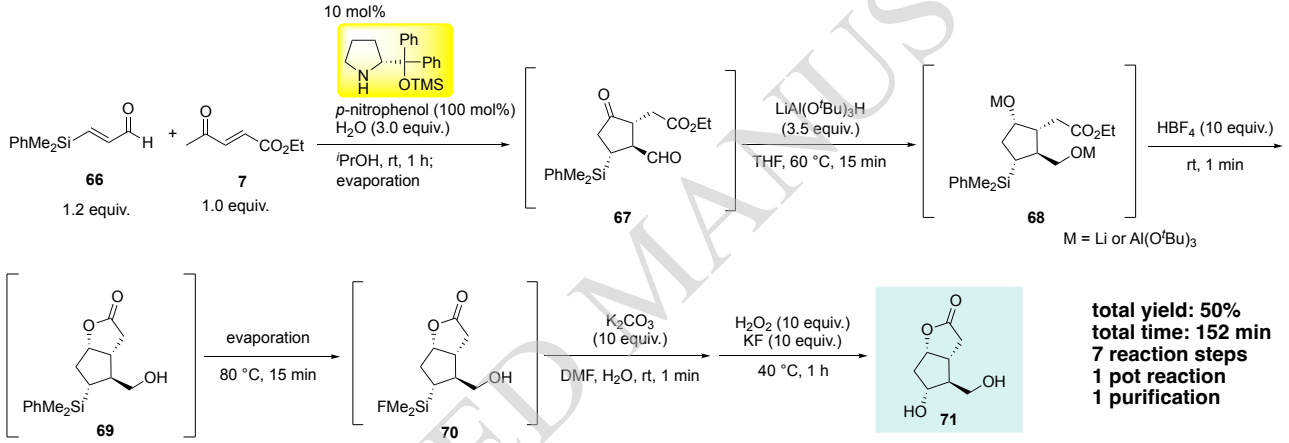
group (C8), followed by the addition reaction of the alkynyl group to aldehyde, occurred to afford **59**. In the reactions from **57** to **59**, there are three possible isomerization steps from the *cis* isomer of cyclopentane to the thermodynamically stable *trans*-isomer. Moreover, there is a possibility that the isomerization occurs at C8 and C12 positions. Using the model study, we concluded that the complete isomerization occurred at the α-position of the formyl group of **58** completely, before the addition reaction of alkyne to the aldehyde. Subsequent dehydration and oxidative Nef reaction provided **61**. Domino hemi-acetalization and oxy-Michael reaction, as developed by our group,[42] proceeded to afford acetal **62** with control of the stereochemistry at C9. Stereoselective reduction of the ketone, deprotection, and dehydroxylation of the propargylic alcohol afforded **66**. Reduction of the triple bond to a double bond by hydrogenation using Lindlar catalyst and deprotection of the protecting groups afforded latanoprost (**44**).[43]

6. Synthesis of prostaglandins based on domino Michael/Michael reaction

6.1 Synthesis of the Corey lactone

As described in the introduction, the Corey lactone is a key intermediate for the synthesis of a variety of prostaglandins (Scheme 1). Its synthesis requires 10 steps according to Corey's method. Our group reported the asymmetric Michael reaction of α,β-unsaturated aldehyde and ketone.[27] We further developed an asymmetric [3+2] cycloaddition reaction based on this reaction *vide supra* (Scheme 13, Eq. 2) and envisioned that this reaction would be suitable for the preparation of the Corey lactone.

Diphenylprolinol silyl ether-mediated [3+2] cycloaddition reaction of β-silyl substituted acrolein **66** and methyl ketone **7**, possessing an α,β-unsaturated ester moiety, proceeded to afford the trisubstituted cyclopentanone **67** in good yield in nearly optically pure form via domino Michael/Michael reaction (Scheme 18). Reduction of the aldehyde and stereoselective reduction of the ketone with the bulky reducing reagent LiAl(Ot-Bu)$_3$H afforded diol **68**. Lactonization and the conversion of the Si–Ph bond into a Si–F bond occurred upon treatment of the reaction mixture with HBF_4. Tamao–Fleming oxidation[44] proceeded by the addition of H_2O_2 and KF to afford the Corey lactone **71**.[27] All reactions could be conducted in a single reaction vessel and the total yield was 50%. Notably, with the total reaction time being only 152 minutes, this is also a time-economical synthesis.[22b]



Scheme 18. One-pot and 152-minute total synthesis of the Corey lactone (**71**)

6.2 Synthesis of clinprost

Clinprost (**72**), the methyl ester of isocarbacyclin, was found to be a potent neuroprotective compound in animal studies and it efficiently crossed the blood–brain barrier (Figure 2).[45] Compound **72** possesses a bicyclo[3.3.0]octene structure with four contiguous stereocenters with two side chains and an endocyclic alkene.

The [3+2] cycloaddition reaction of β-triphenylsilyl substituted acrolein **73** and **7** proceeded to afford the trisubstituted cyclopentanone **74** in good yield in nearly optically pure form (Scheme 19). Protection of the aldehyde with dimethyl acetal afforded **76**. The latter was then treated with LDA, whereupon the ketone moiety was transiently protected as its enolate. Claisen reaction proceeded by the addition of an anion of dimethyl methylphosphonate. Addition of acid in the same reaction vessel converted the enolate into the ketone, and intramolecular Horner–Wadsworth–Emmons reaction proceeded sequentially to afford bicyclo[3.3.0]octenone derivative **81** in a one-pot operation from **76** in good yield (86%).

1,4-Reduction proceeded by the addition of L-Selectride, and the generated enolate was trapped with Tf_2NPh to afford **83**. Suzuki–Miyaura coupling reaction of **83** and **84** proceeded to afford **85**. The C–$SiPh_3$ bond was converted into a C–OH bond by the Tamao–Fleming reaction.[44] Introduction of the side chain via Horner–Wadsworth–Emmons reaction and stereoselective reduction of the ketone using (–)-DIP-Cl[31] afforded clinprost (**72**). By using this approach, clinprost was synthesized in seven pots with 17% total yield.[46]

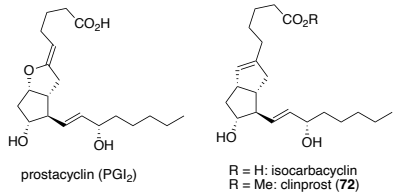
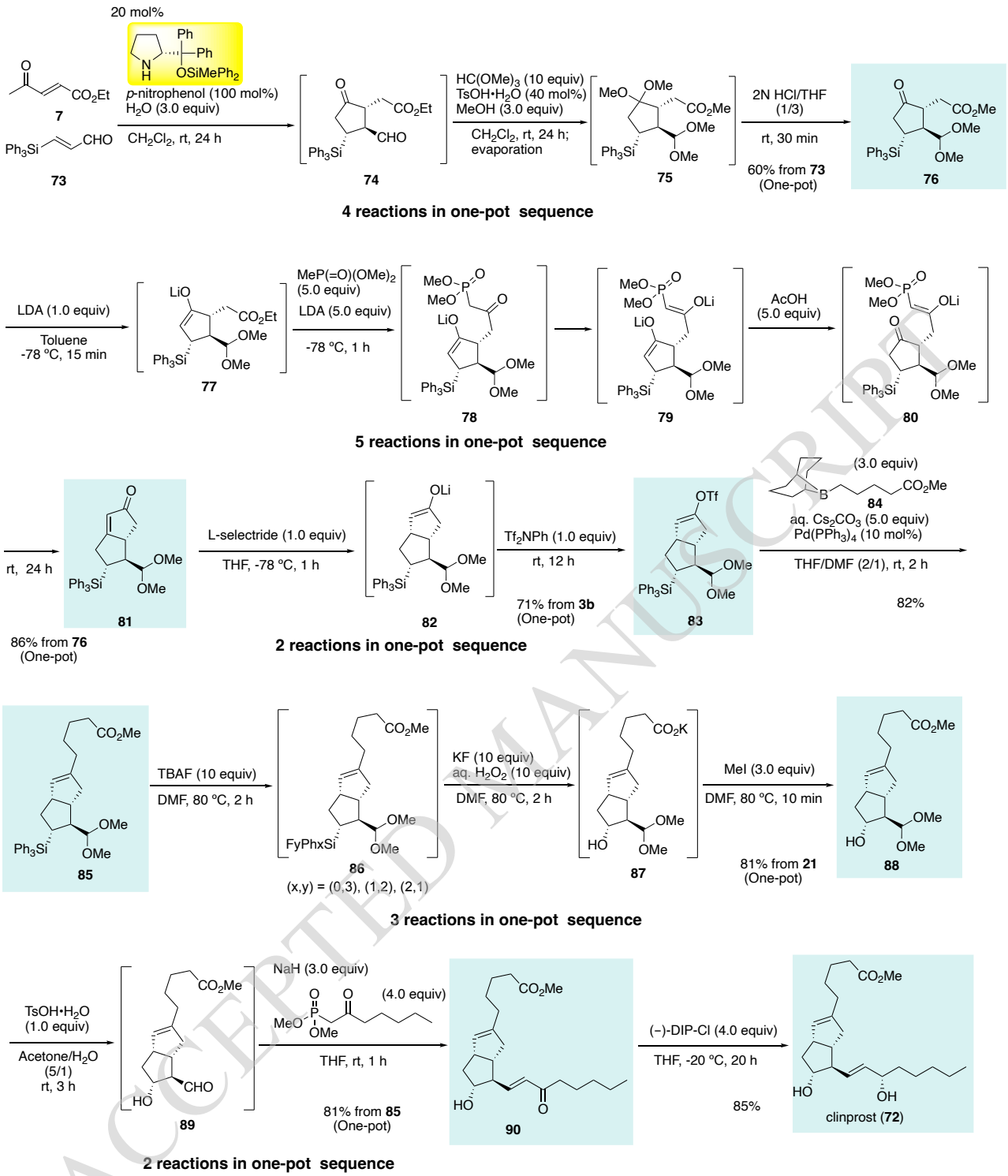


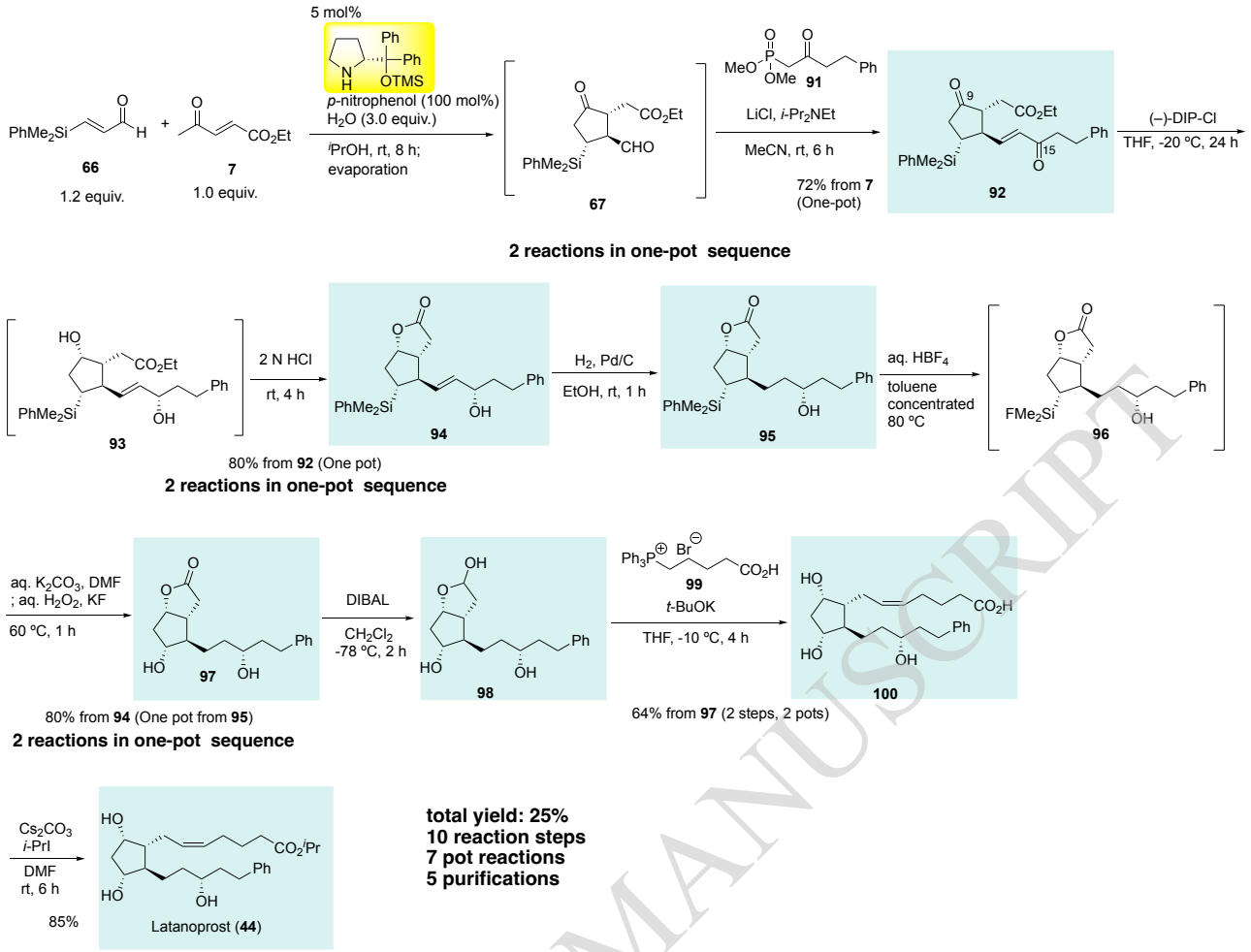
Figure 2. PGI_2, isocarbacyclin and clinprost



Scheme 19. Total synthesis of clinprost (**72**)

6.3 Synthesis of latanoprost (second-generation synthesis)

We previously described the synthesis of latanoprost via the first [3+2] cycloaddition reaction (Section 5.3). The second [3+2] cycloaddition reaction (Eq. 2) was employed for the second-generation synthesis of latanoprost (Scheme 20). The first [3+2] cycloaddition reaction is the same as that used for the synthesis of the Corey lactone. The reaction of **7** and **66** proceeded to afford cyclopentane carbaldehyde **67**, which was treated with Horner–Wadsworth–Emmons reagent **91** in the same reaction vessel to afford α,β-unsaturated ketone **92** in good yield in a single pot. Diastereoselective reduction of the two ketone moieties using (–)-DIP-Cl,[31] followed by lactonization gave **94**. Hydrogenation afforded **95**. Tamao–Fleming reaction[44] and reduction of lactone **97** gave lactol **98**, and Wittig reaction and isopropyl ester formation gave latanoprost (**44**). Overall, latanoprost (**44**) was synthesized in 10 reaction steps and seven pots in a total yield of 25% with five purifications; thus, the synthesis is short and high-yielding.[27b]



Scheme 20. The second-generation total synthesis of latanoprost (**44**)

7. Synthesis of prostaglandin based on Michael reaction and Mukaiyama aldol reaction

7.1 The third-generation synthesis of latanoprost

As latanoprost is one of the most important drugs in the prostaglandin family, we further developed a third-generation synthesis of the compound (Scheme 21). The key cyclopentane ring formation is a two-step process (Eq. 3).

Side chain aldehyde **105** was synthesized from 3-phenylpropanol. Krische allylation[47] gave allyl alcohol **102** with 96% ee. Olefin methathesis[48] with acrolein, protection of the alcohol with TBS, and hydrogenation proceeded in a single pot to afford **105** from **102** in good yield.

Organocatalyst-mediated Michael reaction of aldehyde **105** and nitroalkene **9** proceeded with excellent diastereoselectivity to afford **106**, which was treated with Me_2AlCl to provide **107** via intramolecular Mukaiyama aldol reaction.[49] Compound **107** was treated with NaF and Et_3N to afford methylenecyclopentanone **108** with excellent diastereoselectivity and enantioselectivity. It should be noted that the corresponding alcohol **108'** was also obtained in a small quantity and its diastereomeric purity was found to be low. Thus, kinetic resolution is thought to occur from **106** to **107**. 1,4-Addition reaction of vinyl lithium in the presence of $[CuI(PBu_3)]_4$ and $BF_3{\cdot}OEt_2$[50] proceeded to afford **109** in good yield. *cis*-Selective olefin metathesis using Ru-catalyst **110**,[51] diastereoselective reduction, and deprotection proceeded in a single reaction vessel to afford latanoprost (**44**). This approach allows the total synthesis of nearly optically pure latanoprost with the fewest number of pots (6 pots) in a total yield is 24%.[29]

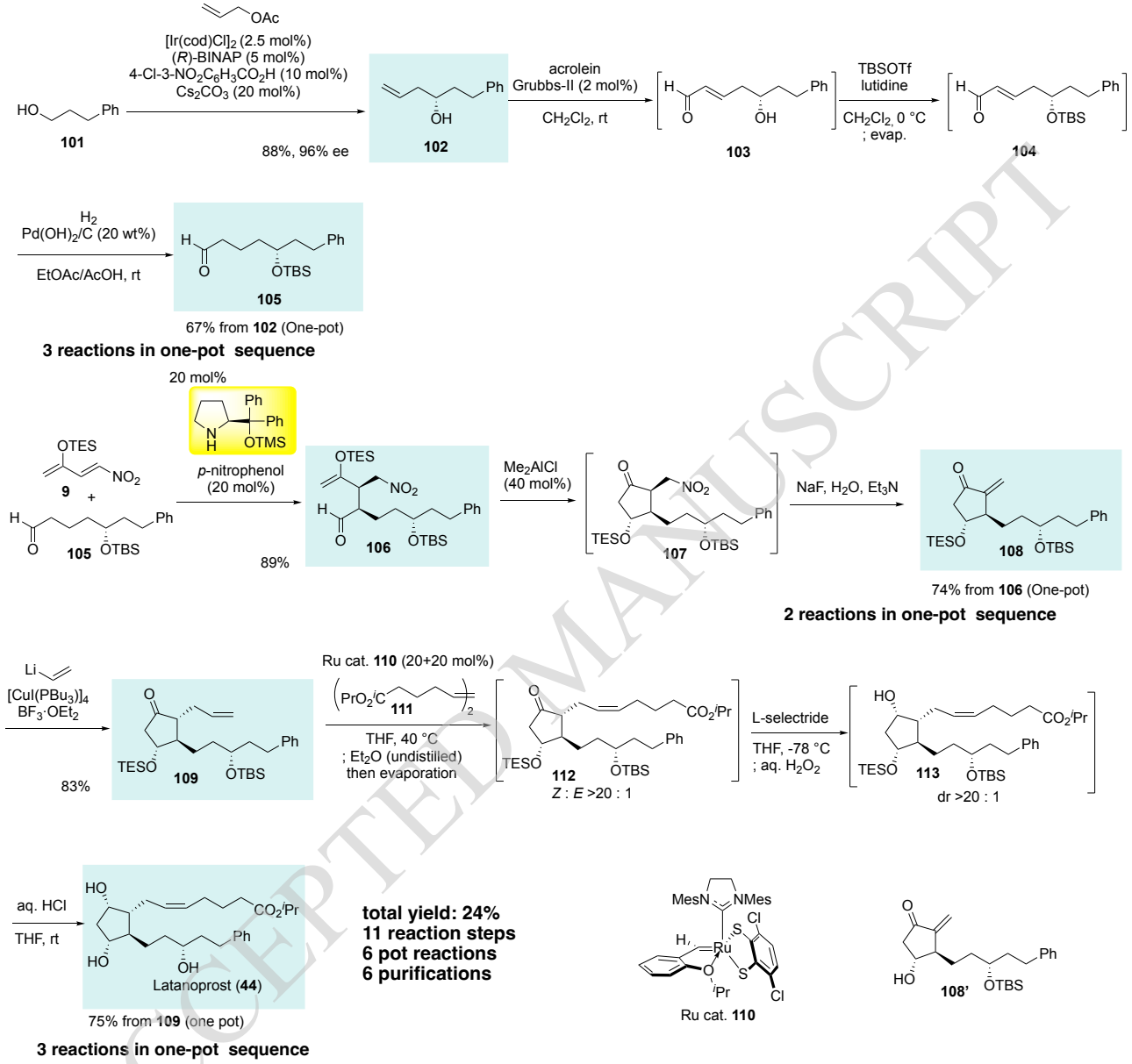
8. Conclusion

Given the biological importance of prostaglandins, new synthetic methods to access these compounds and their derivatives are still being reported today. We have developed three asymmetric formal [3+2] cycloaddition reactions catalyzed by diphenylprolinol silyl ether. The first is a domino reaction consisting of an asymmetric Michael reaction of aldehyde and nitroalkene, and intramolecular Henry reaction (Scheme 13, Eq. 1). The second formal [3+2] cycloaddition reaction is also a domino sequence of asymmetric Michael reaction of α,β-unsaturated aldehyde and methyl ketone, and intramolecular Michael reaction of enamine with α,β-unsaturated ester (Eq. 2). The third reaction is a two-step reaction: The first step is an asymmetric Michael reaction of aldehyde and nitroalkene, and the second step is an intramolecular Mukaiyama aldol reaction (Eq. 3). All three formal [3+2] cycloaddition reactions proceed with excellent enantioselectivity.

In the first and third [3+2] cycloaddition reactions, diphenylprolinol silyl ether catalyst reacts with aldehyde, generating the corresponding chiral enamine, which is the key intermediate. On the other hand, the same catalyst reacts with α,β-unsaturated aldehyde to generate an iminium ion, which is the key intermediate in the second [3+2] cycloaddition reaction. As diphenylprolinol silyl ether is a suitable catalyst in both enamine and iminium ion intermediates, three different [3+2] cycloaddition reactions can be accomplished that are suitable reactions for the synthesis of prostaglandins.

The [3+2] cycloaddition reactions can be successfully employed for the construction of the key chiral substituted cyclopentane framework. Further transformations can be conducted in a pot-economical manner, and several prostaglandins have been synthesized efficiently in a small number of pots.

In this review, the power of the combination of diphenylprolinol silyl ether and pot reactions is demonstrated for the efficient synthesis of biologically useful molecules such as prostaglandins.[23]



Scheme 21. The third-generation total synthesis of latanoprost (**44**)

Acknowledgement

I am grateful to the outstanding collaborators in my group, whose name appear in our papers cited in this account. This work was supported by JSPS KAKENHI Grant Number JP19H05630.

References

1. U. S. von Euler, *Arch. Exp. Pathol. Pharm*. **1934**, *175*, 78.
2. (a) Prostaglandins: Biology and Chemistry of Prostaglandins and Related Eicosanoids, (Ed.: P. B. Curtis-Prior), Churchill Livingstone, 1988. (b) Prostaglandins, Laukotrienes and Other Eicosanoids, (Ed.: F. Marks, G. Fürstenberger), Wiley-VCH, 1999.
3. C. D. Funk, *Science* **2001**, *294*, 1871.
4. a) P. W. Collins, S. W. Djuric, *Chem. Rev.* **1993**, *93*, 1533. b) S. Das, S. Chandrasekhar, J. S. Yadav, R. Grée, *Chem. Rev.* **2007**, *107*, 3286. c) H. Peng, F.-E. Chen, *Org. Biomol. Chem.* **2017**, *15*, 6281.
5. R. B. Woodward, J. Gosteli, I. Ernest, R. J. Friary, G. Nestler, H. Raman, R. Sitrin, C. Suter, J. K. Whitesell, *J. Am. Chem. Soc.* **1973**, *95*, 6853.
6. a) E. J. Corey and X. M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1995. b) E. J. Corey, N. M. Wesinshenker, T. K. Schaaf and W. Huber, *J. Am. Chem. Soc*. **1969**, *91*, 5675. c) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, N. M. Wesinshenker, *J. Am. Chem. Soc.* **1970**, *92*, 397. d) E. J. Corey, S. M. Albonico, U. Koelliker, T. K.

Schaaf, R. K. Varma, *J. Am. Chem. Soc*. **1971**, *93*, 1490. e) E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc*. **1975**, *97*, 6908. f) E. J. Corey, T. P. Loh, *J. Am. Chem. Soc.* **1991**, *113*, 8966.
7. a) G. Stork, M. Isobe, *J. Am. Chem. Soc*. **1975**, *97*, 4745. b) G. Stork, P. M. Sher, H. L. Chen, *J. Am. Chem. Soc.* **1986**, *108*, 6384.
8. a) M. Suzuki, A. Yanagisawa, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 4718. b) Review, see; R. Noyori, M. Suzuki, *Angew. Chem. Int. Ed*. **1984**, *23*, 847.
9. S. J. Danishefsky, M. P. Cabal, K. Chow, *J. Am. Chem. Soc.* **1989**, *111*, 3456.
10. F. Zhang, J. Zeng, M. Gao, L. Wang, G.-Q. Chen, Y. Lu, X. Zhang, *Nat. Chem.* **2021**, *13*, 692.
11. a) R. Kučera, F. W. Goetzke, S. P. Fletcher, *Org. Lett.* **2020**, *22*, 2991. b) L. Cunningham, S. Mishra, L. Matthews, S. P. Fletcher, *Org. Lett*. **2022**, *24*, 8886.
12. X. Yi, X. Long, Y. Chen, X. Cen, P. Tang, F. Chen, *Chem. Commun*. **2022**, *58*, 6000.
13. J. R. Kimbrough, Z. Austin, G. L. Milne, G. A. Sulikowski, *Org. Lett.* **2019**, *21*, 10048.
14. H. S. Sims, P. A. Horn, R. Isshiki, M. Lim, Y. Xu, R. H. Grubbs, M. Dai, *Angew Chem Int. Ed*. **2022**, *61*, e2021115633.
15. a) K. C. Nicolaou, P. Heretsch, A. ElMarrouni, C. R. H. Hale, K. K. Pulukuri, A. K. Kudva, V. Narayan, K. S. Prabh, *Angew Chem Int. Ed*. **2014**, *53*, 10443. b) K. C. Nicolaou, K. K. Pulukuri, R. Yu, S. Rigol, P. Heretsch, C. I. Grove, C. R. H. Hale, A. ElMarrouni, *Chem. Eur. J*. **2016**, *22*, 8559. c) K. C. Nicolaou, K. K. Pulukuri, S. Rigol, P. Heretsch, R. Yu, C. I. Grove, C. R. H. Hale, A. ElMarrouni, V. Fetz, M. Brönstrup, M. Aujay, J. Sandoval, J. Gavrilyuk, *J. Am. Chem. Soc*. **2016**, *138*, 6550.
16. a) J. Li, T. S. Ahmed, C. Xu, B. M. Stoltz, R. H. Grubbs, *J. Am. Chem. Soc*. **2019**, *141*, 154. b) J. Li, B. M. Stoltz, R. H. Grubbs, *Org. Lett*. **2019**, *21*,10139.
17. D. S. Peters, C. R. Pitts, K. S. McClymont, T. P. Stratton, C. Bi, P. S. Baran, *Acc. Chem. Res*. **2021**, *54*, 605.
18. Selected reviews on organocatalysis: a) *Asymmetric Organocatalysis 1; Lewis Base and Acid Catalysts* (Ed.: B. List), Thieme, Stuttgart, **2012**; b) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2013**.
19. a) G. Coulthard, W. Erb, V. K. Aggarwal, *Nature* **2012**, *489*, 278. b) S. Prévost, K. Thai, N. Schützenmeister, G. Coulthard, W. Erb, V. K. Aggarwal, *Org. Lett.* **2015**, *17*, 504. c) H. Baars, M. J. Classen, V. K. Aggarwal, *Org. Lett.* **2017**, *19*, 6008. d) A. Pelss, N. Gandhamsetty, J. R. Smith, D. Mailhol, M. Silvi, A. Watson, I. Perez-Powell, S. Prévost, N. Schützenmeister, P, Moore, V. K. Aggarwal, *Chem. Eur. J.* **2018**, *24*, 9542. e) S. Bennett, G. Coulthard, V. K. Aggarwal, *Chem. Rec.* **2020**, *20*, 936. f) C. Jing, S. Mallah, E. Kriemen, S. H. Bennett, V. Fasano, A. J. J. Lennox, I. Hers, V. K. Aggarwal, *ACS Cen. Sci.* **2020**, *6*, 995. G) C. Jing, V. K. Aggarwal, *Org. Lett.* **2020**, *22*, 6505.h) Z. Wang, S. H. Bennett, B. Kicin, C. Jing, J. A Pradeilles, K. Thai, J. R. Smith, P. D. Bacoş, V. Fasano, C. M. Saunders, V. K. Aggarwal, *J. Am. Chem. Soc.* **2023**, *145*, 14124.
20. a) K. Zhu, S. Hu, M. Liu, H. Peng, F.-E. Chen, *Angew. Chem. Int. Ed.* **2019**, *58*, 9923. b) K. Zhu, M. Jiang, B. Ye, G. -T. Zhang, W. Li, P. Tang, Z. Huang, F. Chen, *Chem. Sci.* **2021**, *12*, 10362.
21. J. Revol-Cavalier, V. Bultel-Poncé, A. Guy, T. Durand, C. Oger, J.-M. Galano, *Org. Lett.* **2020**, *22*, 7455.
22. Review, see; a) Y. Hayashi, *Chem. Sci*. **2016**, *7*, 866. b) Y. Hayashi, *J. Org. Chem.* **2021**, *86*, 1. c) Y. Hayashi, *Acc. Chem. Res*. **2021**, *54*, 1385.
23. a) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.* **2009**, *48*, 1304. b) H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru, Y. Hayashi, *Chem. Eur. J*. **2010**, *16*, 12616. c) H. Ishikawa, M. Honma, Y. Hayashi, *Angew. Chem. Int. Ed.* **2011**, *50*, 2824. d) T. Mukaiyama, H. Ishikawa H. Koshino, Y. Hayashi, *Chem. Eur. J*. **2013**, *52*, 17789. e) T. Mukaiyama, K. Ogata, I. Sato, Y. Hayashi, *Chem. Eur. J*. **2014**, *20*, 13583. f) Y. Hayashi. S. Ogasawara, *Org. Lett.* **2016**, *18*, 3426. g) Y. Hayashi, D. Sakamoto, D. Okamura, *Org. Lett.* **2016**, *18*, 4. h) Y. Hayashi, S. Koshino, K. Ojima, E. Kwon, *Angew. Chem. Int. Ed.* **2017**, *56*, 11812. i) S. Ogasawara, Y. Hayashi, *Synthesis*, **2017**, *49*, 424. j) S. Koshino, E. Kwon, Y. Hayashi, *Eur. J. Org. Chem*. **2018**, *41*, 5629. k) T. Terunuma, Y. Hayashi, *Nature Commun.* **2022**, *13*, 7503. l) T. Terunuma, G. Kawauchi, Y. Hayashi, *Asian. J. Org. Chem.* **2023**, *12*, e202300256.
24. Review of diphenylprolinol silyl ether; a) C. Palomo, A. Mielgo, *Angew. Chem. Int. Ed.* **2006**, *45,* 7876. b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3,* 922. c) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352,* 243. d) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45,* 248. e) H. Gotoh, Y. Hayashi, In *Sustainable Catalysis*; (Ed.: P. J. Dunn, K. K. Hii, M. J. Krische, M. T. Williams), John Wiley & Sons: Hoboken, NJ, 2013; Ch. 13, pp 287-316. f) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, *54,* 13860. g) G. J. Reyes-Rodriguez, N. M. Rezayee, A. Vidal-Albalat, K. A.Jørgensen, *Chem. Rev.* **2019**, *119,* 4221.
25. a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. b) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719. c) Y. Hayashi, S. Ogasawara, *Org. Synth*. **2017**, *94*, 252. d) Y. Hayashi, *Org. Synth*. **2022**, *99*, 68.
26. S. Umemiya, Y. Hayashi, *Eur. J. Org. Chem*. **2015**, 4320.
27. a) N. Umekubo, Y. Suga, Y. Hayashi, *Chem. Sci.* **2020**, *11*, 1205. b) N. Umekubo, Y. Hayashi, *Eur. J. Org. Chem.*, **2020**, 6221.
28. a) N. Umekubo, Y. Hayashi, *Angew. Chem. Int. Ed.* **2018**, *57,* 1958. b) N. Umekubo, T. Terunuma, E. Kwon, Y. Hayashi, *Chem. Sci.* **2020**, *11,* 11293.
29. G. Kawauchi, Y. Suga, S. Toda, Y. Hayashi, *Chem. Sci.* **2023**, *14,* 10081.
30. S. J. Kirtland, *Prostaglandins Leukot Essent Fatty Acids*, **1988**, *32*, 165.
31. a) J. Chandrasekharan, P. V. Ramachandran, H. C. Brown, *J. Org. Chem*. **1985**, *50*, 5446. b) C. Ohta, S. Kuwabe, T. Shiraishi, I. Shinohara, H. Araki, S. Sakuyama, T. Makihara, Y. Kawanaka, S. Ohuchida, T. Seko, *J. Org. Chem*. **2009**, *74*, 8298.
32. a) S. Umemiya, K. Nishino, I. Sato, Y. Hayashi, *Chem. Eur. J.* **2014**, *20*, 15753. Reviews of Nef reaction, see; b) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017. c) R. Ballini, M. Petrini, *Adv. Synth. Catal.* **2015**, *357*, 2371.
33. Y. Hayashi, S. Umemiya, *Angew. Chem. Int. Ed.* **2013**, *52*, 3450.
34. a) K. Ohno, H. Nishiyama, H. Nagase, K. Matsumoto, M. Ishikawa, *Tetrahedron Lett*. **1990**, *31*, 4489. b) H. Wakita, K. Matsumoto, H. Yoshiwara, Y. Hosono, R. Hayashi, H. Nishiyama, H. Nagase, *Tetrahedron* **1999**, *55*, 2449. Syntheses of optically active Beraprost, see; c) H. Nagase, H. Yoshiwara, A. Tajima, K. Ohno, *Tetrahedron Lett*. **1990**, *31*, 4493. d) H. Wakita, H. Yoshiwara, A. Tajima, Y. Kitano, H. Nagase, *Tetrahedron: Asymmetry* **1999**, *10*, 4099. e) H.

Wakita, H. Yoshiwara, H. Nishiyama, H. Nagase, *Heterocycles* **2000**, *53*, 1085. f) H. Wakita, H. Yoshiwara, Y. Kitano, H. Nishiyama, H. Nagase, *Tetrahedron: Asymmetry* **2000**, *11*, 2981.
35. a) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett*. **2007**, *9*, 5307. b) Y. Hayashi, D. Okamura, T. Yamazaki, Y. Ameda, H. Gotoh, S.Tsuzuki, T. Uchimaru, D. Seebach, *Chem. Eur. J.* **2014**, *20*, 17077.
36. a) S. Ohira, *Synth. Commun*. **1989**, *19*, 561. b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521.
37. S. Umemiya, D. Sakamoto, G. Kawauchi, Y. Hayashi, *Org. Lett*. **2017**, *19*, 1112.
38. a) S. S. Patel, C. M. Spencer, *Drugs & Aging* **1996**, *9*, 363. b) C. M. Perry, J. K. McGavin, C. R. Culy, T. Ibbotson, *Drugs & Aging* **2003**, *20*, 597.
39. a) B. Resul, J. Stjernschantz, K. No, C. Liljebris, G. Selen, M. Astin, M. Karlsson, L. Z. Bito *J. Med. Chem.* **1993**, *36*, 243. b) I. Obadalová, T. Pilarčík, M. Slavíková, J. Hájíček, *Chirality* **2005**, *17*, S109. c) J. G. Martynow, J. Jóźwik, W. Szelejewski, O. Achmatowicz, A. Kutner, K. Wiśniewski, J. Winiarski, O. Zegrocka-Stendel, P. Gołębiewski, *Eur. J. Org. Chem.* **2007**, 689. d) G. Zanoni, A. D'Alfonso, A. Porta, L. Feliciani, S. P. Nolan, G. Vidari, *Tetrahedron* **2010**, *66*, 7472. e) K Vijendhar, B Srinivas, S. Boodida, *J. Chem. Sci.* **2015**, *127*, 2023. f) S. A. Sasane, N. B. Bhise, G. P. Shingh, A. Joseph, G. G. Shenoy, *Synth. Commun.* **2019**, *49*, 2350. Formal total syntheses; g) M. Harikrishna, H. R. Mohan, P. K. Dubey, M. Shankar, G. V. Subbaraju, *Asian. J. Chem.* **2011**, *23*, 3121. h) M. L. Contente, P. Zambelli, S. Galafassi, L. Tamborini, A. Pinto, P. Conti, F. Modinari, D. Romano, *J. Mol. Catal. B: Enzym.* **2015**, *114*, 7.
40. a) Y. Hayashi, N. Umekubo, T. Hirama, *Org. Lett*. **2017**, *19*, 4155. Proline-mediated α-aminoxylation, see; b) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293. c) Y. Hayashi, J. Yamaguchi, T. Sumiya, K. Hibino, M. Shoji *J. Org. Chem.* **2004**, *69*, 5966. d) G. Zhong, *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. e) S. P. Brown, M. P. Brochu, C. J Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808.
41. D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806.
42. a) Y. Hayashi, T. Saitoh, H. Arase, G. Kawauchi, N. Takeda, Y. Shimasaki, I. Sato, *Chem. Eur. J.* **2018**, *24*, 4909. b) P. A. Evans, A. Grisin, M. J. Lawler, *J. Am. Chem. Soc.* **2012**, *134*, 2856.
43. G. Kawauchi, S. Umemiya, T. Taniguchi, K. Monde, Y. Hayashi, *Chem. Eur. J.* **2018**, *24*, 8409.
44. a) K. Tamao, M. Akita and M. Kumada, *Organometallics **1983**, 2*, 1694. b) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc., Chem. Commun.* **1984**, 29.
45. a) S. Matsuda, T.-C. Wen, Y. Karasawa, H. Araki, H. Otsuka, K. Ishihara, M. Sakanaka, *Brain Res.* **1997**, *769*, 321. b) T. Minagawa, K. Sakanaka, S. Inaba, Y. Sai, I. Tamai, T. Suwa, A. Tsuji, *J. Pharm. Pharmacol.* **1996**, *48*, 1016.
46. N. Umekubo, Y. Hayashi, *Org. Lett*. **2020**, *22*, 9365.
47. I. S. Kim, M. -Y. Ngai and M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6340.
48. M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
49. a) T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.* **1973**, *2*, 1011. b) J. Matsuo and T. Mukaiyama, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109. c) T. Mukaiyama, *Organic reactions*, *Vol 28* (Eds: W. G. Dauben, G. A. Boswell, Jr., S. Danishefsky, H. W. Gschwend, R. F. Heck, R. F. Hirshchmann, A. S. Kende, L. A. Paquette, G. H. Posner, B. M. Trost, R. Bittman, B. Weinstein), Wiley, New York, **1982**, pp. 203 – 331.
50. Y. Yamamoto, *Angew. Chem. Int. Ed.* **1986**, *25*, 947.
51. a) S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock and A. H. Hoveyda, *Nature* **2011**, *471*, 461. b) M. J. Koh, R. K. M. Khan, S. Torker, M. Yu, M. S. Mikus and A. H. Hoveyda, *Nature* **2015**, *517*, 181. c) C. Xu, X. Shen and A. H. Hoveyda, *J. Am. Chem. Soc.* **2017**, *139*, 10919. d) J. Li, T. S. Ahmed, C. Xu, B. M. Stoltz and R. H. Grubbs, *J. Am. Chem. Soc.* **2019**, *141*, 154. e) J. Li, B. M. Stoltz and R. H. Grubbs, *Org. Lett.* **2019**, *21*, 1013. f) K. C. Nicolaou, K. K. Pulukuri, S. Rigol, Z. Peitsinis, R. Yu, S. Kishigami, N. Cen, M. Aujay, J. Sandoval, N. Zepeda and J. Gavrilyuk, *J. Org. Chem.* **2019**, *84*, 365

Graphical Abstract

Pot-economical total synthesis of prostaglandins via organocatalyst-mediated asymmetric reactions

Yujiro Hayashi

<Diagram>