

Stepwise Palladium-Catalyzed 1,4-Addition of Arylboronic Acids to Enones and Regioselective Baeyer–Villiger Oxidation for Enantioselective Synthesis of β-Diaryl Esters and (+)-(*R*)-Tolterodine

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Baeyer–Villiger oxidation of chiral β-diaryl ketones synthesized by 1,4-addition of arylboronic acids to β-aryl-α,β-unsaturated ketones catalyzed by a palladium(2+)–chiraphos complex provided optically active β-diaryl esters up to 98% ee. The protocol was applied to the synthesis of a potent competitive muscarinic receptor antagonist, (*R*)-tolterodine (**21**), which has a chiral center consisting of two aryl rings.

Enantioselective conjugate additions of nucleophiles to α,β-unsaturated carbonyl compounds are a versatile methodology for forming chiral carbon–carbon bonds.[1] We have reported that aryl- and 1-alkenylboronic acids undergo 1,4-addition to α,β-unsaturated carbonyl compounds in the presence of a rhodium(I) catalyst.[2] The protocol has been proved to be a general reaction for a wide range of selective carbon–carbon bond formations including enantioselective reactions using chiral rhodium–phosphine catalysts.[3] We have also reported that dicationic palladium(II) complexes are excellent catalysts that allow 1,4-additions of organoboron,[4] -silicon,[5] and -bismuth[6] compounds at temperatures lower than room temperature. Palladium(2+) complexes possessing bisphosphines bridged by two carbons, such as chiraphos (2,3-bis(diphenylphosphino)-butane),[6,7] dipamp (1,2-bis[(2-methoxyphenyl)(phenyl)phosphino]ethane),[7] and Me-Duphos (1,2-bis(2,5-dimethylphospholano)benzene),[8] were found to be effective for asymmetric versions of compounds of those elements. Among these three catalysts, the palladium–chiraphos complex exhibited high enantioselectivities for 1,4-additions of arylboronic acids to unsaturated ketones,[7a,7b,7d,7f] aldehydes,[7c] and *N*-acyl amides[7e] having an aryl ring at the β-carbon. Chiral β-diaryl carbonyl compounds thus obtained are key intermediates in the syntheses of a potent competitive muscarinic receptor antagonist (*R*)-tolterodine,[9] a potential therapeutic agent (+)-(*R*)-CDP 840,[7c,10] and endothelin receptor antagonist.[11] Although chiral β-diaryl esters are often desirable for syntheses of those biologically active compounds, this protocol effective for ketones, aldehydes, and *N*-acyl amides does not work for unsaturated esters. The corresponding rhodium catalysts such as [Rh(nbd)$_2$]BF$_4$/chiraphos and [Rh(binap)(nbd)]BF$_4$ meet this purpose; however, enantioselectivities raging from 89 to 90% ee can be improved to 95–98% ee by the use of palladium–chiraphos complex.[7d] Another advantage of palladium(2+) catalysts is higher turnover number (TON) than those of rhodium complexes.[7d,12] The palladium complexes achieved quantitative yields with a less than 0.1 mol % catalyst loading in the presence of less than 1.5 equivalents of arylboronic acids.[7d]

A difficulty in using palladium(2+) catalysts for unsaturated esters is the high stability of palladium(+) *C*-enolate compared to that of *O*-enolate. A proposed catalytic cycle shown in Figure 1 involves an equilibrium formation of *C*-enolate **4** and *O*-enolate **5** as the key intermediates for giving 1,4-addition products **6** via hydrolysis with water. Although ketone substrates selectively produced **6**, the ester derivatives resulted in Heck coupling **7**, thus suggesting slow formation of water-sensitive **5**. Thus, all attempts at using acrylates as the substrates of palladium-catalyzed 1,4-addition failed to give 1,4-addition products **6**.

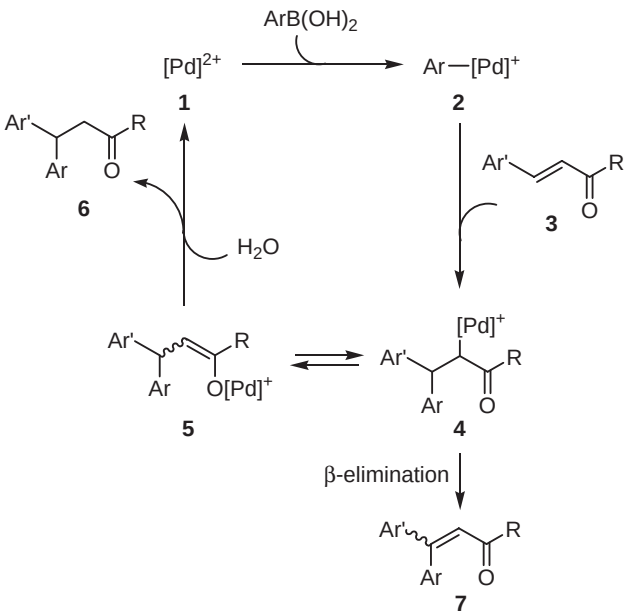

Figure 1. Catalytic cycle.

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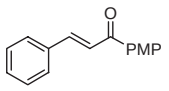
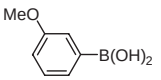
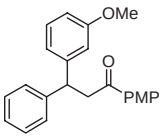
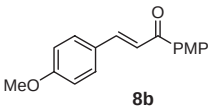
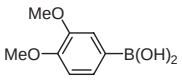
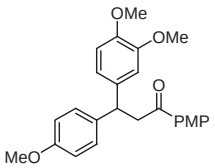
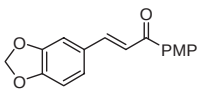
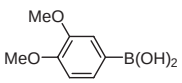
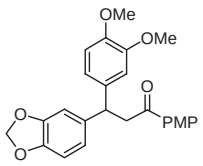
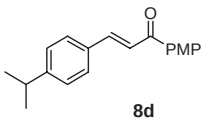
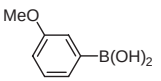
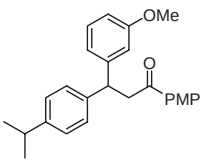
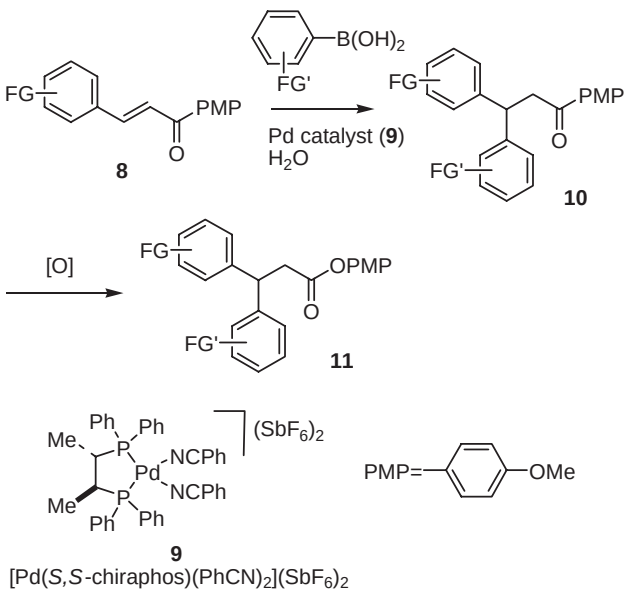
Table 1. Enantioselective Synthesis of β-Diaryl Ketones and Esters (Scheme 1)[a)]

Entry	Enone **8**	Arylboronic acid	**10**				**11**		
			Product	No	Yield/%[b)]	% ee	No	Yield/%[b)]	% ee
1	 **8a**			**10a**	99	95	**11a**	73	95
2	 **8b**			**10b**	86	95	**11b**	72	97
3	 **8c**			**10c**	74[c)]	97	**11c**	67	95
4	 **8d**			**10d**	90	95	**11d**	0	

a) All reactions were carried out at room temperature for 6 h in aqueous acetone in the presence of enone (1 mmol), $ArB(OH)_2$ (1.2 mmol), and $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (*S,S*-chiraphos = (2*S*,3*S*)-(−)-bis(diphenylphosphino)butane) (**9**, 0.5 mol %). Chromatographic isolation of **10** was followed by Baeyer–Villiger oxidation with $NaBO_3$ in acetic acid at 30–50 °C. b) Isolated yields by chromatography. c) In MeOH–water (10/1).



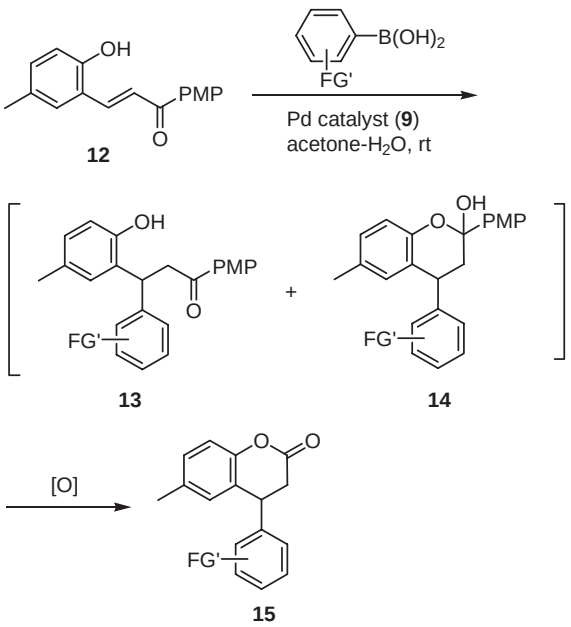
Scheme 1. Stepwise 1,4-addition and Baeyer–Villiger oxidation for synthesis of optically active β-diaryl esters.

As a means to overcome this limitation of the palladium-catalyzed protocol, we report here stepwise 1,4-addition and Baeyer–Villiger oxidation for the synthesis of optically active β-diaryl esters (Scheme 1). We developed two selective methods for Baeyer–Villiger oxidation of *p*-methoxyphenyl 3,3-diarylpropanates and 4-aryldihydrocoumarins which provided a simple access to (*R*)-tolterodine (**21**) with high enantioselectivity.

Results and Discussion

Synthesis of Optically Active 3,3-Diarylpropanoic Esters. Traditional methods for conversion of ketones to the corresponding acids or esters are haloform reaction of methyl ketones or trihalomethyl ketones,[13] oxidative cleavage of β-hydroxy ketones with $(NH_4)_2Ce(NO_3)_6$,[14] and Baeyer–Villiger oxidation of unsymmetrical ketones.[15] Thus, PhCH=CHCOR (R = Me, CF_3, $C(OH)Me_2$, CMe_3, and Ph) are potent substrates that can be finally transformed into desired acids or esters. However, palladium(2+) complex **9** failed to catalyze the additions of phenylboronic acid for trifluoromethyl, dimethyl(hydroxy)methyl, and *t*-butyl ketones, whereas methyl and phenyl ketones afforded excellent yields of 1,4-addition products. Thus, *p*-methoxyphenyl (PMP) enones **8** were finally chosen as the substrates for stepwise 1,4-addition and Baeyer–Villiger oxidation, giving **11** because of higher enantioselectivities of the palladium(2+)/chiraphos catalyst for arylketones than for methyl ketones.[7b] Regioselective cleavage of the PMP ring rather than the primary alkyl group was previously reported by Rüedi and Hansen (Scheme 1).[15b]

Asymmetric addition of arylboronic acids to four β-aryl ketones and oxidation of **10** to **11** with $NaBO_3$ are summarized in Table 1. Arylboronic acids possessing one or two alkoxy groups at para or meta carbons were smoothly added to β-aryl enones **8** at room temperature in the presence of 1.2 equivalents of arylboronic acids and 0.5 mol % of dicationic palla-

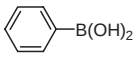
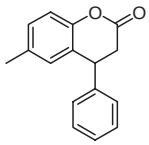
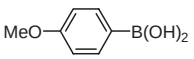
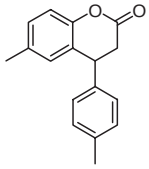
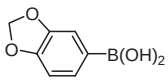
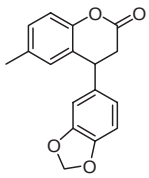
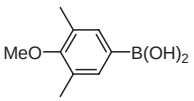
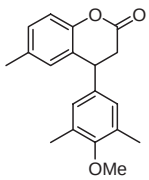


Scheme 2. Synthesis of optically active 4-aryldihydrocoumarins.

dium(II) catalyst **9** in aqueous acetone. The reaction easily achieved 74–99% yields with 95–97% ee. The efficiency of a rhodium–chiraphos catalyst for chalcone derivatives and the enantioselection mechanism proposed on the basis of theoretical calculation of the transition state have been previously reported.[11] Baeyer–Villiger oxidation of **10** suffered from low yields, resulting in complex mixtures. This is mainly due to steric hindrance of substituents on aryl groups around the carbonyl group because unsubstituted Ph_2CHCH_2COPMP resulted in 99% yield by traditional MCPBA oxidation. Oxidation of **10** with $NaBO_3$ resulted in the best yields among the representative methods reported for Baeyer–Villiger oxidation. Oxidation of **10a–10c** with 3 equivalents of $NaBO_3$ at 30–50 °C gave **11a–11c** in 67–73% yields, whereas MCPBA (5 equivalents) and trifluoroacetic acid (TFA) resulted in 38–48% yields (Entries 1–3). A combination of H_2O_2 and TFA or bis(trimethylsilyl)peroxide $(TMSO)_2$ and $SnCl_4$ gave a complex mixture from which it was difficult to isolate pure **11**. All attempts at oxidation of **10d** with these oxidants failed (Entry 4). The enantioselectivities of **10a–10c** remained perfectly intact during the $NaBO_3$ oxidation (Entries 1–3).

Synthesis of Optically Active 4-Aryldihydrocoumarins. In a previous study on the synthesis of optically active 4-aryl-4*H*-chromenes, 1,4-addition of arylboronic acids to β-(2-hydroxyaryl)enones **12** provided chromanol **14** accompanied by a small amount of **13**, which were then led to single chromenes via acid-catalyzed dehydration.[7d] Baeyer–Villiger oxidation of these intermediates **13** and **14** provided 4-aryldihydrocoumarins, which were previously synthesized by rhodium-catalyzed 1,4-addition of arylboronic acids to coumarins[3o] (Scheme 2). Oxidation with MCPBA and $NaBO_3$ resulted in low yields, but $(TMSO)_2$ and $SnCl_4$ were found to be an excellent combination for selective Baeyer–Villiger oxidation. A one-pot two-step procedure without isolation of 1,4-addition intermediates afforded good yields of desired dihydrocoumarins **15** as the sole products with excellent enantioselectivities.

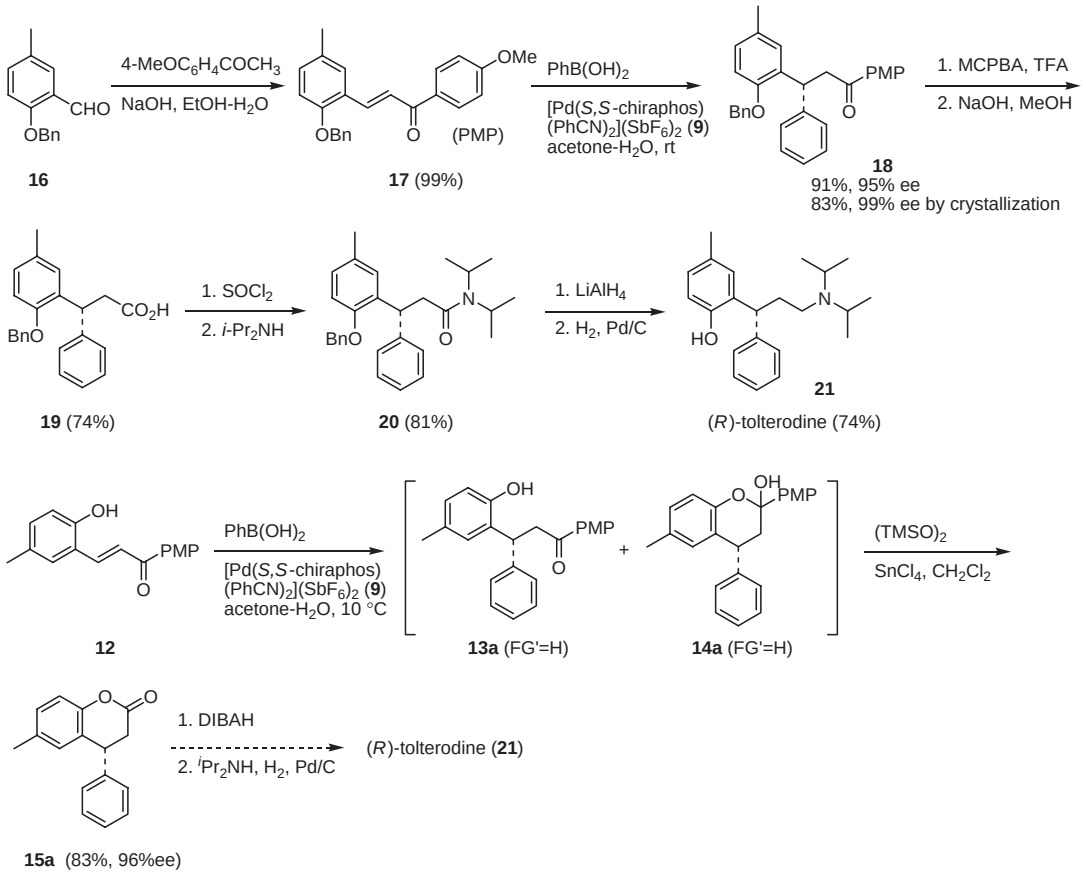
Table 2. Enantioselective Synthesis of 4-Aryldihydrocoumarins (Scheme 2)[a)]

Entry	Arylboronic acid	Product **15**	Yield /%[b)]	% ee
1		 **15a**	83	96
2		 **15b**	75	98
3		 **15c**	70	97
4		 **15d**	74	97

a) All reactions were carried out at 10 °C for 24 h in aqueous acetone in the presence of enone (0.5 mmol), $ArB(OH)_2$ (0.75 mmol), and $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (**9**, 0.5 mol %). The crude product **13**/**14** thus obtained was directly treated with $(TMSO)_2$ (1 mmol) and $SnCl_4$ (0.5 mmol) in CH_2Cl_2. b) Isolated yields by chromatography.

The synthesis of **13**/**14** via asymmetric addition of arylboronic acids to **12** was followed by oxidation with $(TMSO)_2$ at room temperature in the presence of $SnCl_4$ to give optically active 4-aryldihydrocoumarins (Table 2). Total yields of this two-step synthesis of **15** were 70–83%, which were higher than those obtained by an analogous procedure described for the synthesis of 3,3-diarylpropanoic esters (Table 1). Palladium(2+)–chiraphos catalyst **9** again achieved high enantioselectivities in a range of 96 to 98% ee.

Enantioselective synthesis of a potent competitive muscarinic receptor antagonist, (*R*)-tolterodine (**21**), has attracted much attention as a target for enantioselective synthesis of a chiral center consisting of two aryl rings. The synthesis has been achieved by diastereoselective cycloaddition of *o*-quinone methide with a chiral enol ether,[16] 1,4-addition of arylcopper reagent to cinnamic amide of chiral oxazolidinone,[17] catalytic 1,4-addition of arylboronic acids to coumarins[3o] and hydrogenation of 4-arylcoumarin.[18] The present method provided an alternative convenient and practical access to (*R*)-tolterodine (**21**) with high enantioselectivity (Scheme 3). The desired enone **17** synthesized from **16** was subjected to 1,4-addition of phenylboronic acid (1.2 equiv) with the (*S*,*S*)-chiraphos complex **9** (0.5 mol %). Chromatographic separation of **18** resulted in 95% ee, but crystallization from THF furnished enan-



Scheme 3. Synthesis of (*R*)-tolterodine.

tiomerically pure **18** in 83% yield. Baeyer–Villiger oxidation of **18** with MCPBA and TFA in toluene followed by saponification of the ester group afforded an acid **19** which was previously led to (*R*)-tolterodine (**21**) in two steps. Conversion into an *N*,*N*-diisopropylamide **20** in 81% yield was followed by reduction of the carbonyl group and deprotection of the benzyl group to furnish optically pure tolterodine (**21**) in 74% yield.[17] The formation of (*R*)-**18** from the (*S*,*S*)-chiraphos complex **9** was finally established by the specific rotation reported for **21** ($[\alpha]_D^{23}$ +23.9° (*c* 0.58, MeOH)).[3o,9b] Thus, the product was produced by the same mode of face selection as that proposed on the basis of theoretical calculation.[7b]

The alternative protocol provides a simpler access to (*R*)-tolterodine. A one-pot, two-step procedure of stepwise 1,4-addition and Baeyer–Villiger oxidation directly gave a key intermediate **15a** in 96% ee, which has been previously converted into (*R*)-tolterodine (**21**) in two steps.[3o]

Conclusion

In conclusion, we have demonstrated the efficiency of a Pd(2+)–chiraphos complex for the synthesis of β-diaryl ketones and esters that provides a simple access to (*R*)-tolterodine.

Experimental

General. All experiments were carried out under nitrogen atmosphere. HPLC analysis was directly performed with chiral stationary phase columns using Chiralcel IA, IB, OD-H, AD, AD-H, OJ-H, and OB-H purchased from Daicel Co., Ltd. Phenyl-, 3,5-dimethyl-4-methoxyphenyl-, and 3,4-dimethoxyphenylboronic acid were purchased from Wako Chemical Co., Ltd. and Lancaster Co., Ltd.

Preparation of Enones (8 and 12). **8a** was commercially available. Other β-arylenones were synthesized by reported procedures.[19] To a solution of ArCHO (30 mmol) and *p*-methoxyacetophenone (30 mmol) in ethanol (15 mL) was slowly added aqueous NaOH (39 mmol for **8** or 90 mmol for **12**) in water (30 mL). The resulting mixture was stirred overnight at 40 °C. The mixture was acidified with aqueous HCl and extracted with diethyl ether. The product was isolated by crystallization.

8b: 89% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 15.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.67, 163.20, 161.44, 143.73, 131.27, 130.63, 130.48, 127.73, 119.45, 114.31, 113.72, 55.41, 55.33; MS (*m*/*z*) 77 (18.5), 92 (14.4), 133 (10.6), 135 (30.6), 225 (20.0), 237 (17.8), 253 (33.7), 268 (M^+, 100.0); Exact mass calcd for $C_{17}H_{16}O_3$: 268.1100. Found: 268.1082.

8c: 91% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.1 Hz, 2H), 7.73 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 15.6 Hz, 1H), 7.17 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 9.1 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.03 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.58, 163.32, 149.71, 148.36, 143.80, 131.25, 130.70, 129.55, 125.00, 119.90, 113.80, 108.64, 106.62, 101.58, 55.48; MS (*m*/*z*) 77 (11.8), 89 (12.3), 122 (13.0), 135 (31.2), 145 (11.9), 175 (10.2), 251 (10.5), 267 (13.1), 282 (M^+, 100); Exact mass calcd for $C_{17}H_{14}O_4$: 282.0892. Found: 282.0901.

8d: 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 15.6 Hz, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 15.6 Hz, 1H), 7.27 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 2.95 (sept, J = 6.8 Hz, 1H), 1.27 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.36, 162.85, 151.23, 143.58, 132.25, 130.77, 130.29, 128.01, 126.57, 120.49, 113.32, 54.50, 33.64, 23.30; MS (m/z) 77 (10.7), 135 (28.2), 237 (100.0), 238 (19.2), 265 (35.0), 280 (M^+, 56.6); Exact mass calcd for $C_{19}H_{20}O_2$: 280.1463. Found: 280.146.

12: 63% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 16.1 Hz, 1H), 8.06 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 16.1 Hz, 1H), 7.39 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 3.89 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.09, 163.39, 153.68, 140.24, 132.34, 131.23, 130.99, 129.91, 129.40, 122.20, 122.03, 116.54, 113.79, 55.49, 20.46; MS (m/z) 77 (22.3), 92 (12.5), 108 (22.9), 135 (100.0), 161 (10.7), 251 (47.4), 268 (M^+, 31.7); Exact mass calcd for $C_{17}H_{16}O_3$: 268.1010. Found: 268.1088.

General Procedure for 1,4-Addition (Table 1). A solution of [Pd((*S*,*S*)-chiraphos)(PhCN)$_2$](SbF$_6$)$_2$ (**9**, 0.5 mol %), enone substrate (0.5 mmol) and ArB(OH)$_2$ (0.6 mmol) in acetone (3.0 mL) and H_2O (0.3 mL) was stirred at room temperature for 6–12 h. The product was extracted with diethyl ether and the extract was then concentrated in vacuo. Chromatography on silica gel with hexane/EtOAc afforded the desired **10**.

10a: 99% yield, 95% ee; Daicel Chiralcel IB with hexane/2-propanol = 9/1, flow = 1.0 mL min^{-1}, wavelength = 254 nm, t_R = 13.9 min (minor) and 15.5 min (major). The spectral data have been previously reported.[11]

10b: 86% yield, 95% ee; $[\alpha]_D^{23}$ +2.1° (c 0.33, $CDCl_3$), Daicel Chiralcel IA with hexane/2-propanol/dichloromethane = 4/2/1, flow = 0.5 mL min^{-1}, wavelength = 254 nm, t_R = 13.8 min (minor) and 15.6 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.77–6.75 (m, 3H), 4.72 (t, J = 7.3 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.61 (t, J = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.35, 162.97, 157.49, 148.34, 146.93, 136.75, 136.15, 129.87, 129.73, 128.18, 117.78, 113.39, 113.23, 111.03, 110.61, 55.35, 55.32, 54.98, 54.72, 44.45, 44.25; IR (neat) 1598, 1509, 1244, 1169, 1141, 1025, 986, 831, 807, 545 cm^{-1}; MS (m/z) 135 (12.9), 257 (100), 406 (M^+, 18.7); Exact mass calcd for $C_{25}H_{26}O_5$: 406.1780. Found: 406.1283.

10c: 74% yield, 97% ee; $[\alpha]_D^{22}$ +4.8° (c 0.17, $CDCl_3$), Daicel Chiralcel IA with hexane/2-propanol/dichloromethane = 4/2/1, flow = 0.5 mL min^{-1}, wavelength = 254 nm, t_R = 15 min (minor) and 19 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.82–6.67 (m, 6H), 5.88 (s, 2H), 4.68 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.60 (d, J = 7.3 Hz, 1H), 3.59 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.14, 163.00, 148.38, 147.22, 147.02, 145.44, 138.03, 136.45, 129.87, 129.66, 120.03, 118.66, 113.25, 110.95, 110.61, 107.85, 107.68, 100.40, 55.35, 55.34, 54.99, 44.92, 44.11; IR (neat) 1598, 1509, 1486, 1235, 1169, 1141, 1027, 930, 832, 809 cm^{-1}; MS (m/z) 135 (15.6), 271 (100), 420 (M^+, 20.7); Exact mass calcd for $C_{25}H_{24}O_6$: 420.1573. Found: 420.1579.

10d: 90% yield, 95% ee; $[\alpha]_D^{22}$ +3.4° (c 0.22, $CDCl_3$), Daicel Chiralcel OD-H with hexane/2-propanol = 9/1, flow = 0.7 mL min^{-1}, wavelength = 254 nm, t_R = 19.6 min (minor) and 27.9 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.3 Hz, 2H), 7.22–7.12 (m, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.90–6.85 (m, 3H), 6.81 (s, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.75 (t, J = 6.8 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.65 (dd, J = 6.8, 2.9 Hz, 2H), 2.85 (sept, J = 6.8 Hz, 1H), 1.19 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.12, 162.94, 159.11, 146.25, 145.68, 140.98, 129.87, 129.71, 128.95, 127.13, 126.09, 119.76, 113.60, 113.21, 110.67, 54.98, 54.63, 45.19, 43.93, 33.13, 23.49; IR (neat) 1675, 1598, 1253, 1167, 1130, 984, 830, 780, 703, 580 cm^{-1}; MS (m/z) 135 (100), 145 (15.6), 211 (11.1), 239 (52.7), 240 (10.0), 253 (16.1), 388 (M^+, 50.9); Exact mass calcd for $C_{26}H_{28}O_3$: 388.2038. Found: 388.2032.

Baeyer–Villiger Oxidation (Table 1). Baeyer–Villiger oxidation of **10** was carried out by a modified procedure.[20] A solution of 1,4-adduct **10** (0.5 mmol) and $NaBO_3 \cdot 4H_2O$ (2.5 mmol) in acetic acid (3 mL) was stirred at 30–50 °C to room temperature for 24 h. The product was extracted with diethyl ether, washed with brine and concentrated in vacuo. Chromatography on silica gel with hexane/EtOAc afforded **11**.

11a: 73% yield, 95% ee; $[\alpha]_D^{23}$ +6.3° (c 0.10, $CDCl_3$), Daicel Chiralcel IB with hexane/2-propanol = 19/1, flow = 1.0 mL min^{-1}, wavelength = 254 nm, t_R = 15.4 min (minor) and 16.5 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 4H), 7.27–7.20 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.86–6.74 (m, 4H), 6.73–6.66 (m, 2H), 4.62 (t, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.26 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.79, 159.73, 157.19, 144.68, 143.99, 142.90, 129.61, 128.65, 127.73, 126.77, 122.16, 120.04, 114.34, 113.84, 111.77, 55.54, 55.17, 47.32, 40.81; IR (neat) 1752, 1503, 1236, 1191, 1128, 1033, 842, 768, 743, 699 cm^{-1}; MS (m/z): 124 (100.0), 165 (13.2), 197 (30.3), 239 (15.3), 362 (M^+, 4.3); Exact mass calcd for $C_{23}H_{22}O_4$: 362.1518. Found: 362.1502.

11b: 72% yield, 97% ee; $[\alpha]_D^{23}$ +2.4° (c 0.10, $CDCl_3$), Daicel Chiralcel AD-H with hexane/2-propanol = 9/1, flow = 0.5 mL min^{-1}, wavelength = 254 nm, t_R = 70 min (major) and 79 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.0 Hz, 2H), 6.81–6.70 (m, 7H), 6.66–6.61 (m, 2H), 4.48 (t, J = 8.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 3.14 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.90, 158.26, 157.19, 148.90, 147.68, 143.99, 136.02, 135.44, 128.58, 122.16, 119.31, 114.36, 113.97, 111.18, 111.13, 55.86, 55.82, 55.53, 55.24, 46.14, 41.32; IR (neat) 1751, 1505, 1243, 1190, 1127, 1027, 838, 810, 760, 539 cm^{-1}; MS (m/z): 124 (25.9), 257 (100.0), 258 (17.8), 270 (31.0), 298 (35.0), 422 (M^+, 23.6); Exact mass calcd for $C_{25}H_{26}O_6$: 422.1729. Found: 422.1747.

11c: 67% yield, 95% ee; $[\alpha]_D^{23}$: +3.6° (c 0.19, $CDCl_3$), Daicel Chiralcel IA with hexane/2-propanol = 9/1, flow = 1.0 mL min^{-1}, wavelength = 254 nm, t_R = 46.5 min (major) and 53.2 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86–6.71 (m, 10H), 5.91 (s, 2H), 4.52 (t, J = 8.3 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.19 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.75, 157.21, 148.94, 147.83, 147.78, 146.24, 143.96, 137.34, 135.68, 122.14, 120.44, 119.21, 114.38, 111.13, 111.12, 108.19, 108.16, 100.97, 55.86, 55.84, 55.53, 46.58, 41.20; IR (neat) 1503, 1481, 1237, 1191, 1127, 1029, 910, 811, 761, 728 cm^{-1}; MS (m/z) 124 (31.7), 271 (100), 284 (29.9), 312 (53.3), 436 (31.2); Exact mass calcd for $C_{25}H_{24}O_7$: 436.1522. Found: 436.1535.

General Procedure for Synthesis of 4-Aryldihydrocoumarins (Table 2). A solution of [Pd((*S*,*S*)-chiraphos)(PhCN)$_2$](SbF$_6$)$_2$ (**9**, 0.5 mol %), enone **12** (0.5 mmol), and ArB(OH)$_2$ (0.75 mmol) in acetone (3.0 mL) and H_2O (0.3 mL) was stirred

at 10 °C for 24 h. The mixture was passed through a short pad of silica gel with diethyl ether as eluent. The filtrate was concentrated in vacuo to give crude **13**/**14**.

Baeyer–Villiger oxidation of crude **13**/**14** was carried out by a reported procedure.[21] The residue thus obtained was dissolved in CH_2Cl_2 (5 mL) and treated with $(TMSO)_2$ (0.5 mmol). To this mixture was slowly added $SnCl_4$ (0.5 mmol) (1.0 M solution in heptane) at 0 °C and the mixture was stirred for 15 min at 0 °C and at room temperature for 1 h. Additional $(TMSO)_2$ (0.5 mmol) was then added and stirred for 3 h. The product was extracted with diethyl ether, washed with saturated K_2CO_3 in water and concentrated in vacuo. Chromatography on silica gel with hexane/EtOAc afforded **15**.

15a and **15b** have been previously reported.[3o]

15c: 70% yield, 97% ee; $[\alpha]_D^{23}$ +9.4° (*c* 0.9, $CDCl_3$), Daicel Chiralcel IB with hexane/2-propanol/dichloromethane = 50/1/3, flow = 0.5 mL min^{-1}, wavelength = 254 nm, t_R = 29 min (minor) and 33 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H), 6.76 (d, J = 8.8 Hz, 1H), 6.65–6.55 (m, 2H), 5.95 (s, 2H), 4.22 (t, J = 6.6 Hz, 1H), 3.02 (dd, J = 16, 5.9 Hz, 1H), 2.94 (dd, J = 16, 7.6 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.79, 149.52, 148.21, 146.96, 134.33, 134.29, 129.31, 128.58, 125.33, 120.80, 116.84, 108.61, 107.70, 101.18, 40.41, 37.36, 20.74; IR (neat) 1487, 1443, 1239, 1198, 1164, 1150, 1118, 1036, 927, 812 cm^{-1}; MS (*m*/*z*): 152 (12.6), 182 (15.6), 210 (19.6), 239 (81.7), 264 (41.8), 282 (M^+, 100); Exact mass calcd for $C_{17}H_{14}O_4$: 282.08921. Found: 282.08827.

15d: 74% yield, 97% ee; $[\alpha]_D^{23}$ +2.6° (*c* 0.45, $CDCl_3$), Daicel Chiralcel IA with hexane/2-propanol = 9/1, flow = 0.5 mL min^{-1}, wavelength = 254 nm, t_R = 12 min (minor) and 14 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 8.3 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 6.68 (s, 2H), 4.09 (t, J = 6.8 Hz, 1H), 3.62 (s, 3H), 2.92 (dd, J = 16, 6.1 Hz, 1H), 2.86 (dd, J = 16, 7.1 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.98, 156.17, 149.47, 135.67, 134.19, 131.41, 129.11, 128.64, 127.68, 125.47, 116.07, 59.56, 40.08, 37.16, 20.69, 16.11; IR (neat) 1764, 1488, 1223, 1200, 1154, 1128, 1010, 924, 894, 815 cm^{-1}; MS (*m*/*z*) 195 (10.3), 223 (37.0), 239 (81.1), 253 (19.1), 263 (28.0), 278 (31.8), 296 (M^+, 100); Exact mass calcd for $C_{19}H_{20}O_3$: 296.1413. Found: 296.1400.

Synthesis of 16. To a mixture of 5-methylsalicylaldehyde (50 mmol) and K_2CO_3 (55 mmol) in ethanol (100 mL) and water (50 mL) was slowly added benzyl chloride (55 mmol) and the mixture was then stirred overnight at reflux. The product was obtained by crystallization. 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 7.66 (s, 1H), 7.46–7.30 (m, 6H), 6.95 (d, J = 8.4 Hz, 1H), 5.17 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.93, 159.15, 136.54, 136.24, 130.44, 128.68, 128.42, 128.19, 127.25, 124.84, 113.08, 70.54, 20.26; MS (*m*/*z*) 65 (10.3), 91 (100.0), 135 (8.2), 226 (M^+, 7.5); Exact mass calcd for $C_{15}H_{14}O_2$: 226.0994. Found: 226.0987.

Synthesis of 17. To a solution of **16** (77 mmol) and *p*-methoxyacetophenone (77 mmol) in ethanol (18 mL) was slowly added aqueous NaOH (100 mmol, 36 mL). The mixture was stirred overnight at 40 °C and then acidified with hydrochloric acid at room temperature. The product was obtained by crystallization. 99% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 15.6 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 15.6 Hz, 1H), 7.49 (d, J = 6.3 Hz, 2H), 7.45–7.35 (m, 4H), 7.14 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.88 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.63, 155.69, 139.65, 136.20, 131.35, 130.89, 130.29, 129.78, 128.23, 127.63, 127.36, 123.52, 122.68, 113.26, 111.96, 70.15, 54.95, 31.10, 22.17, 19.93; MS (*m*/*z*) 77 (11.2), 91 (100), 135 (89.0), 160 (16.0), 251 (47.3), 358 (M^+, 12.5); Exact mass calcd for $C_{24}H_{22}O_3$: 358.1569. Found: 358.1581.

Synthesis of 18. The procedure shown in general for 1,4-addition (Table 1) gave **18**. 91% yield; 95% ee. $[\alpha]_D^{23}$ +13.3° (*c* 0.28, $CDCl_3$), Daicel Chiralcel AD with hexane/2-propanol = 9/1, flow = 1.0 mL min^{-1}, wavelength = 254 nm, t_R = 17 min (minor) and 205 min (major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.31–7.12 (m, 10H), 6.98 (s, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 7.3 Hz, 2H), 6.77 (d, J = 8.3 Hz, 1H), 5.16 (t, J = 7.3 Hz, 1H), 5.01 (d, J = 14.6 Hz, 1H), 4.98 (d, J = 14.6 Hz, 1H), 3.83 (s, 3H), 3.65 (d, J = 7.3 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.98, 163.19, 153.81, 143.74, 137.26, 132.60, 130.32, 130.17, 129.84, 129.04, 128.38, 128.18, 128.14, 127.68, 127.62, 127.36, 125.94, 113.54, 112.05, 70.14, 55.39, 43.38, 40.40, 20.72; IR (neat) 1659, 1598, 1571, 1501, 1450, 1312, 1263, 1238, 1178, 1120, 1044, 1022, 994 cm^{-1}; MS (*m*/*z*) 91 (30.7), 135 (100), 241 (11.7), 345 (18.6), 345 (18.6), 436 (M^+, 1.8); Exact mass calcd for $C_{30}H_{28}O_3$: 436.2038. Found: 436.2059.

Syntheses and spectral data of **19**, **20**, and (*R*)-tolterodine (**21**) have been previously reported.[17]

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