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1,4-Addition of arylboronic acids to β -aryl- α,β -unsaturated ketones and esters catalyzed by a rhodium(I)-chiraphos complex for catalytic and enantioselective synthesis of selective endothelin A receptor antagonists

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Abstract: An enantioselective synthesis of acyclic β -diaryl ketones and esters *via* 1,4-addition of arylboronic acids to β -aryl- α,β -unsaturated ketones or esters is described. The complex *in situ* prepared from $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ and chiraphos was found to be an excellent catalyst to achieve high enantioselectivities in a range of 83-89%ee for the ketone derivatives and 78-94%ee for *t*-butyl β -arylacrylate derivatives. The protocol provided a catalytic method for the enantioselective synthesis of selective endothelin A receptor antagonists (**7**, **8**) reported by SmithKline Beecham and Merck-Banyu. The enantioselection

mechanism and efficiency of the chiraphos ligand for β -aryl- α,β -unsaturated ketones and esters are discussed on the basis of results of DFT computational studies on the modes of coordination of the enone substrates to the phenylrhodium(I)/(S,S)-chiraphos complex.

1. Introduction

1,4-Additions of electrophiles to α,β -unsaturated carbonyl compounds are a versatile methodology for forming carbon-carbon bonds.¹ Among these extensive studies in conjugate additions, we have disclosed the rhodium-catalyzed reaction of aryl- and 1-alkenylboronic acids.² Since the reaction yields a stereogenic center at the β -carbon, considerable efforts have been devoted to the development of asymmetric syntheses via metal-catalyzed 1,4-addition of organoboron,³ -silicon,⁴ -magnesium,⁵ -zinc,⁶ -tin,⁷ -bismuth,⁸ -titanium⁹ and -indium¹⁰ compounds to cyclic and acyclic α,β -unsaturated ketones,³ esters,³ amides,¹¹ phosphonates,¹² and nitro¹³ compounds. A rhodium(I)-binap catalyst was the first catalyst to be successfully used in enantioselective 1,4-addition of aryl- and 1-alkenylboronic acids to cyclic and acyclic enones.^{3a} Other ligands effective for rhodium(I) catalysts are bisphosphine ligands of chiraphos¹⁴ and diphosponites,^{3e} P-N ligands of amidomonophosphines,¹⁵ bis(alkene) ligands based on a norbornadiene skeleton,¹⁶ and monophosphine ligands of

phosphoramidites.¹⁷ For the corresponding palladium-catalyzed reactions of organoboron,¹⁸⁻²⁰ -silicon²⁰⁻²² and -bismuth^{20,22} compounds, bisphosphines bridged by two carbons, such as chiraphos and dipamp, resulted in high yields and high enantioselectivities. Among these extensive studies on 1,4-addition of organoboronic acids, the synthesis of β -diaryl carbonyl ketones or esters (**4**) has attracted much attention in recent years (Scheme 1). Since compounds incorporating a diarylmethine stereogenic centers are an important class of compounds due to the frequent occurrence of these fragments in natural products,²³ there are excellent precedents achieved by Friedel-Crafts alkylation of arenes²⁴ and 1,4-addition of electron-rich arenes to enals.²⁵ Another reliable and flexible approach for introducing two different aryl-fragments is 1,4-addition of aryl metal reagents to α,β -unsaturated carbonyl compounds, which was recently accomplished by using rhodium complexes of chiral dienes (**5**)¹⁶ or a dicationic palladium(II)-chiraphos complex (**3**).^{19,20,22} In this paper, we show the efficiency of a rhodium(I)-chiraphos complex (**3**) for enantioselective preparation of β -diaryl carbonyl compounds (**4**) *via* the 1,4-addition of arylboronic acids (**2**) to β -aryl- α,β -unsaturated ketones or esters (**1**). The protocol provides the first catalytic method for enantioselective synthesis of endothelin receptor antagonists.

<<Scheme 1>>

2. Results and discussion

2.1 Enantioselective addition to β -aryl- α,β -unsaturated ketones and esters

The performance of a rhodium-chiraphos catalyst (**3a**, 3 mol%) in the 1,4-addition of 3-methoxyphenylboronic acid (1.5 equivalents) to (*E*)-4-phenyl-3-buten-2-one (entries 1-5) or (*E*)-cinnamates (entries 6-13) was investigated (Table 1). The catalyst was prepared *in situ* by mixing (*S,S*)-chiraphos (3.3 mol%) and [Rh(nbd)₂]BF₄ (3 mol%) at room temperature. The addition to (*E*)-4-phenyl-3-buten-2-one was very slow at room temperature (entry 1), but inorganic bases exerted a remarkable accelerating effect (entries 2-4), as has been demonstrated in related 1,4-addition reactions using other phosphine-rhodium complexes.^{3k} This effect of bases on yields was in the order of their basic strength: KOH > K₂CO₃ > KHCO₃. The reaction temperature effects on the enantioselectivity as being increased at lower temperature. Reaction at room temperature resulted in 84%ee (entry 4) and selectivity was increased to 89%ee by lowering the reaction temperature to 0 °C (entry 5). The bulkiness of ester groups of cinnamates greatly affected on both the reaction rates and enantioselectivities (entries 6-9). The reaction was slow at room temperature, but the best enantioselectivity (92%, 93%ee) was obtained by using the most hindered *t*-butyl cinnamate at 50 °C in the presence of KOH (1 equivalent) (entry 8) rather than methyl and isopropyl esters (entries 6 and 7). Carbonates, fluorides and triethylamine were less effective (entries 9-13). These results are in contrast to the low efficiency of previous rhodium(I)-binap catalysts for β -aryl- α,β -unsaturated carbonyl compounds. A Rh(acac)(C₂H₄)₂-binap catalyst resulted in 28% yield and 78%ee for isopropyl cinnamate^{3d} and 4-tolylboronic acid at 100 °C, and [Rh(binap)(nbd)]BF₄ resulted in 84% yield and 76%ee in addition of 3-methoxyphenylboronic acid to 4-phenyl-3-buten-2-one at 50 °C in the presence of Et₃N.²⁰

<<Table 1>>

1,4-Additions of representative arylboronic acids to β -aryl- α,β -unsaturated ketones and *t*-butyl esters with a rhodium(I)/(*S,S*)-chiraphos catalyst are shown in Table 2. All additions to ketones were completed within 5 h at room temperature with enantioselectivities in a range of 83-89%ee (entries 1-5). Additions to *t*-butyl esters were carried out at 50 or 80 °C, but these reactions resulted in 5-10% higher enantioselectivities than those of ketone series (entries 6-16). Substituents on arylboronic acids (FG in **2**) and β -substituents of carbonyl compounds (Ar in **1**) affected the enantioselectivities, suggesting their participation in enantioselection as is discussed in the mechanistic section. Substituents of arylboronic acids increased the selectivities in the order of 3,4-methylenedioxy (entries 2 and 9) > 4-methoxy (entries 1 and 6) > 3-methoxy (entry 7) > 3,4-dimethoxy (entry 8) >> 4-dimethylamino (entry 10). In additions of 3-methoxyphenylboronic acid to a series of β -arylacrylates, the selectivities of 4-methoxyphenyl, 4-methylphenyl and 2-methoxyphenyl derivatives were comparable to that of the phenyl group (entries 7 and 11-13), but 4-trifluoromethylphenyl and 2-naphthyl derivatives resulted in significantly lower enantioselectivities presumably due to steric reason (entries 14 and 15). Although the pyridine nitrogen often retards metal-catalyzed reactions due to its strong ability to coordinate to most metal catalysts, it was interesting that arylboronic acids underwent very smooth addition to *t*-butyl 3-pyridylacrylate under standard conditions (entry 16). The absolute configurations of most products were not known, but the formation of *S*-product from (*S,S*)-chiraphos complex was established by the specific rotation reported for (*S*)-3-(3-methoxyphenyl)-1,3-diphenylpropan-1-one ($[\alpha]_D +7.1$ (*c* 0.71, CHCl₃))²⁰ (entry 4).

<<Table 2>>

2.2 Synthesis of endothelin receptor antagonists

Much effort has been made by many research groups to prepare selective antagonists of endothelin receptors, which are currently being evaluated as potential therapeutic agents for the treatment of hypertension, congestive heart failure and renal diseases. 1,3-Diarylindan-2-carboxylic acid derivatives are highly potent antagonists selective for endothelin receptors among non-peptide antagonists reported by Shionogi,²⁶ Hoffmann-La Roche,²⁷ Bristol-Myers Squibb,²⁸ SmithKline Beecham (**6**, **7**),²⁹ and Merck-Banyu (**8**).³⁰ Two general and flexible methods for the synthesis such a fused five-membered ring with three contiguous chiral centers have recently been accomplished by SmithKline Beecham³¹ and Merck-Banyu.³⁰ In these approach, the major challenge of Merck-Banyu's group was enantioselective 1,4-addition of arylmetal reagents to β -aryl- α,β -unsaturated esters to build a five-membered ring and three chiral centers based on the first stereogenic center. Although they achieved excellent enantioselectivities by using a stoichiometric chiral auxiliary for 1,4-addition of aryllithium reagents, the catalytic protocol is preferred in large-scale preparations of these antagonists

<<Figure 1>>

2.2.1 SmithKline Beecham's antagonist (7)

Most rhodium(I)-catalysts previously reported for 1,4-addition of arylboronic acids achieved significantly higher enantioselectivity for cyclic enones and

esters than those for acyclic derivatives. Thus, addition to benzo-fused 2-cyclopentenone **9** was the first choice for the synthesis of endothelin receptor antagonists (**6** and **7**) reported by SmithKline Beecham (Scheme 2). However, the substrate **9** was unfortunately very labile as neat or even in solutions. Thus, all attempts at using **9** as the starting compound failed. [Rh(nbd)₂]BF₄-chiraphos (**3a**) resulted in 27% yield and 8% ee.

<<Scheme 2>>

An alternative approach for the synthesis of **7** from arylboronic acids and acyclic unsaturated esters is shown in Scheme 3. An aryl moiety **14** desired for introduction of the top functionality of **7** via palladium-catalyzed cross-coupling was obtained from readily available 4-bromoresorcinol (**11**). Chemoselective protection of the 4-hydroxy group of **11** with tosyl chloride was directly followed by treatment with ClCH₂CH₂OMOM. Deprotection and methylation of **12** furnished **13** in 75% total yield. A sequential treatment of **13** with magnesium turning and B(OMe)₃ gave the desired boronic acid **14** in 73% yield.

<<Scheme 3>>

The α,β -unsaturated ester (**17**) desired as a substrate for enantioselective 1,4-addition was synthesized by Heck coupling of 2-bromo-5-propoxybenzaldehyde (**16**), which was obtained from 2-bromo-5-hydroxybenzaldehyde (**15**) via an etherification, oxidation and esterification sequence. (*E*)-Selective Heck coupling with *t*-butyl acrylate then furnished the Michael acceptor (**17**) in 55% yield from **15**. Addition of 3,4-methylenedioxyphenylboronic acid (1.5 equivalents) to **17** smoothly occurred at 60 °C under optimal conditions shown in Table 1. The desired enantiomer (**18**) was obtained with 89% ee when (*R,R*)-chiraphos (3.3 mol%) was used for [Rh(nbd)₂]BF₄ (3 mol%). Claisen cyclization of **18** with NaHMDS gave **19** in

76% ee. The absolute configuration of **18** ($[\alpha]_{\text{D}}^{22} -46.5$, (c 0.70, CHCl_3)) was established to be *S* by conversion of **19** to the known compound **23** ($[\alpha]_{\text{D}}^{22} +49.7$, (c 0.25, CHCl_3)) *via* decarboxylation of the resulting keto ester **19** (Scheme 4) The specific rotation of **23** reported in the literature is ($[\alpha]_{\text{D}}^{25} = +43.6$ (*S*, 94% ee))³¹. The enantiomer thus obtained was produced by the same mode of face selection as that discussed in the later section.

<<Scheme 4>>

The chiral diester **19** thus obtained was led to the target antagonist **7** by a method similar to that previously reported by SmithKline Beecham. Thus, the enolate resulting from **19** with NaH was sulfonylated with trifluoromethanesulfonic anhydride to yield the triflate **20** in 72% yield (89% ee). Cross-coupling of **20** with **14** in the presence of $\text{PdCl}_2(\text{dppf})$ and K_2CO_3 to give **21** in 90% yield was followed by olefin reduction with H_2 and a palladium catalyst to give **22** in 90% yield. Finally, epimerization of the *t*-butyl ester group in **22** was followed by deprotection of *t*-butyl ester and MOM group to furnish **7**.³¹

The strategy thus achieved by asymmetric 1,4-addition and cross-coupling reaction of arylboronic acids has a structural flexibility for both top and bottom aryl groups for parallel synthesis of candidates.

2.2.2 Merck-Banyu's antagonists

For the synthesis of Merck-Banyu's antagonist **8**, an unsaturated ester (**27**) was chosen as a substrate for the enantioselective addition of arylboronic acids to introduce the chiral stereogenic center, which was previously achieved by 1,4-addition of aryllithiums to unsaturated esters possessing an chiral auxiliary

(Scheme 5). The ester **27** was obtained in a high yield by the reported procedures starting from 2,6-dichloropyridine (**24**).³² With the substrate **27** in hand, the key asymmetric step was then investigated. The optimal conditions shown in Table 1 worked well for variously functionalized arylboronic acids with selectivities in a range of 90-95% ee, thus allowing the parallel synthesis of chiral β -aryl ester derivatives (**28a-e**). It was interesting that neither the substituents on the pyridyl ring nor the two nitrogens of **27** significantly affected the yields or enantioselectivities. They were comparable or even higher than those of unsaturated esters shown in Table 2. The absolute configurations of **28e** thus obtained by the (*R,R*)-chiraphos complex was established to be *S* by the specific rotation reported for (*S*)-**28e**.³³ Thus, the product was produced by the same mode of face selection same as that discussed in the later section (Figure 3). In five steps, **28e** completes a formal synthesis of one of Merck-Banyu's antagonists (**8**).³²

<<Scheme 5>>

2.3 DFT computational study on enantioselection

The catalytic cycle of rhodium(I)-catalyzed 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds in aqueous media involves (i) transmetalation of an arylboronic acid to a HO-[Rh] complex (**29**) giving an Ar'-[Rh] species (**30**), (ii) insertion of alkene into the Ar'-Rh bond (**31**) to yield a rhodium enolate (**32**) and finally (iii) formation of an addition product (**4**) and regeneration of **29** via hydrolysis of the rhodium enolate intermediate with water.^{3j}

<<Figure 2>>

Thus, absolute configuration and enantioselectivity can be determined at the insertion step of alkenes into an arylrhodium(I)-phosphine intermediate (**31**). There is a precedent for the X-ray structure of a rhodium(I)-chiraphos complex; however, the solid-state structure of such a conformationally flexible complex, in general, is not reliable for the mechanism of enantioselection since the intermediate conformation differs from the structure of the catalyst precursor. Thus, the mode of a coordination of (*E*)-4-phenyl-3-buten-2-one to the [Rh(Ph)(*S,S*-chiraphos)] intermediate was calculated, *i.e.*, the reaction stage directly preceding the stereodetermining insertion step by DFT computations at the B3LYP/LANL2DZ level of theory. The four modes of coordination of the enone substrate to the current phenylrhodium(I) intermediate are shown in Scheme 5. Two stable adducts between [Pd(Ph)(*S,S*-chiraphos)] and (*E*)-4-phenyl-3-buten-2-one located computationally are shown in **33** and **35**, which are skewed 28.9° and 127°, respectively, from the orientation required for insertion of an enone (**34** and **36**). Although both *si*- and *re*-coordination of the substrate is preferred thermodynamically without significant steric interaction, only the precursor of the experimentally observed enantiomer giving an *S* product has a low energy barrier (**34**, 20.8 kcal/mol) for parallel coordination of the C-C double bond to the Pd-P bond. In mode **34**, the two phenyl groups on rhodium and phosphine atoms constitute a planar free space for coordination of an enone to the metal center and the upper-right area is being blocked by one of the equatorial phenyl groups of the (*S,S*)-chiraphos ligand. The efficiency of chiraphos for planer α,β -unsaturated carbonyl compounds, the participation of Rh-bound aryls in enantioselectivity, and the substituent effect of arylboronic acids can be interpreted by this model (**34**). On the other hand, the coordination of an enone from its opposite *re* face is also probable with an analogous low energy level

(**35**, 1.6 kcal/mol), but the subsequent insertion process can be strongly retarded, because of a high energy barrier for parallel orientation of the C-C double bond and the Ph-Rh bond (**36**, 231.8 kcal/mol).

<<Figure 3>>

3. Conclusion

We have documented the successful use of a traditional chiraphos ligand for rhodium(I)-catalyzed 1,4-additions of arylboronic acids to β -aryl unsaturated ketones and esters for enantioselective synthesis of β -diaryl carbonyl compounds. The high flexibility of this ligand widely applicable even for sterically hindered carbonyl compounds or substrates possessing a donating pyridine nitrogen was demonstrated in two syntheses of selective endothelin antagonists. The DFT calculation revealed that the catalyst has a planar free space for coordination of an enone to the metal center and that one of quadrants is being blocked by an equatorial phenyl group of the chiraphos ligand, thus suggesting high performance in recognition of planar alkene substrates such as β -aryl ketones and esters. This model would present an alkene recognition mechanism with square planar metal-chiraphos complexes.

4. Experimental

4.1 General

All experiments were carried out under an argon or nitrogen atmosphere. HPLC analysis was directly performed with chiral stationary phase column, Chiralcel OD-H, AD, AD-H, OJ-H, and OB-H purchased from Dical Co., Ltd. Phenylboronic acid and (4-methylphenyl)boronic acid were commercially available from Lancaster. Other boronic acids were synthesized from the corresponding Grignard or lithium reagents and trimethyl borate or isopropyl borate.³⁴ [Rh(nbd)₂]BF₄,³⁵ PdCl₂(MeCN)₂³⁶ and PdCl₂(dppf)³⁷ were synthesized by reported procedures. (*S,S*)-chiraphos and (*R,R*)-chiraphos were purchased.

4.2 Asymmetric addition to α,β -unsaturated ketones and esters (Table 2), A general procedure: A solution of [Rh(nbd)₂]BF₄ (3.0 mol%) and (*S,S*)-chiraphos (3.3 mol%) in 1,4-dioxane (3.0 mL) and water (0.1 mL) was stirred for 15 min at room temperature under N₂ atmosphere. Alkene (0.5 mmol), aqueous KOH (0.4 mL, 1.25 M), and arylboronic acid (1.5 mmol) were then added. The mixture was stirred at the temperature shown in Table 1. The product was purified by column chromatography on silica gel.

Following products were synthesized by the above general method. The spectral data of compounds **4a**,³⁸ **4c**,²⁰ **4d**,²⁰ and **4f**³⁹ were previously reported.

4.2.1 Compound (4b): colorless oil; [α]_D²³ (*c* 0.41, CHCl₃): +1.8; IR (neat): 1486, 1230, 1036, 699, 533 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.10 (s, 3H), 3.14 (d, *J* = 7.3 Hz, 2H), 4.52 (t, *J* = 7.6 Hz, 1H), 5.91 (s, 2H), 6.70-6.74 (m, 3H), 7.17-7.31 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 30.6, 45.7, 49.7, 100.9, 108.2, 108.2, 120.5, 126.5, 127.5, 128.6, 137.8, 143.9, 146.0, 147.7, 206.7; MS(*m/z*) 77 (4.8), 152 (22), 211 (100), 225 (3.2), 268 (44, M⁺); exact mass calcd

for C₁₇H₁₆O₃: 268.1099; found 268.1101.

4.2.2 Compound (4e): colorless oil; $[\alpha]_D^{21}$ (*c* 0.63, CHCl₃): +11; IR (neat): 1252, 1597, 1167, 832, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.67 (d, *J* = 7.3 Hz, 2H), 3.85 (s, 3H), 4.77 (s, 3H), 4.79 (t, *J* = 7.3 Hz, 1H), 6.69-6.72 (m, 1H), 6.80-6.92 (m, 4H), 7.15-7.27 (m, 6H), 7.90-7.94 (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 44.3, 46.0, 55.1 55.4, 111.2, 113.7, 114.0, 120.2, 126.3, 127.8, 128.5, 129.5, 130.3, 144.1, 145.9, 159.6, 163.4, 196.4; MS (*m/z*) 77 (12), 107 (5.8), 197 (22), 211 (36), 346 (51, M⁺); exact mass calcd for C₂₃H₂₂O₃: 346.1569; found 346.1565.

4.2.3 Compound (4g): colorless oil; $[\alpha]_D^{23}$ (*c* 0.52, CHCl₃): +2.2; IR (neat): 1725, 1255, 1141, 769, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.18 (s, 9H), 2.85 (d, *J* = 8.3 Hz, 2H), 3.61 (s, 3H), 4.35 (t, *J* = 8.3 Hz, 1H), 6.59-6.62 (m, 1H), 6.69-6.75 (m, 2H), 7.03-7.17 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 27.9, 41.9, 47.3, 54.9, 80.3, 111.4, 113.7, 120.0, 126.3, 127.6, 128.3, 129.3, 143.3, 145.1, 159.5, 170.9; MS (*m/z*) 197 (100), 210 (30.2), 211 (7.8), 239 (12.7), 312 (6.0, M⁺); exact mass calcd for C₂₀H₂₄O₃: 312.1725; found 312.1719.

4.2.4 Compound (4h): colorless oil; $[\alpha]_D^{23}$ (*c* 0.21, CHCl₃): +0.71; IR (neat): 1253, 1138, 1028, 700, 511cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.28 (s, 9H), 2.93 (d, *J* = 8.3 Hz, 2H), 3.80 (s, 6H), 4.43 (t, *J* = 8.1 Hz, 1H), 6.75-6.80 (m, 3H), 7.13-7.27 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 27.8, 42.1, 46.8, 55.5,

80.2, 110.9, 111.1, 119.3, 126.2, 127.4, 128.2, 136.0, 143.6, 147.4, 148.6, 170.8; MS (m/z) 57 (10.1), 227 (100), 269 (5.9), 285 (78.1), 342 (34.6, M^+); exact mass calcd for $C_{21}H_{26}O_4$: 342.1831; found 342.1827.

4.2.5 Compound (4i): colorless oil; $[\alpha]_D^{22}$ (c 0.43, $CHCl_3$): +0.35; IR (neat): 1243, 1141, 1037, 699, 515 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.91-2.93 (m, 2H), 4.41 (t, $J = 8.1$ Hz, 1H), 5.87 (s, 2H), 6.70-6.75 (m, 3H), 7.17-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 42.1, 47.0, 80.4, 100.8, 108.0, 108.2, 120.5, 126.4, 127.5, 128.4, 137.5, 143.6, 146.0, 147.6, 170.9; MS (m/z) 57 (6.8), 211 (100), 253 (9.7), 269 (43.9), 326 (15.4, M^+); exact mass calcd for $C_{20}H_{22}O_4$: 326.1518; found 326.1519.

4.2.6 Compound (4j): white solids; mp 76-77°C; $[\alpha]_D^{23}$ (c 0.18, $CHCl_3$): +3.8; IR (neat): 1716, 1149, 812, 696, 533 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 2.88 (s, 6H), 2.92 (d, $J = 8.8$ Hz, 2H), 4.38 (t, $J = 8.3$ Hz, 1H), 6.63-6.67 (m, 2H), 7.05-7.27 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8, 40.6, 42.3, 46.5, 80.2, 112.7, 126.1, 127.7, 128.2, 128.3, 131.7, 144.3, 149.2, 171.3; MS (m/z) 57 (6.6), 210 (100), 224 (3.9), 268 (56.0), 325 (29.0, M^+); exact mass calcd for $C_{21}H_{27}NO_2$: 325.2042. Found: 325.2044; anal. calcd for $C_{21}H_{27}NO_2$: C, 77.50%; H, 8.36%. Found: C, 77.55%; H, 8.35%.

4.2.7 Compound (4k): white solids; mp 54-55 °C; $[\alpha]_D^{22}$ (c 0.41, $CHCl_3$): +1.3; IR (neat): 1247, 1511, 1176, 1142, 1036 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$):

δ 1.19 (s, 9H), 2.82 (d, $J = 8.3$ Hz, 2H), 3.62-3.63 (m, 6H), 4.31 (t, $J = 8.3$ Hz, 1H), 6.59-6.62 (m, 1H), 6.67-6.73 (m, 4H), 7.04-7.09 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 27.7, 42.1, 46.5, 54.9, 55.0, 80.3, 111.3, 113.6, 113.7, 119.9, 128.5, 129.3, 135.5, 145.5, 158.0, 159.5, 171.0; MS (m/z): 57 (6.0), 227 (100), 269 (6.4), 285 (54), 342 (8.0, M^+); exact mass calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4$: 342.1831. Found: 342.1826; anal. calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4$: C, 73.66%; H, 7.65%. Found: C, 73.81%; H, 7.69%.

4.2.8 Compound (4l): colorless oil; $[\alpha]_{\text{D}}^{23}$ (c 0.47, CHCl_3): +21; IR (neat): 1490, 1242, 1142, 752, 696 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.26 (s, 9H), 2.89 (dd, $J = 8.7, 15$ Hz, 1H), 2.96 (dd, $J = 7.8, 15$ Hz, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.87 (t, $J = 8.3$ Hz, 1H), 6.66-6.69 (m, 1H), 6.78-6.88 (m, 4H), 7.11-7.19 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 27.7, 40.4, 40.8, 54.9, 55.2, 80.0, 110.5, 111.1, 113.9, 120.2, 120.3, 127.4, 127.7, 128.9, 131.7, 144.9, 156.7, 159.3, 171.2; MS (m/z) 57 (21), 227 (29), 241 (9.8), 269 (22), 342 (5.0, M^+); exact mass calcd for $\text{C}_{21}\text{H}_{26}\text{O}_4$: 342.1831. Found: 342.1843.

4.2.9 Compound (4m): colorless oil; $[\alpha]_{\text{D}}^{21}$ (c 0.53, CHCl_3): -1.0; IR (neat): 1726, 1255, 1142, 779, 697 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 1.19 (s, 9H), 2.18 (s, 3H), 2.83 (d, $J = 7.8$ Hz, 2H), 3.63 (s, 3H), 4.36 (t, $J = 8.1$ Hz, 1H), 6.59-6.62 (m, 1H), 6.69-6.74 (m, 2H), 6.96-7.11 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 27.8, 42.0, 46.9, 55.0, 80.3, 111.4, 113.7, 120.0, 127.5, 129.0, 129.3, 135.8, 140.4, 145.4, 159.5, 171.0; MS (m/z) 57 (21), 211 (100), 225 (3.9), 253 (7.9), 269 (16), 326 (4.9, M^+); exact mass calcd for $\text{C}_{21}\text{H}_{26}\text{O}_3$: 326.1882. Found: 326.1887.

4.2.10 Compound (4n): colorless oil; $[\alpha]_D^{22}$ (c 0.55, CHCl₃): +2.5; IR (neat): 1323, 1257, 1113, 1068, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.29 (s, 9H), 2.96 (t, $J = 8.3$ Hz, 2H), 3.74 (s, 3H), 4.52 (t, $J = 8.1$ Hz, 1H), 6.73-6.82 (m, 3H), 7.18-7.23 (m, 1H), 7.36 (d, $J = 8.3$ Hz, 2H), 7.52 (d, $J = 8.3$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 27.7, 41.5, 47.1, 55.0, 80.7, 111.7, 113.8, 119.9, 122.8, 125.3, 125.3, 128.0, 129.6, 144.2, 147.5, 159.7, 170.5; MS (m/z) 57 (24), 265 (64), 279 (9.9), 307 (18), 323 (7.2), 380 (6.0, M⁺); exact mass calcd for C₂₁H₂₃F₃O₃: 380.1599. Found: 380.1608.

4.2.11 Compound (4o): white solids; mp 72°C; $[\alpha]_D^{23}$ (c 0.51, CHCl₃): -18; IR (neat): 1719, 1244, 1140, 758, 712 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.16 (s, 9H), 2.89-2.99 (m, 2H), 3.60 (s, 3H), 4.53 (t, $J = 8.1$ Hz, 1H), 6.59-6.61 (m, 1H), 6.73-6.77 (m, 2H), 7.07 (t, $J = 7.8$ Hz, 1H), 7.21-7.33 (m, 3H), 7.59-7.68 (m, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 27.8, 41.8, 47.3, 55.0, 80.4, 111.5, 113.9, 120.2, 125.4, 125.6, 125.9, 126.5, 127.5, 127.7, 128.1, 129.4, 132.2, 133.3, 140.8, 145.0, 159.6, 171.0; MS (m/z) 57 (9.0), 247 (100), 261 (3.2), 289 (8.3), 305 (32), 362 (12, M⁺); exact mass calcd for C₂₄H₂₆O₃: 362.1882. Found: 362.1879; anal. calcd for C₂₄H₂₆O₃: C, 79.53%; H, 7.23%. Found: C, 79.62%; H, 7.37%.

4.2.12 Compound (4p): colorless oil; $[\alpha]_D^{22}$ (c 0.52, CHCl₃): +9.7; IR (neat): 1723, 1257, 1143, 715, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.21 (s, 9H), 2.84-2.94 (m, 2H), 3.68 (s, 3H), 4.39 (t, $J = 8.3$ Hz, 1H), 6.66-6.75 (m, 3H), 7.10-7.21 (m, 2H), 7.45-7.47 (m, 1H), 8.36-8.37 (m, 1H), 8.48-8.51 (m, 1H); ¹³C

NMR (100 MHz, CDCl₃): δ 27.8, 41.5, 44.9, 55.1, 80.9, 111.8, 113.7, 119.9, 123.3, 129.6, 135.0, 138.8, 143.9, 147.9, 149.3, 159.7, 170.4; MS (*m/z*) 57 (35), 198 (44), 212 (100), 240 (12), 313 (7.0, M⁺); exact mass calcd for C₁₉H₂₃NO₃: 313.1678. Found: 313.1674.

4.3 SmithKline Beecham's antagonist (Scheme 3)

4.3.1 Toluene-4-sulfonic acid 4-bromo-3-(2-methoxymethoxyethoxy)phenyl ester (12).^{40a} A mixture of 4-bromoresorcinol (**11**) (5.5 g, 29.1 mmol), K₂CO₃ (14g, 101 mmol) and *p*-TsCl (6 g, 35.7 mmol) in acetone (100 mL) was refluxed for 21 h. The solvent was removed in vacuo and 1-chloro-2-methoxymethoxyethane (5.5 g, 44.4 mmol), K₂CO₃ (5.5 g, 39.9 mmol), NaI (2.9 g, 19.3 mmol) and DMF (100 mL) were then added. The resulting mixture was stirred for 24 h at 90 °C. The product (**12**) was isolated by chromatography on silica gel (hexane/EtOAc = 10/1 to 5/1) (11.3 g, 90 %) colorless viscous oil; ¹H NMR (CDCl₃, 400 MHz) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.72 (s, 2H), 4.06–4.08 (m, 2H), 3.89–3.91 (m, 2H), 3.40 (s, 3H), 2.45 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.7, 149.4, 145.6, 133.3, 131.9, 129.8, 128.5, 115.4, 110.4, 108.1, 96.5, 68.8, 65.3, 55.3, 21.7; IR (neat) 2938, 2885, 1594, 1477, 1372, 1273, 1191, 1179, 1143, 1117, 1036, 983, 810, 784, 724, 661, 549 cm⁻¹; MS (*m/z*): 45 (87), 91 (100), 155 (67), 430 (M⁺, 18), 432 (M⁺+2, 19); exact mass calcd for C₁₇H₁₉BrO₆S: 430.0085. Found: 430.0087.

4.3.2 1-Bromo-4-methoxy-2-(2-methoxymethoxyethoxy)benzene (13). A solution of **12** (8.3 g, 19.2 mmol) and KOH (5.9 g, 105 mmol) in EtOH (250 mL)

and water (30 mL) was heated under reflux for 2 h. The solvent was evaporated to reduce the volume. 4 M HCl was added at room temperature until pH 4. The product (**13**) extracted with Et₂O was isolated by chromatography on silica gel (hexane/EtOAc=25/1 to 5/1) (4.1 g, 74 %). colorless oil; ¹H NMR (CDCl₃, 400 MHz) δ 7.39 (d, *J* = 8.7 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.74 (s, 2H), 4.15–4.17 (m, 2H), 3.92–3.95 (m, 2H), 3.78 (s, 3H), 3.41 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 160.0, 155.8, 133.1, 106.3, 103.0, 101.1, 96.6, 68.5, 65.5, 55.5, 55.3; IR (neat, cm⁻¹) 2937, 2885, 1582, 1485, 1442, 1304, 1281, 1203, 1168, 1116, 1060, 1022, 917, 823, 608; MS (*m/z*): 45 (100), 89 (47), 202 (7), 290 (M⁺,16), 292 (M⁺+2, 16); exact mass calcd for C₁₁H₁₅BrO₄: 290.0153. Found: 290.0155.

4.3.3 4-Methoxy-2-(2-methoxymethoxyethoxy)phenylboronic acid (14). A solution of **13** (4.4 g, 15 mmol) in THF (5 mL) was dropwise added to Mg turnings (368 mg, 16 mmol) to prepare Grignard solution. To this solution was then added (MeO)₃B (2 mL, 18 mmol in 10 mL of THF) at -78 °C. The resulting mixture was allowed to stir overnight, treated with dil. HCl, extracted with Et₂O, and finally washed with brine. A pure boronic acid (**14**) was isolated by recrystallization (2.8 g, 11 mmol, 73% yield). white solids; mp 67-68 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.76 (d, *J* = 8.3 Hz, 1H), 6.57 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 5.87 (s, 2H), 4.73 (s, 2H), 4.20–4.22 (m, 2H) 3.91–3.93 (m, 2H), 3.86 (s, 3H), 3.44 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 165.0, 163.4, 138.0, 105.8, 99.1, 96.5, 67.5, 65.7, 55.4, 55.3; anal. calcd for C₁₁H₁₇BO₆: C, 51.60%; H, 6.69%. Found: C, 51.45%; H, 6.62%.

4.3.4 2-(2-*tert*-Butoxycarbonylvinyl)-5-propoxybenzoic acid methyl ester (17). A solution of 2-bromo-5-hydroxybenzaldehyde (**15**)^{40b} (6 g, 30.0 mmol), 1-bromopropane (4.5 mL, 50.0 mmol) and K₂CO₃ (6.6 g, 48.0 mmol) in EtOH (60 mL) and water (20 mL) was heated under reflux for 17 h. The solvent was then evaporated and the residue was filtrated through silica gel pad with hexane/EtOAc (1:1). The combined filtrate was concentrated to dryness.

The crude product was dissolved in acetone (56 mL) and water (18 mL), and slowly treated with KMnO₄ (9.5 g, 60.0 mmol) with stirring on a water bath. After being stirred for 30 min, it was heated for 1 h at 70 °C. The reaction mixture was passed through Celite 545, rinsed with acetone, and then concentrated to a small volume. The reaction mixture was extracted with AcOEt and the organic layer was washed with dil. HCl. The organic layer was dried over MgSO₄ and, finally, concentrated to dryness.

The crude product was dissolved in MeOH (100 mL) and H₂SO₄ (2 mL), and heated under reflux for 6 h using Dean-Stark apparatus. The solution was concentrated to a small volume and extracted with Et₂O. The organic layer was washed successively with brine and water. The organic layer was dried over MgSO₄ and concentrated to dryness to give crude **16** (6.3 g).

A solution of the crude **16**, PdCl₂(MeCN)₂ (204 mg, 0.79 mmol), P(*o*-tol)₃ (458 mg, 1.50 mmol) and *tert*-butyl acrylate (3.6 mL, 24.9 mmol) in DMF (23 mL) and Et₃N (7.6 mL) was stirred at 100 °C for 10 h. The product (**17**) was isolated by recrystallization from pentane (4 steps from **15**, 5.3 g, 55 %). white solids; mp 67-68 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.26 (d, *J* = 15.8 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.03 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.18 (d, *J* = 8.3 Hz, 1H), 3.97 (t, *J* = 6.8, 7.3 Hz, 2H) 3.93 (s, 3H), 1.83 (sext, *J* = 6.8, 7.3 Hz, 2H), 1.53 (s, 9H), 1.04 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100

MHz) δ 167.3, 166.2, 159.8, 141.8, 131.4, 129.0, 128.2, 120.8, 118.8, 115.7, 80.3, 69.8, 52.4, 28.2, 22.4, 10.4; IR (neat) 2975, 1719, 1707, 1601, 1499, 1296, 1238, 1142, 1065, 982, 866, 831, 784, 593, 566 cm^{-1} ; MS (m/z): 177 (39), 219 (100), 320 (M^+ , 13); exact mass calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$: 320.1624. Found: 320.1626; anal. calcd for $\text{C}_{18}\text{H}_{24}\text{O}_5$: C, 67.48%; H, 7.55%. Found: C, 66.43%; H, 7.38%.

4.3.5 (-)-(S)-2-(1-Benzo[1,3]dioxol-5-yl-2-*tert*-butoxycarbonylethyl)-5-propoxy- benzoic acid methyl ester (18). To the round-bottom-flask charged with $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ (39.2 mg, 3.0 mol%), (*R,R*)-chiraphos (49.2 mg, 3.3 mol%) and **17** (1.2 g, 3.5 mmol) was added 1,4-dioxane (10.5 mL) and water (0.7 mL). After being stirred for 15 min at ambient temperature, a KOH solution (1.25 M in H_2O , 4.2 mL) and 3,4-(methylenedioxy)phenylboronic acid (970 mg, 5.3 mmol) were added. The mixture was stirred at 60 $^\circ\text{C}$ for 20 h. The mixture was filtered through a silica and MgSO_4 pad, and the pad was then rinsed with hexane/EtOAc (1:1). The product (**18**, 1.36 g, 88%) was isolated by chromatography on silica gel with hexane/EtOAc (20 :1). 89 %ee (Chiralcel AD-H, *n*-hexane/2-propanol=9/1). colorless oil; $[\alpha]_{\text{D}}^{22} = -46.5^\circ$ (*c* 0.70, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 7.30 (d, $J = 2.9$ Hz, 1H), 7.22 (d, $J = 8.8$ Hz, 1H), 6.97 (dd, $J = 8.8, 2.9$ Hz, 1H), 6.74–6.86 (m, 3H), 5.87 (s, 2H), 5.31 (t, $J = 8.3$ Hz, 1H), 3.90 (t, $J = 6.3, 6.8$ Hz, 2H), 3.87 (s, 3H), 2.87 (dd, $J = 3.4, 8.3$ Hz, 2H), 1.76 (sex, 6.8, 7.3 Hz, 2H), 1.01 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.8, 168.0, 157.0, 147.5, 145.7, 137.8, 136.2, 131.0, 129.4, 120.6, 118.3, 115.7, 108.6, 107.8, 100.7, 80.3, 69.6, 52.0, 42.6, 41.3, 27.8, 22.4, 10.4; IR (neat) 2971, 1720, 1487, 1436, 1285, 1216, 1143, 1073, 1038, 933, 803 cm^{-1} ; MS (m/z): 57 (12), 253 (20), 267 (18), 295 (65), 309 (41), 327 (40), 340 (54), 354 (100), 367 (27), 386 (68), 442 (M^+ , 11); exact mass calcd for $\text{C}_{25}\text{H}_{30}\text{O}_7$: 442.1992.

Found: 442.1995.

4.3.6 1-Benzo[1,3]dioxol-5-yl-3-oxo-5-propoxyindan-2-carboxylic acid *tert*-butyl ester (19). A solution of NaHMDS (1M, 3.6 mL) in THF was slowly added to a solution of **18** (797 mg, 1.8 mmol) in THF (18 mL) at $-78\text{ }^{\circ}\text{C}$. The mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ and for 3 h at $-15\text{ }^{\circ}\text{C}$. The reaction was quenched with sat. aqueous NH_4Cl . Isolation by chromatography on neutral silica gel with hexane/EtOAc (30/1 to 20/1) gave **19** (560 mg, 76 % yield). pale yellow oil; ^1H NMR (CDCl_3 , 400 MHz) δ 7.15–7.21 (m, 3H), 6.75 (d, $J = 7.8\text{ Hz}$, 1H), 6.65 (dd, $J = 1.4, 7.8\text{ Hz}$, 1H), 6.53 (s, 1H), 5.93 (s, 1H), 4.77 (d, $J = 4.4\text{ Hz}$, 1H), 3.96 (t, $J = 6.3, 6.8\text{ Hz}$, 1H), 3.50 (d, $J = 4.4\text{ Hz}$, 2H), 1.82 (sext, 6.8, 7.3 Hz, 2H), 1.49 (s, 9H), 1.04 (t, $J = 7.3\text{ Hz}$, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 167.5, 159.4, 148.8, 148.1, 146.7, 136.4, 136.2, 127.3, 125.3, 121.1, 108.4, 107.8, 105.6, 101.1, 82.1, 69.9, 65.3, 47.7, 28.2, 22.3, 10.4; IR (neat) 2971, 1708, 1486, 1440, 1273, 1228, 1145, 1037, 931, 842, 823, 801, 766 cm^{-1} ; MS (m/z): 59 (81), 149 (24), 266 (39), 308 (98), 336 (100), 354 (81), 410 (M^+ , 33); exact mass calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6$: 410.1729. Found: 410.1733.

4.3.7 1-Benzo[1,3]dioxol-5-yl-5-propoxy-3-trifluoromethanesulfonyloxy-1H-indene- 2-carboxylic acid *tert*-butyl ester (20). A solution of **19** (324 mg, 0.79 mmol) and NaH (38 mg, 1.58 mmol) in ether (7.9 mL) was stirred for 45 min at $-5\text{ }^{\circ}\text{C}$. Tf_2O (0.22 mL, 1.18 mmol) was added and the mixture was then stirred for 1 h at $-5\text{ }^{\circ}\text{C}$. The product was extracted with Et_2O and the organic layer was washed successively with brine and water. Isolation by chromatography

on silica gel (hexane/EtOAc=30/1 to 15/1) gave **20** (390 mg, 72 % yield). white solids; mp 105-106 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.10 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 6.91 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.67 (dd, *J* = 1.4, 7.8 Hz, 1H), 6.44 (d, *J* = 1.4 Hz, 1H), 5.90 (dd, *J* = 1.4, 7.3 Hz, 1H), 4.77 (s, 1H), 3.93 (t, *J* = 6.8 Hz, 2H), 1.82 (sext, *J* = 6.8, 7.3 Hz, 2H), 1.40 (s, 9H), 1.04 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 161.0, 159.2, 150.3, 147.7, 146.7, 138.3, 135.5, 130.7, 130.5, 125.3, 121.3, 119 (q, *J* = 320 Hz), 117.1, 108.3, 107.5, 105.2, 100.9, 82.5, 69.8, 52.5, 27.8, 22.4, 10.4; IR (neat) 2966, 1702, 1490, 1423, 1337, 1249, 1202, 1124, 1040, 860, 808, 601 cm⁻¹; MS (*m/z*): 57 (69), 309 (100), 325 (55), 353 (45), 542 (M⁺, 60); exact mass calcd for C₂₅H₂₅O₈F₃S: 542.1222. Found: 542.1211; anal. calcd for C₂₅H₂₅O₈F₃S: C, 55.35%; H, 4.64%. Found: C, 54.29%; H, 4.58%.

4.3.8 1-Benzo[1,3]dioxol-5-yl-3-[4-methoxy-2-(2-methoxymethoxyethoxy)phenyl]-5-propoxy-1H-indene-2-carboxylic acid *tert*-butyl ester (21). A solution of **20** (155 mg, 0.29 mmol), boronic acid **14** (80.5 mg, 0.31 mmol) and K₂CO₃ (59 mg, 0.43 mmol) in toluene (1.1 mL) and water (0.19 mL) was stirred for 4 h at 70 °C. The mixture was filtered through a silica gel and MgSO₄ pad, and the pad was then rinsed with hexane/EtOAc (1:1). The coupling product (**21**) was isolated by chromatography on silica gel (hexane/EtOAc=5/1 to 3/1) (155 mg, 90 % yield). pale yellow oil; ¹H NMR (CDCl₃, 400 MHz) δ 7.32 (d, *J* = 8.3 Hz, 0.44H), 7.13 (d, *J* = 8.3 Hz, 0.56H), 7.07 (d, *J* = 8.3 Hz, 1H), 5.88–6.82 (m, 7H), 5.87 (m, 2H), 4.79 (s, 0.44H), 4.78 (s, 0.56H), 4.46–4.48 (m, 2H), 4.05–4.15 (m, 2H), 3.86 (s, 3H), 3.70–3.83 (m, 4H), 3.19 (s, 1.3H), 3.13 (s, 1.7H) 1.73–1.75 (m, 2H), 1.17–1.19 (m, 9H), 0.96–1.00 (m, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 163.6, 160.74, 160.70, 158.7, 156.9, 149.2, 147.5, 147.4, 146.1, 146.0, 145.0, 141.0, 140.8, 139.6, 139.2, 133.8, 133.5, 130.9,

130.8, 124.3, 124.2, 121.28, 121.25, 117.0, 116.4, 114.6, 114.4, 108.4, 108.2, 108.1 108.0, 107.7, 107.4, 104.6, 100.7, 100.6, 99.8, 99.7, 96.49, 96.46, 79.8, 79.7, 69.6, 67.8, 67.6, 65.9, 65.7, 55.37, 55.33, 55.2, 54.9, 27.9, 27.8, 22.5, 10.5 ; IR (neat) 2932, 1694, 1595, 1578, 1502, 1484, 1440, 1352, 1242, 1220, 1151, 1111, 1035, 919, 799, 782 cm^{-1} ; MS(m/z): 441 (35), 472 (86), 503 (96), 530 (100), 604 (M^+ , 42); exact mass calcd for $\text{C}_{35}\text{H}_{40}\text{O}_9$: 604.2672. Found: 604.2674.

4.3.9 1-Benzo[1,3]dioxol-5-yl-3-[4-methoxy-2-(2-methoxymethoxyethoxy)phenyl]-5-propoxyindan-2-carboxylic acid *tert*-butyl ester (22). The coupling product (**21**, 155 mg, 0.26 mmol) was dissolved in EtOH (1.3 mL) and treated with 20 wt% $\text{Pd}(\text{OH})_2/\text{C}$ (8.9 mg) for 5 h at 60 °C under hydrogen atmosphere (0.3 MPa). The mixture was filtered through Celite 545 and the pad was rinsed with EtOH. The product (**22**) was isolated by chromatography on silica gel (hexane/EtOAc=5/1 to 2/1) (140 mg, 90 % yield). colorless oil; ^1H NMR (CDCl_3 , 400 MHz) δ 7.37 (d, $J = 8.3$ Hz, 1H), 7.09 (d, $J = 8.3$ Hz, 1H), 6.90 (s, 1H), 6.88–6.90 (m, 2H), 6.79–6.80 (m, 2H), 6.74 (d, $J = 7.8$ Hz, 1H), 6.48 (m, 1H), 6.44 (dd, $J = 2.4, 8.7$ Hz, 1H), 5.90 (dd, $J = 1.4, 11.7$ Hz, 1H), 5.05 (d, $J = 7.8$ Hz, 1H), 4.75 (s, 2H), 4.66 (d, $J = 7.8$ Hz, 1H), 4.11–4.23 (m, 2H), 3.83–3.99 (m, 5H), 3.78 (s, 3H), 3.43 (s, 3H), 1.78 (sext, $J = 6.8, 7.3$ Hz, 2H), 1.03 (t, $J = 7.3$ Hz, 3H), 0.78 (s, 9H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 170.2, 159.5, 158.4, 158.1, 147.0, 146.1, 145.7, 136.1, 133.3, 130.9, 125.2, 123.0, 119.8, 112.9, 111.2, 110.4, 107.6, 104.0, 100.7, 98.9, 96.5, 79.2, 69.7, 67.7, 66.0, 58.8, 55.3, 55.2, 52.3, 46.0, 27.4, 22.6, 10.5; IR (neat) 2933, 1727, 1609, 1488, 1441, 1366, 1283, 1248, 1229, 1198, 1145, 1113, 1036, 917, 815, 796, 731 cm^{-1} ; MS (m/z): 251 (24), 321 (80), 337 (53), 473 (40), 487 (100), 505 (49), 606 (M^+ , 22); exact mass calcd for $\text{C}_{35}\text{H}_{42}\text{O}_9$: 606.2828. Found: 606.2824.

4.4 Merck-Banyu's antagonists (Scheme 4)

4.4.1 3-[6-Benzyl-isopropyl-amino]-2-chloro-pyridine-3-yl]acrylic acid *tert*-butyl ester (26)³²: To the vessel was added **25** (5.0 g, 17.3 mmol),³² THF (75 mL), and *tert*-butyl diethylphosphonoacetate (4.6 g, 18.2 mmol), and the mixture was then stirred for 5 h at 40 °C. The completion of the reaction was confirmed by HPLC. *i*-PrOAc (50 mL) and aqueous NaOH (0.5 M, 20 mL) were added at ambient temperature. The resulting aqueous layer was extracted again with *i*-PrOAc (20 mL). The combined organic layers were washed with brine and concentrated to ca. 20 mL. To this slurry was added *n*-heptane (50 mL) to precipitate the product. The compound **26** was collected by filtration and washed with *n*-heptane/*i*-PrOAc (5/1, 20 mL). The wet solid was dried under reduced pressure at 40 °C to afford 5.7 g of slightly yellow solids (85% yield). mp 103–105 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.86 (d, *J* = 15.9 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.18–7.35 (m, 5H), 6.20 (d, *J* = 8.8 Hz, 1H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.10 (sept, *J* = 6.7 Hz, 1H), 4.56 (s, 2H), 1.52 (s, 9H), 1.20 (t, *J* = 6.7 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 166.4, 158.3, 150.3, 138.9, 138.4, 136.6, 128.7, 127.0, 126.2, 117.6, 116.2, 106.1, 80.3, 46.9, 46.5, 28.2, 20.2; IR (KBr) 2975, 1702, 1601, 1532, 1485, 1363, 1140, 981, 935, 862, 832, 803, 719, 696, 681, 635, 609, 463 cm⁻¹; exact mass calcd for C₂₂H₂₈ClN₂O₂ (M⁺+H): 387.1839. Found: 387.1867.

4.4.2 6-(*N*-Benzyl-*N*-isopropylamino)-3-(2-*tert*-butoxycarbonylvinyl)pyridine-2- carboxylic acid butyl ester (27): To the vessel were added **26** (5 g, 12.9

mmol), AcONa•3H₂O (2.6 g, 19.1 mmol), toluene (19 mL), and *n*-BuOH (38 mL). The mixture was degassed three times by vacuum/N₂ cycle. Pd(OAc)₂ (145 mg, 5 mol%) and DPPF (536 mg, 7.5 mol%) were then added, and the vessel was again degassed twice. The mixture was stirred at 120 °C for 16 h. After the completion of the reaction was confirmed by HPLC, the vessel was cooled to ambient temperature. The insoluble material was filtered through Celite and rinsed with EtOAc. The product was isolated by column chromatography (*n*-heptane/EtOAc = 20/1 to 10/1) to give **27** as oil. The oil was dissolved in EtOAc (30 mL) and was treated with activated carbon (Darco KB-B, 250 mg) for 2 h. Filtration through Celite and concentration to dryness under reduced pressure gave 5.1 g (87% yield) of **27** as yellow viscous oil. *R_f* = 0.65 (*n*-heptane/ethyl acetate=2/1); ¹H NMR (CDCl₃, 500 MHz) δ 7.91 (d, *J* = 15.8 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.21–7.31 (m, 5H), 6.40 (d, *J* = 9.1 Hz, 1H), 6.07 (d, *J* = 15.8 Hz, 1H), 5.13 (bt, *J* = 6.2 Hz, 1H), 4.59 (s, 2H), 4.37 (t, *J* = 6.6 Hz, 2H), 1.73–1.79 (m, 2H), 1.51 (s, 9H), 1.43–1.52 (m, 2H), 1.21 (d, *J* = 6.7 Hz, 6H), 0.96 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 166.8, 166.3, 158.0, 148.3, 139.1, 138.8, 135.7, 128.6, 126.9, 126.3, 118.3, 117.8, 109.3, 80.1, 65.5, 46.7, 46.6, 30.7, 28.3, 28.2, 20.2, 19.2, 13.7; IR (neat) 2972, 1712, 1597, 1547, 1484, 1143, 1075, 982, 870, 814, 732, 609 cm⁻¹; exact mass calcd for C₂₇H₃₇N₂O₄ (M⁺+H): 453.2753. Found: 453.2714.

4.4.3 Rh-catalyzed asymmetric addition to 27: To a round-bottom-flask was added 1,4-dioxane (2.0 mL) and water (0.5 mL), and the flask was then degassed three times by vacuum/N₂ cycle. To this solution was added [Rh(nbd)₂]BF₄ (3.0 mol%) and (*R,R*)-chiraphos (3.3 mol%) and the flask was again degassed twice. After the mixture was aged for 15 min at ambient temperature, unsaturated ester (**27**, 0.4 mmol) in 1,4-dioxane (1.0 mL), KOH (0.8 mmol),

and arylboronic acid (1.2 mmol) were added. The flask was degassed twice. The mixture was heated to 50 °C for 14 h with vigorous stirring. The product was purified by column chromatography on silica gel.

The following compounds were synthesized by the above general procedure.

4.4.4 *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-phenylpropanoate (28a). 90% yield; $R_f = 0.61$ (*n*-heptane/ethyl acetate = 2/1); 89.8 %ee (Chiralcel OD-H, *n*-hexane/2-propanol=90:10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28a**: 8.3 min, t_R for enantiomer: 9.7 min); $[\alpha]_D^{20} = -40.2^\circ$ (*c* 3.01, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.12–7.28 (m, 11H), 6.31 (d, $J = 9.0$ Hz, 1H), 5.04 (sept, $J = 6.7$ Hz, 1H), 4.96 (t, $J = 8.2$ Hz, 1H), 4.48 (s, 2H), 2.87 (d, $J = 8.2$ Hz, 2H), 1.68–1.76 (m, 2H), 1.40–1.48 (m, 2H), 1.25 (s, 9H), 1.16 (d, $J = 6.7$ Hz, 6H), 0.94 (t, $J = 7.3$ Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 170.8, 167.6, 156.2, 146.4, 143.1, 139.8, 137.5, 128.4, 128.3, 127.8, 127.6, 126.6, 126.3, 125.7, 109.3, 80.4, 65.1, 46.6, 46.2, 42.0, 41.0, 30.6, 27.9, 27.8, 20.2, 20.1, 19.2, 13.7; exact mass calcd for C₃₃H₄₃N₂O₄ (M⁺+H): 531.3223. Found: 531.3319.

4.4.5 *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(4-methoxyphenyl)propanoate (28b). 89% yield; $R_f=0.48$ (*n*-heptane/ethyl acetate=2/1); 92.1 %ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28b**: 9.7 min, t_R for enantiomer: 13.7 min); $[\alpha]_D^{20} = -28.4^\circ$ (*c* 2.125, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.15–7.28 (m, 8H), 6.78 (d, $J = 8.7$ Hz, 2H), 6.31 (d, $J = 8.9$ Hz, 1H),

5.04 (sept, $J = 6.7$ Hz, 1H), 4.89 (t, $J = 8.3$ Hz, 1H), 4.48 (s, 2H), 4.30–4.34 (m, 2H), 3.74 (s, 3H), 2.83 (d, $J = 8.3$ Hz, 2H), 1.72 (m, 2H), 1.38–1.50 (m, 2H), 1.26 (s, 9H), 1.16 (d, $J = 6.7$ Hz, 6H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.8, 167.6, 158.0, 156.2, 146.4, 139.8, 137.4, 135.3, 128.7, 128.4, 126.6, 126.3, 126.0, 113.7, 109.3, 80.4, 65.0, 55.2, 46.6, 46.2, 42.1, 40.3, 30.6, 27.9, 27.8, 20.2, 20.1, 19.2, 13.7; IR (KBr) 2972, 1730, 1600, 1553, 1481, 1146, 1077, 1037, 961, 843, 731, 697 cm^{-1} ; exact mass calcd for $\text{C}_{34}\text{H}_{45}\text{N}_2\text{O}_5$ (M^+H): 561.3328. Found: 561.3418.

4.4.6 *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3- pyridinyl]-3-(4-bromo-3-fluorophenyl)propanoate (28c). 82% yield; $R_f = 0.68$ (*n*-heptane/ethyl acetate=2/1); 95.4 %ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28c**: 8.4 min, t_R for enantiomer: 11.8 min); $[\alpha]_{\text{D}}^{20} = -32.8^\circ$ (c 1.145, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 7.40 (dd, $J = 7.5, 8.0$ Hz, 1H), 7.18–7.28 (m, 6H), 7.03 (dd, $J = 1.8, 9.9$ Hz, 1H), 6.94 (dd, $J = 1.5, 8.3$ Hz, 1H), 6.34 (d, $J = 9.0$ Hz, 1H), 5.03 (sept, $J = 6.7$ Hz, 1H), 4.98 (t, $J = 8.1$ Hz, 1H), 4.50 (s, 2H), 4.29–4.35 (m, 2H), 2.83 (d, $J = 8.1$ Hz, 2H), 1.68–1.73 (m, 2H), 1.40–1.47 (m, 2H), 1.28 (s, 9H), 1.18 (dd, $J = 1.5, 6.7$ Hz, 6H), 0.94 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 170.3, 167.3, 156.4, 146.3, 139.5, 137.2, 133.2, 128.5, 126.7, 126.3, 124.7, 116.1, 115.9, 109.5, 80.8, 65.2, 46.7, 46.3, 41.5, 40.3, 30.6, 27.8, 20.1, 19.2, 13.7; exact mass calcd for $\text{C}_{33}\text{H}_{41}\text{BrFN}_2\text{O}_4$ (M^+H): 627.2234. Found: 627.2415.

4.4.7 *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3- pyridinyl]-3-(3,4-methylenedioxyphenyl)propanoate (28d). 91% yield; R_f

= 0.52 (*n*-heptane/ethyl acetate=2/1); 89.8 %ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28d**: 10.0 min, t_R for enantiomer: 13.0 min); $[\alpha]_D^{20} = -36.5^\circ$ (*c* 1.76, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.18–7.28 (m, 6H), 6.73 (s, 1H), 6.67–6.72 (m, 2H), 6.32 (d, *J* = 9.0 Hz, 1H), 5.87 (s, 2H), 5.04 (sept, *J* = 6.7 Hz, 1H), 4.88 (t, *J* = 8.2 Hz, 1H), 4.49 (s, 2H), 4.31–4.34 (m, 2H), 2.80 (d, *J* = 8.2 Hz, 2H), 1.69–1.75 (m, 2H), 1.41–1.48 (m, 2H), 1.28 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 170.7, 167.6, 156.2, 147.6, 146.4, 145.9, 139.7, 137.3, 137.2, 128.4, 126.6, 126.3, 125.7, 120.5, 109.3, 108.6, 107.9, 100.8, 80.5, 65.1, 46.6, 46.2, 42.1, 40.7, 30.7, 27.9, 20.2, 20.1, 19.2, 13.7; IR (KBr) 2974, 1731, 1600, 1553, 1484, 1146, 1039, 937, 813, 731, 697 cm⁻¹; exact mass calcd for C₃₄H₄₃N₂O₆ (M⁺+H): 575.3121. Found: 575.3218.

4.4.8 *tert*-Butyl-(3*S*)-3-[6-(*N*-benzyl-*N*-isopropylamino)-2-butoxycarbonyl-3-pyridinyl]-3-(2,3-dihydro-1-benzofuran-6-yl)propanoate (28e). 80% yield;

$R_f = 0.55$ (*n*-heptane/ethyl acetate=2/1); 90.3 %ee (Chiralcel OD-H, *n*-hexane/2-propanol=90/10, flow rate=0.5 mL/min, temp=27 °C, t_R for **28e**: 11.2 min, t_R for enantiomer: 16.9 min); $[\alpha]_D^{20} = -39.7^\circ$ (*c* 1.06, CHCl₃); ¹H NMR (CDCl₃, 500 MHz) δ 7.18–7.28 (m, 6H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.67 (s, 1H), 6.31 (d, *J* = 9.0 Hz, 1H), 5.04 (sept, *J* = 6.6 Hz, 1H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.50 (t, *J* = 8.6 Hz, 2H), 4.49 (s, 2H), 4.30–4.35 (m, 2H), 3.11 (t, *J* = 8.6 Hz, 2H), 2.82 (d, *J* = 8.1 Hz, 2H), 1.69–1.74 (m, 2H), 1.40–1.47 (m, 2H), 1.27 (s, 9H), 1.16 (d, *J* = 6.6 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 170.8, 167.5, 160.3, 156.2, 146.4, 143.7, 139.8, 137.4, 128.4, 126.6, 126.3, 125.8, 124.8, 124.5, 120.0, 109.3, 108.7, 80.4, 71.2, 65.0, 46.6, 46.2, 42.0, 40.8, 30.7, 29.5, 27.9, 20.2, 20.1, 19.2, 13.7; IR (KBr) 2975, 1730, 1599, 1481, 1147, 1078, 989, 947, 813, 759, 697 cm⁻¹; exact mass calcd

for C₃₅H₄₅N₂O₅ (M⁺+H): 573.3328. Found: 573.3412.

4.5 Computational details.

Geometries of all stationary points were optimized using analytical energy gradients of self-consistent-field⁴¹ and density functional theory (DFT).⁴² The latter utilized Becke's three-parameter exchange-correlation functional⁴³ including the nonlocal gradient corrections described by Lee-Yang-Parr (LYP),⁴⁴ as implemented in the Gaussian 03 program package.⁴⁵ All geometry optimizations were performed using the LANL2DZ basis set.⁴⁶

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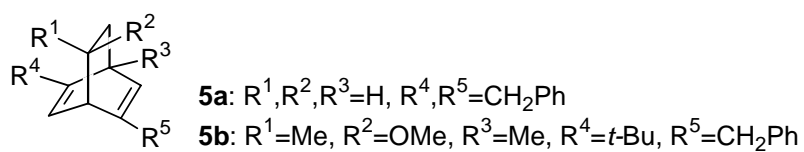
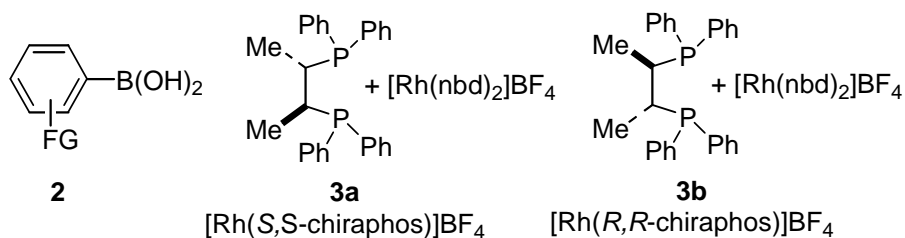
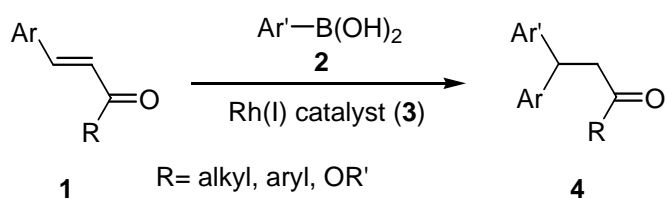
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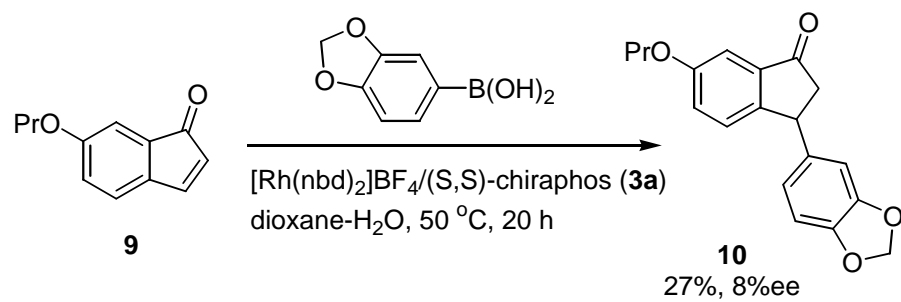
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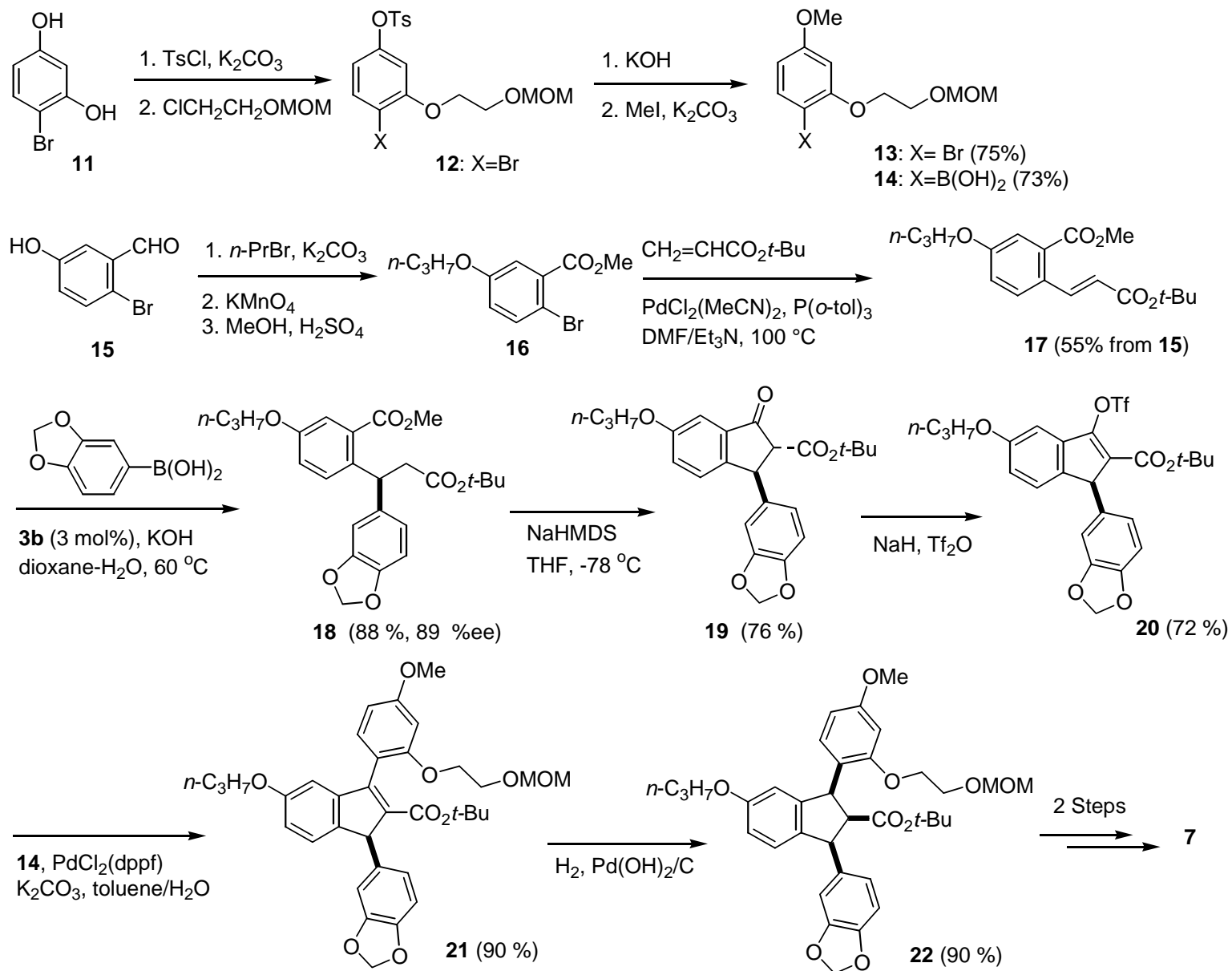
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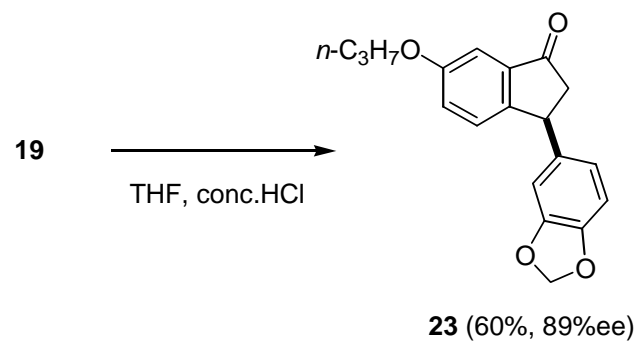
Scheme 1. Rhodium(I)-catalyzed 1,4-addition of arylboronic acids to β -aryl α,β -unsaturated ketones and esters



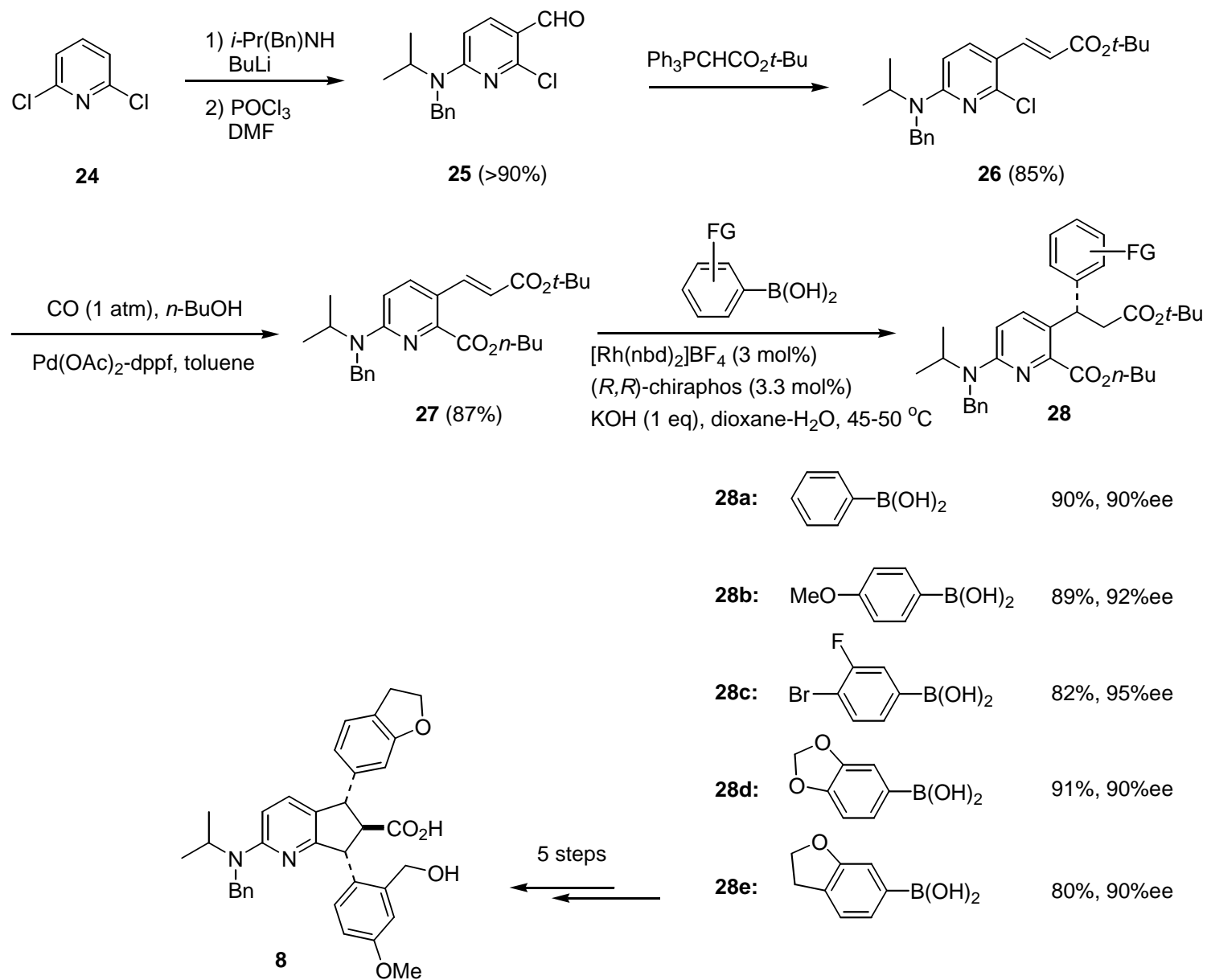
Scheme 2. 1,4-Addition to indenone (**9**)



Scheme 3. SmithKline Beecham's antagonist (**7**)



Scheme 4. Absolute configuration of **23**



Scheme 5. Merck-Banyu's endothelin A receptor antagonists (**8**)

Table 1. Effects of reaction temperatures, catalysts and bases on yields and enantioselectivities^a

entry	1 (Ar=Ph) R=	base (eqs)	temp/time (°C/h)	yield/% ^b	%ee ^c
1	Me	none	20/5	0	-
2	Me	KHCO ₃ (1)	20/5	0	-
3	Me	K ₂ CO ₃ (1)	20/5	94	84
4	Me	KOH (1)	20/5	99	84
5	Me	KOH (1)	0/18	31	89
6	OMe	KOH (1)	20/21	94	84
7	O <i>i</i> -Pr	KOH (1)	20/19	58	92
8	O <i>t</i> -Bu	KOH (1)	50/6	92	93
9	O <i>t</i> -Bu	K ₂ CO ₃ (1)	65/21	76	91
10	O <i>t</i> -Bu	Cs ₂ CO ₃ (1)	65/21	83	92
11	O <i>t</i> -Bu	KF (3)	65/21	75	80
12	O <i>t</i> -Bu	CsF (3)	65/21	77	83
13	O <i>t</i> -Bu	NEt ₃ (1)	65/21	40	91

^a A mixture of an unsaturated ketone or ester (**1**, Ar=Ph) (0.5 mmol), 4-MeOC₆H₄B(OH)₂ (0.75 mmol), and base (0.5 mmol) in dioxane-H₂O (3 ml/0.5 ml) was stirred in the presence of [Rh(nbd)₂]BF₄ (3 mol%) and (*S,S*)-chiraphos (3.3 mol%).

^b Isolated yields by chromatography.

^c Enantiomer excess determined by a chiral stationary column.

Table 2. Asymmetric addition of arylboronic acids to β -aryl- α,β -unsaturated ketones and esters (**1**)^a

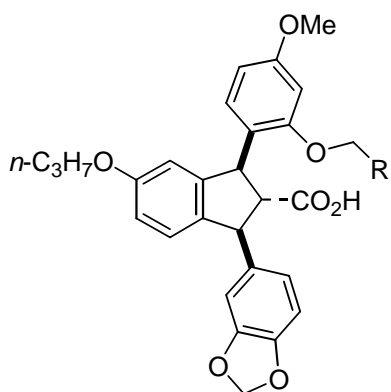
entry	1		2 FG=	base	temp/time (°C/h)	product	yield/% ^b	%ee ^c
	Ar=	R=						
1	Ph	Me	4-MeO	K ₂ CO ₃	20/5	4a	96	84
2	Ph	Me	3,4-(CH ₂) ₂ O ^d	K ₂ CO ₃	20/5	4b	99	89
3	2-naphthyl	Me	3-MeO	K ₂ CO ₃	20/5	4c	95	83
4	Ph	Ph	3-MeO	K ₂ CO ₃	20/5	4d	99	86 (S)
5	Ph	4-MeOC ₆ H ₄	3-MeO	K ₂ CO ₃	20/5	4e	99	83
6	Ph	<i>Ot</i> -Bu	4-MeO	KOH	50/6	4f	92	93
7	Ph	<i>Ot</i> -Bu	3-MeO	KOH	50/6	4g	95	90
8	Ph	<i>Ot</i> -Bu	3,4-(MeO) ₂	KOH	50/6	4h	88	88
9	Ph	<i>Ot</i> -Bu	3,4-(CH ₂) ₂ O ^d	KOH	50/6	4i	94	94
10	Ph	<i>Ot</i> -Bu	4-Me ₂ N	KOH	50/6	4j	59	82
11	4-MeOC ₆ H ₄	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4k	97	90
12	2-MeOC ₆ H ₄	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4l	96	91
13	4-MeC ₆ H ₄	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4m	92	91
14	4-CF ₃ C ₆ H ₄	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4n	94	85
15	2-naphthyl	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4o	81	78
16	3-pyridyl	<i>Ot</i> -Bu	3-MeO	KOH	80/6	4p	90	89

^a A mixture of **1** (1 mmol), ArB(OH)₂ (1.5 mmol) and base (1 mmol) in dioxane-H₂O (6/1) was stirred in the presence of [Rh(nbd)₂]BF₄ (3 mol%) and (*S,S*)-chiraphos (3.3 mol%).

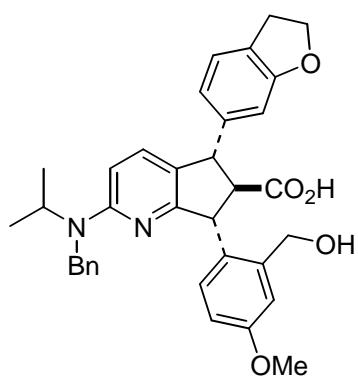
^b Isolated yields by chromatography.

^c Enantiomer excess determined by a chiral stationary column.

^d (CH₂)₂O is a methylenedioxy group.



6: R=CO₂H (SB-209670)
7: R=CH₂OH (SB-217242)



8

Figure 1. Endothelin receptor antagonists reported by SmithKline Beecham and Merck-Banyu

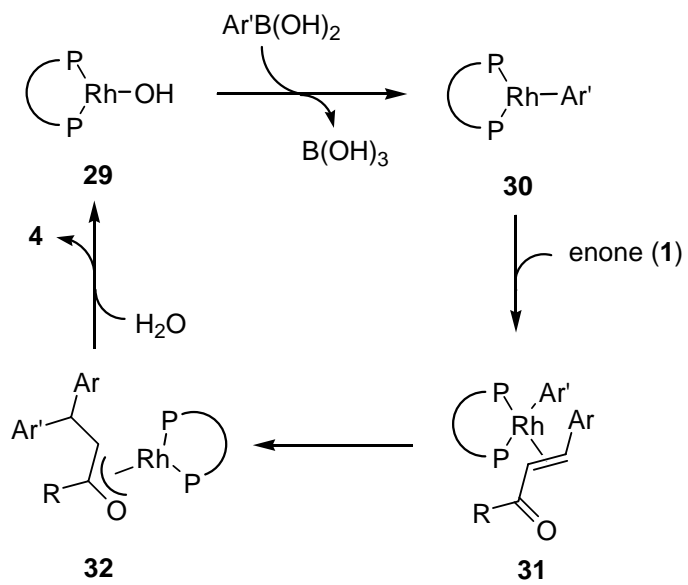
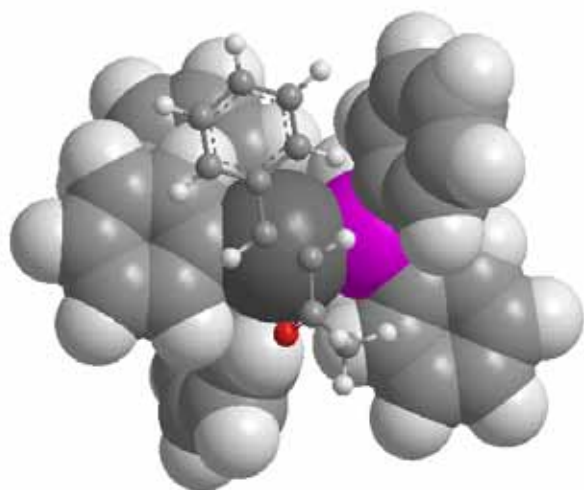
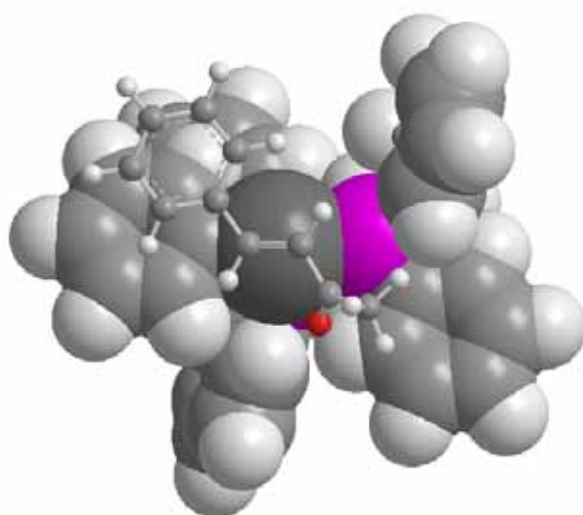


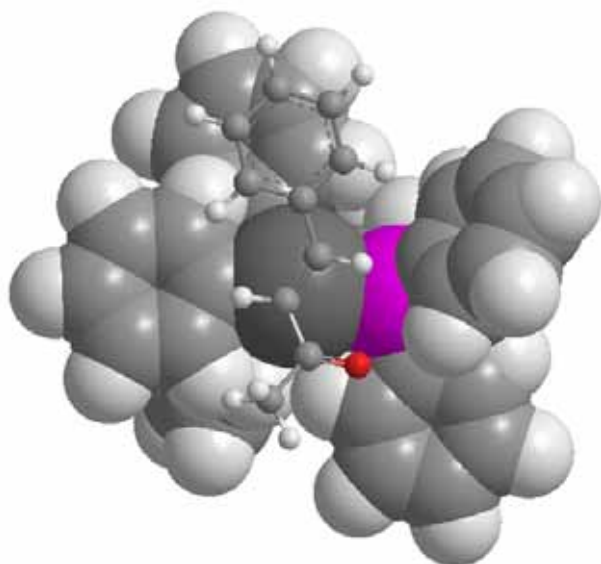
Figure 2. A catalytic cycle



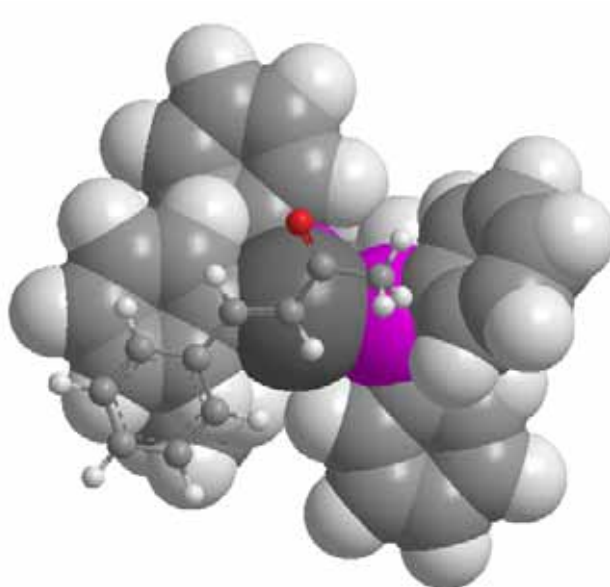
33 (si, $\angle 28.9^\circ$, 0 kcal/mol)



34 (si, $\angle 0^\circ$, 20.8 kcal/mol)



35 (re, $\angle 127^\circ$, 1.6 kcal/mol)



36 (re, $\angle 0^\circ$, 231.8 kcal/mol)

Figure 3. Transition states for coordination of (*E*)-PhCH=CHCOCH₃ to a [Rh(Ph)(*S,S*-chiraphos)] intermediate

