# An asymmetric Suzuki-Miyaura approach to prostaglandins: Synthesis of Tafluprost

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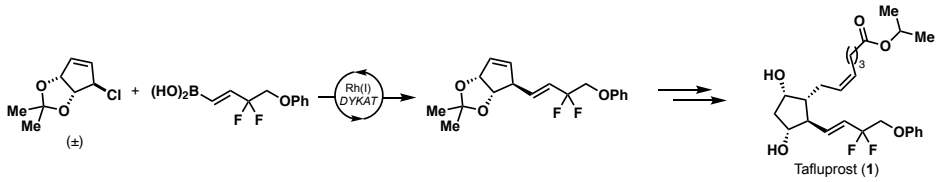
*Supporting Information Placeholder*



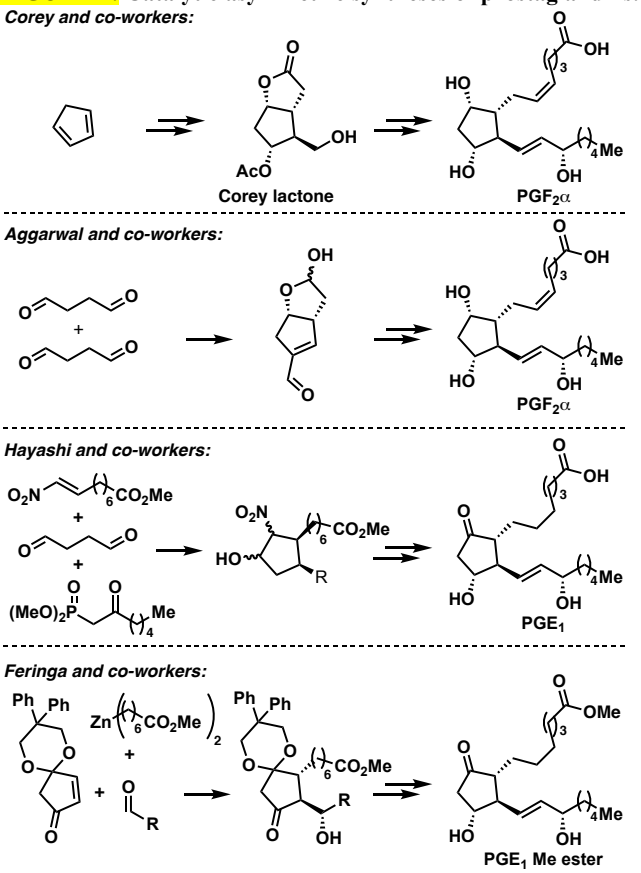

**ABSTRACT:** We report the catalytic asymmetric synthesis of Tafluprost (**1**), a prostaglandin analogue. This synthesis demonstrates a new approach to prostaglandins involving symmetrization-desymmetrization of a racemic precursor to control the absolute and relative stereochemistry of the cyclopentyl core. Key steps include a diastereo- and enantioselective Rh-catalyzed Suzuki-Miyaura reaction of a racemic bicyclic allyl chloride and an alkenyl boronic acid, and a regio- and diastereoselective Pd-catalyzed Tsuji-Trost reaction with an enolate surrogate.

Prostaglandins are hormone-like lipid compounds that elicit an unusually diverse array of physiological responses. For example, they play a role in the origin of pain and fever and have several regulatory functions.[1] All prostaglandins contain twenty carbon atoms arranged in a 5-membered core bearing two aliphatic side chains and differ in the oxidation state of this core, and unsaturation of the side chains.[2] Because of their versatile properties many prostaglandins and analogues are used clinically, and the development of new synthetic strategies of those natural products has been a vibrant area of chemical research.[2,3]

Corey's synthesis of $PGE_2$ and $PGF_2\alpha$ 50 years ago was a true landmark in complex molecule synthesis.[4,5] Indeed many contemporary routes to prostaglandin derivatives still rely on the Corey aldehyde benzoate as a key intermediate.[2] While many stereospecific and diastereoselective approaches to prostaglandins have been developed, so far catalytic asymmetric approaches in which the asymmetry is exclusive controlled by a chiral catalyst are rare.[2] Those include Aggarwal's and Hayashi's syntheses *via* asymmetric aldol and Michael reactions,[6,7] Feringa's enantioselective 1,4-addition followed by enolate tapping,[2,8,9] and Nicolaou's asymmetric allylic alkylation approach.[10]

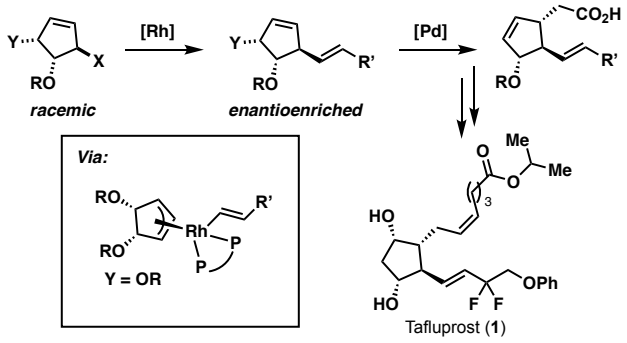
Tafluprost – developed by Asahi Glass Co., Ltd., and Santen Pharmaceutical Co. – is Santen's, and Merck Sharp & Dohme's prostaglandin $PGF_2\alpha$ analogue for the treatment of intraocular pressure in open-angle glaucoma and ocular hypertension.[11] Previous syntheses of Tafluprost (**1**) have relied on the

**FIGURE 1: Catalytic asymmetric syntheses of prostaglandins.**



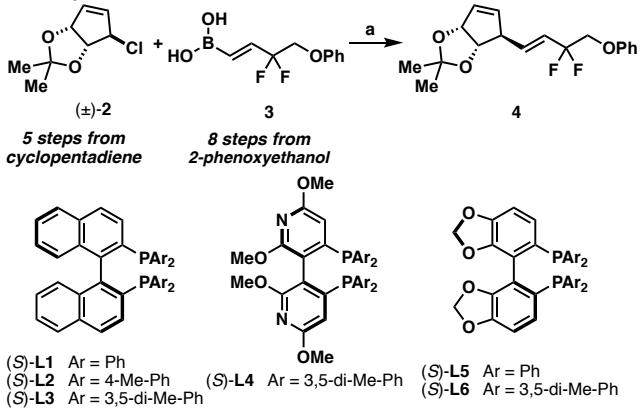
Corey lactone to access the densely functionalized cyclopentane core.[4, 12]

**FIGURE 2: Our strategy towards Tafluprost.**




Allylic substitution reactions are powerful tools for the construction of complex organic molecules.[13] In this context, our group has developed a series of asymmetric rhodium-catalyzed Suzuki–Miyaura coupling reactions between racemic allylic chlorides and (hetero)aryl- and alkenylboronic acids.[14] Recently, we have shown that racemic bicyclic allylic chlorides undergo highly enantio- and diastereoselective cross-coupling with boronic acids.[15] Enantioconvergence in these reactions is believed to occur *via* a DYKAT mechanism with a pseudo-*meso* Rh-π-allyl intermediate.[14,15] We envisioned that this method could be used to construct a key carbon-carbon bond and set the absolute and relative stereochemistry of the cyclopentyl core of prostaglandins in a single reaction (Fig. 2). We were intrigued by the complexity of the side chain of Tafluprost (**1**) and thought it was a highly demanding test of our method.

**TABLE 1: Asymmetric Suzuki-Miyaura coupling of bicyclic allyl halide.**[a]



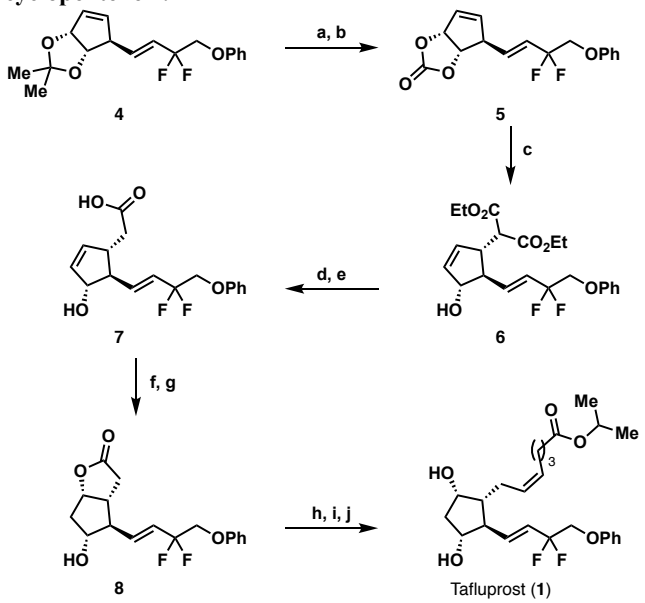

| entry | ligand | yield (%)[b] | ee (%)[c] | dr[d] |
|---|---|---|---|---|
| 1 | **L1** | 87 | 77 | >20:1 |
| 2 | **L2** | 79 | 80 | >20:1 |
| 3 | **L3** | 83 | 78 | >20:1 |
| 4 | **L4** | 83 | 77 | 11.5:1 |
| 5 | **L5** | 79 | 90 | 7.2:1 |
| **6**[e] | **L6** | **80** | **90** | **7.2:1** |

[a]Reactions run on 0.20 mmol scale. [a]*Reagents and conditions*: $[Rh(COD)OH]_2$ (2.5 mol%), ligand (6 mol%), boronic acid (1.5 equiv.), 50 wt% aq. CsOH (1.0 equiv.), THF (0.25M). [b]Isolated yield of the major diastereomer. [c]The ee values were determined by SFC analysis on a chiral non-racemic stationary phase. [d]The dr values were determined by $^1$H NMR spectroscopy of the crude reaction mixture. [e]Performed on 1.9 mmol scale.

Our synthesis commenced with the preparation of suitable coupling partners for the asymmetric Suzuki-Miyaura coupling. The allyl halide (±)-**2** was prepared from cyclopentadiene in 5 steps and alkenylboronic acid **3** was prepared from 2-phenoxyethanol in 35% overall yield in 8 steps following literature procedures (for details see SI).[15,16,17] The two coupling partners were subjected to reaction conditions previously used to couple alkenylboronic acids to (±)-**2** giving **4** in 87% yield and >20:1 dr, albeit only with moderate (77% ee) enantioselectivity (Table 1, entry 1).[15] To improve the enantioselectivity of the reaction, different bidentate phosphine ligands were tested (entries 3–6). 90% ee was only obtained with SEGPHOS ligands **L5** and **L6** at the slight expense of diastereoselectivity to set the absolute stereochemistry of Tafluprost.

The protected allylic alcohol moiety in **4** allowed for regio- and diastereoselective introduction of the second side-chain *via* allylic substitution with an enolate surrogate. We used a cyclic carbonate as a traceless activation strategy for the allylic alcohol. The acetonide **4** was converted in two-steps to the corresponding cyclic carbonate **5** in 80% overall yield. Palladium-catalyzed allylic substitution with diethyl malonate afforded **6** as the major regioisomer in 89% yield with overall retention of the relative stereochemistry (for details on the formation of the minor regioisomer see SI).[18] Next, the malonate was transformed into the carboxylic acid **7** *via* a hydrolysis / decarboxylation sequence with 1,1′-carbonyldiimidazole (CDI), and iodolactonization stereoselectively introduced the second cyclopentyl hydroxy group in 73% yield over three steps (for structure see SI: **S16**).

**SCHEME 1: Synthesis of Tafluprost from bicyclic alkenylcyclopentene 4.**[a]




[a]*Reagents and conditions*: (a) AcOH/$H_2O$, 40 °C, 19 h, 88% (94% brsm); (b) triphosgene, pyridine, $CH_2Cl_2$, r.t. 20 min, 91%; (c) diethyl malonate, $[Pd(dppf)Cl_2]_2$ (3 mol%), THF, r.t., 1 h, 89%; (d) NaOH, THF/$H_2O$, r.t., 24 h; (e) CDI, THF, r.t., 3 h, then aq. NaOH, r.t., 20 h; (f) KI/$I_2$, $NaHCO_3$, THF/$H_2O$, r.t., 24 h, 73% over 3 steps; (g) $Bu_3SnH$, AIBN, $C_6H_6$, 80 °C, 1 h, 79%; (h) DIBAL-H, $CH_2Cl_2$ –78 °C to r.t., 89%; (i) (4-carboxybutyl)triphenylphosphonium bromide, KHMDS, THF/toluene, 0 °C, 2 h; (j) 2-iodopropane, DBU, $(CH_3)_2CO$, r.t., 22 h, 65% over two-steps (90% brsm). *Abbreviations: brsm = based on recovered starting material, dppf = 1,1′-bis(diphenylphosphino)ferrocene, r.t. = room temperature, CDI =1,1′-*

*carbonyldiimidazole, AIBN = azobisisobutyronitrile, DIBAL-H = diisobutylaluminum hydride, KHMDS = Potassium bis(trimethylsilyl)amide, DBU = 1,8-diazabicyclo(5.4.0)undec-7-ene.*

The synthesis of Tafluprost (**1**) was completed following a well precedented strategy in the prostaglandin literature.[4] Radical deiodination using $Bu_3SnH$ in 79% yield and subsequent lactone reduction gave rise to hemiacetal in 89% yield previously synthesized by Matsumura and co-wokers.[12a,19] Finally, a *Z*-selective Wittig reaction of the hemiacetal **8** with an excess of non-stabilized ylid followed by an esterification with isopropyl iodide in the presence of DBU afforded Tafluprost in 65% yield over 2 steps.[12a]

Overall, we established an asymmetric synthesis of Tafluprost in 19 steps over the longest linear sequence in 6.7% overall yield. The synthesis features an asymmetric rhodium catalyzed Suzuki–Miyaura reaction of two complex coupling partners to introduce the alkenyl chain with high diastereoselectivity, and a palladium catalyzed allylic substitution to control the stereochemistry of the allyl chain. We envision that our modular approach to Tafluprost will enable the synthesis of prostaglandins and new prostaglandin analogues.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General methods, detailed experimental procedure, chromatograms, and spectral data.

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### Notes

Oxford University Innovation has filed a patent application (PCT/GB2016/051612) with S.P.F. named as an inventor. R.K. and F.W.G. declare no competing financial interests.

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