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Rh-catalyzed enantioselective conjugate addition of arylboronic acids to 3-arylpropenoates: enantioselective synthesis of (R)-Tolterodine

Valerio Zullo and Anna Iuliano*[a]

Abstract: A highly enantioselective conjugate addition of arylboronic acids to 3-arylpropenoates is presented. The rhodium complexes obtained from deoxycholic acid derived binaphthyl phosphites showed good activity as well as very high enantioselectivity (ee up to 99%) in the conjugated addition to ethyl-3-arylpropenoates having different structure, allowing to obtain useful chiral building blocks for the synthesis of active pharmaceutical ingredients. The method was applied to the enantioselective synthesis of the antimuscarinic drug (R)-Tolterodine.

Introduction

The gem-diaryl substituted stereogenic tertiary carbon is a recurring structural motif in biologically active compounds, which are active pharmaceutical ingredients of commercially available drugs (**Figure 1**).[1]

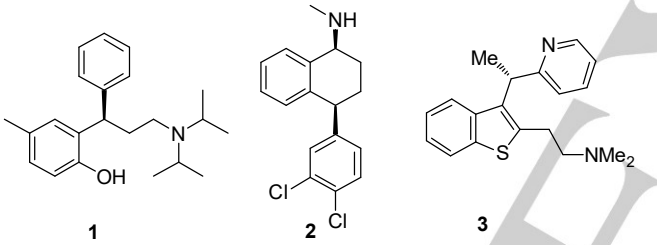

Figure 1: Structure of (R)-Tolterodine (**1**), (+)-Sertraline (**2**), H1-antihistamine (**3**)

For this reason many synthetic efforts have been devoted to the development of efficient strategies aimed at installing these subunits in highly enantioselective way,[2] and, among them, the enantioselective conjugate addition of aryl nucleophiles to electron-deficient olefins substituted with another aryl group at the β-position has attracted considerable attention.[3] As a significant example, optically active tolterodine **1** has been obtained using the conjugate addition of arylboronic acids to arylmethylene cyanoacetates.[3g]

Optically active 3,3-diarylpropanoates might represent useful chiral building blocks for the synthesis of these targets: indeed their carboxylic ester function is a versatile group for further transformations, leading to the desired compounds without appreciable racemization of the β stereogenic centre. These optically active intermediates can be obtained by enantioselective conjugate addition of aryl organometallic reagents to 3-arylpropenoates and to this aim the asymmetric Rh-catalysed conjugate addition of arylboronic acids to electron-deficient olefins can be the synthetic strategy of choice. However, although this reaction has been extensively studied on various electron-poor olefin substrates and different chiral ligands affording high enantiomeric excesses of the conjugate addition products are described in the literature,[4] few examples concern the conjugate addition on 3-arylpropenoates.[5] These examples deal with the use of bidentate ligands, such as diphosphines,[5b,5c] dienes[5a] and mixed olefine-sulfoxide ligands,[5d] and, to the best of our knowledge, only one example concerning the use of libraries of monodentate P-ligands[4f] is reported in the literature.

Our longstanding experience in the use of monodentate biaryl phosphites derived from deoxycholic acid as chiral ligands in the Rh-catalyzed enantioselective conjugate addition of arylboronic acids to electron-poor alkenes,[6] prompted us to explore their use as chiral promoters of the enantioselective C-C bond formation to obtain optically active 3,3-diarylpropanoates from 3-arylpropenoates.

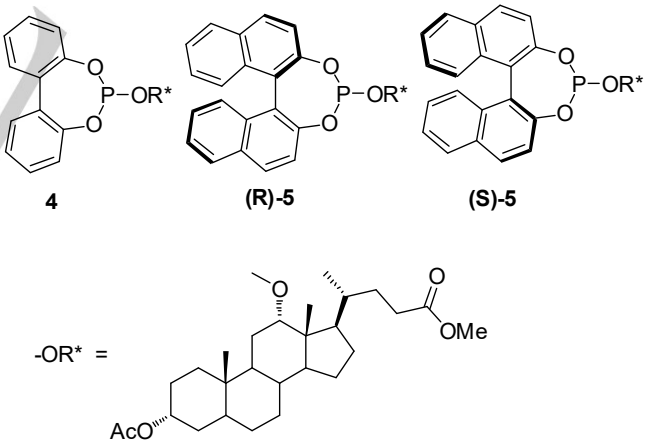

Figure 2: Structure of the phosphite ligands.

This approach sounds interesting because the deoxycholic acid derived monophosphite ligands are easily synthesised from economical starting material,[7] making the achievement of these chiral building blocks, and their conversion into active paharmaceutical ingredients, a valuable procedure. We present here the results obtained in the enantioselective Rh-catalyzed conjugate addition of arylboronic acids to 3-arylpropenoates using the deoxycholic acid derived biphenyl and binaphthyl phosphites **4** and **5** (**Figure 2**) as Rh-ligands, and the application of this procedure to the synthesis of (R)-Tolterodine

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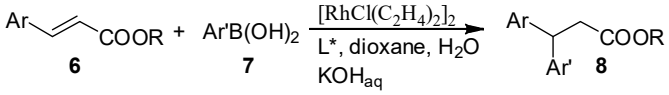
1 (**Figure 1**), a potent and competitive muscarinic antagonist used for the treatment of urinary urge incontinence and other overactive bladder disorders.[8]

Results and Discussion

The results concerning the use of the chiral phosphite ligands **4** and **5** in the Rh-catalysed conjugate addition of arylboronic acids to alkyl cinnamates are reported in Table 1.

Table 1. Conjugate addition of aryl boronic acids to alkyl 3-arylpropenoates: study of the reaction[a]



a: Ar, Ar' = Ph; **b**: Ar, Ar' = 4-CF_3-Ph; **c**: Ar, Ar' = 4-OMePh; **d**: Ar, Ar' = 4-MePh

Entry	Ar	Ar'	R	L*	T [h]	Yield [%][b]	ee [%][c] (AC)[d]
1	Ph	4-CF_3Ph	Et	**4**	22	98 (**8ab**)	88 (S)
2	4-CF_3Ph	Ph	Et	**4**	22	99 (**8ba**)	80 (R)
3	Ph	4-OMePh[e]	Et	**4**	38	92 (**8ac**)	74 (S)
4	4-OMePh	Ph	Et	**4**	26	83 (**8ca**)	70 (R)
5	Ph	4-MePh	Et	**4**	22	99 (**8ad**)	78 (S)
6	4-MePh	Ph	Et	**4**	22	99 (**8da**)	74 (R)
7	Ph	4-MePh	Et	**(S)-5**	22	62 (**8ad**)	84 (R)
8	Ph	4-MePh	Et	**(R)-5**	22	84 (**8ad**)	94 (S)
9[f]	Ph	4-MePh	Et	**(R)-5**	30	nr[g]	-
10[h]	Ph	4-MePh	Et	**(R)-5**	48	nr[g]	-
11	Ph	4-MePh	Me	**(R)-5**	24	73	Nd
12	Ph	4-MePh	tBu	**(R)-5**	24	16	Nd

[a]The reaction was carried out with 3-arylpropenoate **6** (1 mmol), arylboronic acid **7** (2 equiv.), KOH 1M (1 mmol) in dioxane: H_2O (4:2 mL) at room temperature in the presence of 1.5 mol% of the catalyst generated from $[RhCl(C_2H_4)_2]_2$ and ligand (Rh:L=1:2) unless otherwise noted.

[b] Isolated yield.

[c] Determined by HPLC analysis on chiral stationary phase (see Supporting Information).

[d] Absolute configuration, assigned by comparing the elution order with the literature data.

[e] A further equivalent of arylboronic acid was added after 20h

[f] KF was used as base.

[g] No reaction.

[h] The catalyst was generated from $[RhCl(C_2H_4)_2]_2$ and ligand (Rh:L=1:1).

The effect of some reaction parameters, such as ligand, ester substituent and Rh:P ratio, as well as some stereochemical features were investigated using the optimized reaction conditions for enone substrates[6c] and the reactions were carried out until complete substrate conversion or when it did not proceed further.

The conjugate addition of arylboronic acids bearing both electron withdrawing and electron donating substituents at the 4-position to ethyl cinnamate **6a**, performed in the presence of phosphite **4** as Rh-ligand, gave the corresponding ethyl-3,3-diarylpropanoates in high to almost quantitative yields and with ee ranging from 74 to 88% (entries 1,3,5). Also the conjugate addition of phenyl boronic acid **7a** to ethyl propanoates bearing the same substituents at the 4-position of the aryl moiety worked well, affording the chiral products in very high yields and ee from 70 to 80%. (entries 2,4,6). Thanks to the good enantioselectivity obtained with both substituted and unsubstituted ethyl cinnamates and phenylboronic acids both the enantiomers of the same compound can be obtained simply by exchanging the substituents between the aryl boronic acid and the 3-arylpropenoate (entries 1 and 2, 3 and 4, 5 and 6), as observed with other kind of electron poor alkenes.[6d] These data clearly show that phosphite **4**, bearing the flexible biphenyl moiety, is capable of asymmetric induction, as in other cases:[6],[9] in fact, even if it has been demonstrated that its Rh-complexes, both mono and di-substituted, exist in solution as equimolar mixture of rapidly interconverting diastereoisomers,[6c] they have different reactivity:[6c],[6d] the most reactive enters in the catalytic cycle shifting the *tropo*-inversion[10] equilibrium toward itself and determining the stereochemical outcome of the reaction. This means also that, using the atropoisomeric analogues **5**, diastereoisomeric Rh-complexes having different activity and enantioselectivity can be obtained, one of which will be more active and/or more enantioselective than the other. Since this diastereoisomer generally results also more enantioselective than the flexible analogue, both diastereomeric atropoisomeric phosphites **(S)-5** and **(R)-5** were assayed as chiral promoters of the addition of 4-methylphenyl boronic acid **7d** to ethylcinnamate. As expected, the catalytic Rh-complexes of the diastereomeric phosphites showed different activity and enantioselectivity: using phosphite **(S)-5**, lower yield and ee of the addition product was obtained (entry 7), whereas phosphite **(R)-5**, gave product **8ad** with higher ee than both **(S)-5** and **4** (entry 8)**.** Therefore the (R)-binaphthyl phosphite moiety and the asymmetric cholestanic backbone are in a matched relationship, giving rise to the best performing ligand. In addition, these results clearly show the important role played by the cholestanic moiety in the asymmetric induction exherted by the atropoisomeric ligands, as already demonstrated.[7a] The yield is lower than that obtained using ligand **4**, probably because of the higher steric hindrance of the binaphthyl moiety with respect to the biphenyl one. The absolute configuration of the prevailing enantiomer of the addition products depended on the absolute configuration of the binaphthyl moiety (entries 7 and 8): it is to note that the *tropos* phosphite **4** gave a (S)-configurated addition product, as the best performing atropoisomeric ligand **(R)-5**, suggesting that the biphenyl moiety of **4** assumes a *M* screw sense, corresponding to the (R) absolute configuration of the binaphthyl moiety, in the catalytically active Rh-complex. The attempt to catalyse the reaction with a mono-substituted Rh-complex did not collect success: the catalyst generated by mixing ligand and $[RhCl(C_2H_4)_2]_2$ in 1:1 Rh:P ratio[6b] did not give the product (entry 10). No reaction was observed also changing the base from KOH to KF (entry 9). Finally, to verify the influence of the alkyl

ester group on the outcome of the reaction methyl and tert-butyl cinnamates were used as substrates: lower yields of the addition products were obtained in both cases (entries 11 and 12), especially using the tert-butyl ester, suggesting that the ethyl ester is the best substrate for this reaction.

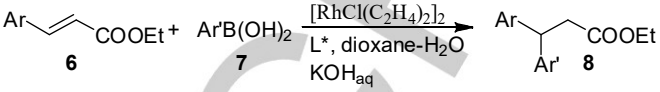
The reaction conditions affording the best results in terms of ee of the conjugate addition products, i.e. the use of the atropoisomeric ligands **5**, the ethyl ester group on the substrate and KOH as a base, were used to expand the scope of the method toward both ethyl 3-arylpropenoates and arylboronic acids having different structure and the results are collected in Table 2. Since the diastereomeric ligands, **(R)-5** and **(S)-5**, gave product **8ad** in higher ee than the flexible ligand **4**, even if **(R)-5** was the best performing one, both were used as chiral promoters of the enantioselective conjugate addition, to check if **(R)-5** afforded the most active and enantioselective catalyst also using different substrates and arylboronic acids. All the reactions were stopped at the reference time of 30 h, but when arylboronic acids prone to the proto de-boronation reaction (**7j-k**) were used, a further equivalent of these was added after 15 h, to guarantee the presence of a sufficient amount of the organometallic reagent in the reaction medium.

The reaction carried out on 3-arylpropenoates and arylboronic acids bearing fluorine or chlorine substituents at the para position of the aromatic ring, gave the conjugate addition products in good to excellent yields (entries 1-8), both using ligand **(R)-5** and **(S)-5**, whereas the ees of the products depended on the stereochemistry of the ligand. In the case of compounds **6f (R)-5** was the most enantioselective ligand (entries 5 and 6), whereas with **6e** and with the aryl boronic acids **7e** and **7f**, the ligand affording the highest ees was **(S)-5** (entries 1 and 2, 3 and 4, 7 and 8). A strong matched-mismatched effect of the ligand stereochemistry on the outcome of the reaction was found in the case of both 3-arylpropenoate and arylboronic acid possessing the 2-naphthyl group: in these cases the best performing catalyst was the one obtained from ligand **(R)-5** (entries 9 and 11), the diastereomeric ligand **(S)-5** affording a catalyst not only less enantioselective (entry 10) but also very less active so that no reaction was observed between **6a** and **7g** (entry 12).

The same trend was observed when the aryl group was 3-fluoro-4-methylphenyl (entries 13-16). By contrast, in the case of 3-arylpropenoates and arylboronic acids bearing substituents at the position 2 of the phenyl ring, the most enantioselective catalyst and also the most active, except in one case (entry 22), is that one obtained from ligand **(S)-5** (entries 22-28): the strongest matched-mismatched effect was found using orto-tolylboronic acid, which did not react with ethylcinnamate in the presence of the less active Rh-catalyst generated from **(R)-5** (entry 27).

The reaction of conjugate esters or arylboronic acids possessing substituents at the position 3 of the phenyl ring proceeded with similar or equal enantioselectivity in the presence of both the diastereomeric catalytic systems, which also demonstrated similar catalytic activity (entries 17-20). These results suggest that, unlike conjugate addition promoted by the same catalytic systems on different electron poor alkenes,[6] the best performing diastereomeric ligand is not always the same, but the structure of substrate and/or arylboronic acid plays the fundamental role in determining activity and/or enantioselectivity of the chiral Rh-catalyst formed in the catalytic cycle, in a sort of "substrate dependent asymmetric activation".[11] As a rule of thumb in the presence of substrates or organometallic reagents bearing one ortho-or meta substituent the best performing ligand is **(S)-5,** whereas in the other cases **(R)-5** give the best results, apart from the case of 4-halo substituted phenylboronic acids (entries 4 and 8) and ester **6e** (entry 2).

Table 2: Conjugate addition of aryl boronic acids to ethyl 3-arylpropenoates[a]



a: Ar, Ar' = Ph; **e**: Ar, Ar' = 4-FPh; **f**: Ar, Ar' = 4-ClPh; **g**: Ar, Ar' = 2-Naph; **h**: Ar, Ar' = 3-F-4MePh; **i**: Ar = 3-PhOPh; **j**: Ar' = 3-MeOPh; **k**: Ar, Ar' = 2-MeOPh; **l**: Ar, Ar' = 2-MePh

Entry	Ar	Ar'	L*	Yield [%][b]	ee[%][c] (CA)
1	4-FPh	Ph	**(R)-5**	99 (**8ea**)	92 (-)[d]
2	4-FPh	Ph	**(S)-5**	99 (**8ea**)	94 (+)[d]
3	Ph	4-FPh	**(R)-5**	90 (**8ae**)	92 (+)[d]
4	Ph	4-FPh	**(S)-5**	95 (**8ae**)	96 (-)[d]
5	4-ClPh	Ph	**(R)-5**	91 (**8fa**)	92 (R)[e]
6	4-ClPh	Ph	**(S)-5**	85 (**8fa**)	86 (S)[e]
7	Ph	4-ClPh	**(R)-5**	95 (**8af**)	92 (S)[e]
8	Ph	4-ClPh	**(S)-5**	99 (**8af**)	94 (R)[e]
9	2-Naph	Ph	**(R)-5**	90 (**8ga**)	94 (R)[e]
10	2-Naph	Ph	**(S)-5**	31(**8ga**)	84 (S)[e]
11	Ph	2-Naph	**(R)-5**	95 (**8ag**)	94 (S)[e]
12	Ph	2-Naph	**(S)-5**	nr[f]	-
13	3-F,4-MePh	Ph	**(R)-5**	90 (**8ha**)	92 (-)[d]
14	3-F,4-MePh	Ph	**(S)-5**	85(**8ha**)	88 (+)[d]
15	Ph	3-F,4-MePh	**(R)-5**	99(**8ah**)	90 (+)[d]
16	Ph	3-F,4-MePh	**(S)-5**	nr[f]	-
17	3-PhOPh	Ph	**(R)-5**	99 (**8ia**)	90 (-)[d]
18	3-PhOPh	Ph	**(S)-5**	92 (**8ia**)	94 (+)[d]
19	Ph	3-OMePh[g]	**(R)-5**	90 (**8aj**)	94 (R)[e]
20	Ph	3-OMePh[g]	**(S)-5**	99(**8aj**)	94 (S)[e]
22	2-OMePh	Ph	**(R)-5**	70 (**8ka**)	92 (R)[e]
23	2-OMePh	Ph	**(S)-5**	60 (**8ka**)	96 (S)[e]
24	Ph	2-OMePh[g]	**(S)-5**	45 (**8ak**)	99 (R)[e]
25	2-MePh	Ph	**(R)-5**	75 (**8la**)	94 (R)[e]
26	2-MePh	Ph	**(S)-5**	99 (**8la**)	96 (S)[e]
27	Ph	2-MePh	**(R)-5**	nr[f]	-
28	Ph	2-MePh	**(S)-5**	95 (**8al**)	96 (R)[e]

[a] The reaction was carried out with ethyl 3-arylpropenoate **6** (1 mmol), arylboronic acid **7** (2 equiv.), KOH 1M (1 mmol) in dioxane: H_2O (4:2 mL) at room temperature for 30h in the presence of 1.5 mol% of the catalyst generated from $[RhCl(C_2H_4)_2]_2$ and ligand (Rh:L=1:2) unless otherwise noted.

[b] Isolated yield

[c] Determined by HPLC analysis on chiral stationary phase column (see Supporting Information)

[d] Sign of the optical rotation of the prevailing enantiomer

[e] Absolute configuration, assigned by comparing the sign of optical rotation with the literature data.

[f] No reaction

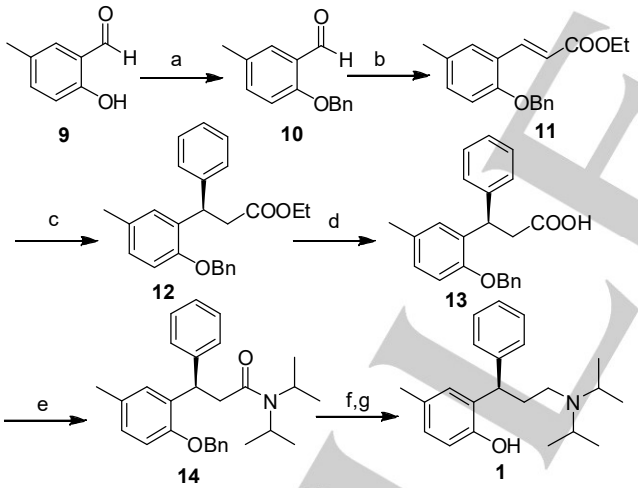
[g] A further equivalent of arylboronic acid was added after 15h

.

The absolute configuration of the prevailing enantiomer of the addition product still depended on the absolute configuration of the binaphthyl moiety of the chiral ligand, allowing to obtain both the enantiomer of the addition product using the two diastereomeric ligands. In addition, when a strong matched-mismatched effect was observed, preventing the achievement of one of the two enantiomeric products (entries 11 and 12, 15 and

16, 27 and 28), the same result can be obtained simply by exchanging the aryl groups of alkene and organometallic reagent (entries 9 and 11, 13 and 15, 26 and 28), because yields and the ee are from good to excellent with all the couples substrate/arylboronic acid.

To further demonstrate the synthetic utility of this methodology, the synthesis of pharmaceutically active ingredient Tolterodine **1** was carried out, starting from commercially available aldehyde **9** and phenylboronic acid **7a** (**Scheme 1**). According to **Scheme 1**, the ethyl 3-arylpropenoate **11** was obtained in two steps from 5-methylsalycilaldehyde **9**, in 78% overall yield. The conjugate addition of phenylboronic acid to **11** was performed, under the standard reaction conditions, using ligand **(R)-5**, which give the (R) prevailing enantiomer of the addition product of phenylboronic acid on ethyl-3-arylpropenoates bearing an ortho substituent (Table 2), obtaining a 71% conversion of **11** to **12**. The addition product was obtained in 96% ee, but separation from the precursor was impossible, the two compounds showing the same R_f, under several chromatographic conditions. Thus the mixture of **11** and **12** was reacted with NaOH solution to hydrolyze the ester group and the resulting mixture of the two carboxylic acids was treated with diisopropyl amine in the presence of EDC, affording, after chromatographic purification of the crude, the pure amide **14**, in 40% overall yield from **11**. Reduction of the amide and hydrogenolysis of the benzyl protecting group gave almost quantitative yield of (R)-(+)-Tolterodine, whose absolute configuration was inferred by the sign of the optical rotation, [2b] so confirming also the absolute configuration of all the optically active intermediates.



Reagents and conditions: a) K_2CO_3, 18-c-6, acetone, BnBr, reflux, 3h; b) NaH, $(OEt)_3POCH_2COOEt$, THF, r.T., 2h; c) $PhB(OH)_2$, $[Rh(C_2H_4)_2Cl]_2$ (1.5 mol%), **(R)-5** (6 mol%), dioxane, H_2O, KOH, r.T., 24h; d) 10% NaOH, reflux, 3h; e) $(^iPr)_2NH$, EDC, DMAP, CH_2Cl_2, r.T., 24h,; f) BH_3DMS, THF, reflux, 20h; g) H_2, Pd/C, r.T., 24h

Scheme 1: Synthesis of (R)-(+)-Tolterodine

Conclusions

A Rh-catalyzed enantioselective conjugate addition of arylboronic acids to ethyl 3-arylpropenoates has been developed, leading to the optically active addition products in good yields and with excellent enantioselectivity (ee up to 99%). The enantioselective catalytic system, obtained starting from easily accessible and economic deoxycholic acid-derived biaryl phosphites, is versatile giving good results independently of the structure of both alkene substrate and arylboronic acid. This enantioselective reaction represents an efficient protocol to achieve enantiomerically enriched useful chiral building blocks, bearing a gem-diaryl substituted stereogenic tertiary carbon and its usefulness is highlighted by the enantioselective synthesis of (R)-Tolterodine.

Experimental Section

General Methods and Materials

All the reactions involving sensitive compounds were carried out under dry N_2, in flame-dried glassware. CH_2Cl_2, 1,4-dioxane and THF were dried through distillation on proper drying agent. H_2O, acetic acid and aqueous KOH solution were disareated by nitrogen bubbling. Methanol was disareated by cycles of vacuum-nitrogen purging. The (E)-3-aryl-2-propenoates (**6a-l**),[12] the racemic 3,3-diaryl propanoates[13] and phosphites[7a,7c] **4**, **(R)-5** and **(S)-5** were synthesized according to a literature procedure and matched the reported characteristics. If not noted otherwise, the other compounds were commercially available and used as received. TLC analyses were carried out with Merk 60 F254 plates (0.2mm) and chromatography purifications were carried out with Biotage Isolera™ Chromatograph equipped with an UV-Vis detector. The ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 at 200MHz or on a Bruker 400MHz NMR spectrometer. The following abbreviations are used: s=singlet, bs=broad signal, d=doublet, dd=double doublet, t=triplet, td=triple doublet, q=quartet, qd=quadruple doublet, qui=quintet, m=multiplet. ^{13}C NMR spectra were recorded at 100 MHz. ^1H and ^{13}C NMR chemical shifts (ppm) are referred to TMS as external standard. HPLC analyses were performed on a JASCO PU-1580 intelligent HPLC pump equipped with a JASCO UV-975 detector. GC analyses were performed on a Perkin-Elmer Autosystem XL chromatograph equipped with an Agilent DB-1701 (14%-Cyanopropyl-phenyl)-methylpolysiloxane column (25m × 0.25mm × 0.25µm), using nitrogen as carrier gas. Peak identification was performed using independently synthesized samples. Optical rotations were measured in 1dm cells at the sodium D line, using a Jasco DIP 360 polarimeter. Melting points were measured using a Büchi Melting Point B-545. Elemental analyses were obtained using an Elementar Vario MICRO cube equipment.

General procedure for the synthesis of Alkyl (E)-3-Aryl-2-propenoates[12]

Under a nitrogen atmosphere, trimethyl-, triethyl- or tertbutyl, diethyl-phosphonoacetate (1.1mmol) was added dropwise to a suspension of NaH (60% mineral oil dispersion, 1.3mmol of NaH) in dry THF (5mL) at 0 °C (ice-water bath). The mixture was stirred for 20 minutes and then a solution of the corresponding aldehyde (1.0mmol) in dry THF (1.3mL) was added dropwise. The ice-bath was removed and the mixture was stirred at room temperature, monitoring the reaction by GC-FID analysis. After 2-4 hours of stirring the mixture was quenched with H_2O (5mL) and extracted with CH_2Cl_2 (3 x 5mL). The combined organic extracts were washed with H_2O (5mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to yield **6a-l** as chemically pure compounds.

General procedure for the synthesis of racemic Alkyl 3,3-diarylpropranoates[13]

Under a nitrogen atmosphere, Arylboronic acid (3.0mmol), Alkyl (E)-3-Aryl-2-propenoate (1.0mmol), $Pd(OAc)_2$ (5mol%), 2,2'-bipyridyl (20mol%), disareated acetic acid (1mL), dry THF (0.5mL) and disareated H_2O (0.3mL) were stirred at 50°C. The reaction was monitored by GC-FID analysis and after 72h the reaction was quenched with 5% NaOH solution (15mL) and extracted with Et_2O (3 x 8mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by filtration on silica gel (n-Hexane:Ethyl Acetate 97:3) or by Biotage Isolera™ Chromatograph (n-Hexane:Ethyl Acetate 97:3).

General procedure for rhodium-catalyzed asymmetric conjugate addition of arylboronic acids to (E)-3-arylpropenoates

Under nitrogen atmosphere, freshly distilled 1,4-dioxane (4mL) was added to $[RhCl(C_2H_4)_2]_2$ (1.5mol%) and phosphite **4** or **(S)-5**, **(R)-5** (6mol%). The mixture was stirred for 30 min at room temperature and then disareated H_2O (2mL), disareated KOH solution (1M, 1mL), arylboronic acid (2.0mmol) and the (E)-3-arylpropenoate (1mmol) were added. The mixture was stirred at room temperature and the reaction was monitored by GC-FID analysis. The reaction was quenched after 30h, if not noted otherwise, with 5% NaOH (15mL) and extracted with Et_2O (3 x 8mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to give the crude product. Chromatographic purification with Biotage Isolera™ Chromatograph (n-Hexane:Ethyl Acetate 97:3) gave the pure product.

Ethyl 3-phenyl-3-(4-trifluoromethylphenyl)propanoate[14]

8ab: after 22h reaction yield 98%, 315 mg; **8ba**: after 22h reaction yield 99%, 318 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ=7.57 (d, *J*=8.0 Hz, 2H), 7.39 (d, *J*=8.1 Hz, 2H), 7.36–7.29 (m, 2H), 7.29–7.20 (m, 3H), 4.65 (t, *J*=8.0 Hz, 1H), 4.07 (q, *J*=7.1 Hz, 2H), 3.09 (d, *J*=8.0 Hz, 2H), 1.15 (t, *J*=7.1 Hz, 3H). **HPLC:** Daicel Chiracel OD-H; n-Hexane:2-Propanol 99:1; 1.0mL/min; 220nm; t_R(1)=7.5min, t_R(2)=9.2min. **8ab obtained using ligand 4: $[\alpha]_D^{25°C}$**= -2.3 (c=0.991, $CHCl_3$) for 88% ee **8ba obtained using ligand 4: $[\alpha]_D^{25°C}$**= +2.1 (c=0.983, $CHCl_3$) for 80% ee

Ethyl 3-(4-Methoxyphenyl)-3-phenylpropanoate[14]

8ac: after 38h reaction yield 92%, 261 mg; **8ca**: after 26h reaction yield 83%, 235 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ=7.34 –7.15 (m, 7H), 6.86 (d, *J*=8.7 Hz, 2H), 4.54 (t, *J*=8.0 Hz, 1H), 4.07 (q, *J*=7.1 Hz, 2H), 3.79 (s, 3H), 3.06 (d, *J*=8.1 Hz, 2H), 1.15 (t, *J*=7.1 Hz, 3H). **HPLC:** Daicel Chiracel OD-H; n-Hexane:2-Propanol 99:1; 1.0mL/min; 220nm; t_R(1)=11.6min, t_R(2)=14.3min. **8ac obtained using ligand 4: $[\alpha]_D^{25°C}$**= -1.6 (c=0.991, $CHCl_3$) for 74% ee **8ca obtained using ligand 4: $[\alpha]_D^{25°C}$**= +1.5 (c=0.995, $CHCl_3$) for 70% ee

Ethyl 3-(4-Methylphenyl)-3-phenylpropanoate[14]

After 22 h reaction **8ad**: with ligand **4** yield 99%, 265 mg; with ligand **(S)-5** yield 62%, 166 mg; with ligand **(R)-5** yield 84%, 225 mg; **8da**: with ligand **4** yield 99%, 265 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ=7.36–7.11 (m, 9H), 4.58 (t, *J*=8.0 Hz, 1H), 4.09 (q, *J*=7.1 Hz, 2H), 3.09 (d, *J*=8.1 Hz, 2H), 2.35 (s, 3H), 1.17 (t, *J*=7.1 Hz, 3H). **HPLC:** Lux 5µm Cellulose-1; n-Hexane:2-Propanol 97:3; 1.0mL/min; 220nm; t_R(1)=5.8min, t_R(2)= 8.8min. **8ad obtained using ligand 4: $[\alpha]_D^{25°C}$**= +1.4 (c=0.990, $CHCl_3$) for 78% ee **8da obtained using ligand 4: $[\alpha]_D^{25°C}$**= -1.4 (c=0.982, $CHCl_3$) for 74% ee **8ad obtained using ligand (S)-5: $[\alpha]_D^{25°C}$**= -1.5 (c=0.965, $CHCl_3$) for 84% ee **8ad obtained using ligand (R)-5: $[\alpha]_D^{25°C}$**= +1.7 (c=0.971, $CHCl_3$) for 94% ee

Ethyl 3-(4-Fluorophenyl)-3-phenylpropanoate[13]

8ea: with ligand **(R)-5** yield 99%, 269 mg; with ligand **(S)-5** yield 99%, 269 mg; **8ae**: with ligand **(R)-5** yield 99%, 245 mg; with ligand **(S)-5** yield 95%, 258 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$, 25°C) δ=7.33-7.16 (m, 7H), 6.96 (t, J=8.7 Hz), 4.53 (t, J=8.0 Hz, 1H), 4.03 (q, J=7.1 Hz, 2H), 3.02 (d, J=8.0 Hz, 2H), 1.11 (t, J=7.1 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$, 25°C) δ=171.6, 162.7, 160.3, 143.3, 139.2 129.2, 129.1, 128.6, 127.6, 126.7, 115.4, 115.2, 60.5, 46.4, 41.0, 14.1. **HPLC-FSC:** Lux 5µm Cellulose-1; 1.0 mL/min; n-Hexane:2-Propanol 99:1; 220 nm. t_R(1)=7.9min, t_R(2)=10.0min. **8ea obtained using ligand (R)-5: $[\alpha]_D^{28°C}$**= -6.4 (c=0.740, $CHCl_3$) for 92% ee **8ea obtained using ligand (S)-5: $[\alpha]_D^{28°C}$**= +6.5 (c=0.654, $CHCl_3$) for 94% ee **8ae obtained using ligand (R)-5: $[\alpha]_D^{28°C}$**= +6.4 (c=0.946, $CHCl_3$) for 92% ee **8ae obtained using ligand (S)-5: $[\alpha]_D^{28°C}$**= -6.7 (c=0.831, $CHCl_3$) for 96% ee

Ethyl 3-(4-Chlorophenyl)-3-phenylpropanoate[14]

8fa with ligand **(R)-5** yield 91%, 263 mg; with ligand **(S)-5** yield 85%, 245 mg; **8af** with ligand **(R)-5** yield 95%, 274 mg; with ligand **(S)-5** yield 99%, 285 mg. **^{1}H NMR:**(400 MHz, $CDCl_3$, 25°C) δ=7.33-7.14 (m, 9H), 4.52 (t, *J*=8.0 Hz, 1H), 4.04 (q, *J*=7.1 Hz, 2H), 3.02 (d, *J*=8.0 Hz, 2H), 1.12 (t, *J*=7.1 Hz, 3H). **^{13}C NMR:**(100 MHz, $CDCl_3$, 25°C) δ=171.5, 143.0, 142.0, 132.3, 129.1, 128.7, 127.6, 126.7, 60.6, 46.5, 40.7, 14.1. **HPLC:** Lux 5µm Cellulose-1; 1.0mL/min; n-Hexane:2-Propanol 99:1; 230 nm. t_R(1)=9.8min, t_R(2)=14.8min. **8fa obtained using ligand (R)-5: $[\alpha]_D^{24°C}$**= +1.5 (c=0.983, $CHCl_3$) for 92% ee **8fa obtained using ligand (S)-5: $[\alpha]_D^{24°C}$**= -1.4 (c=0.876, $CHCl_3$) for 86% ee **8af obtained using ligand (R)-5: $[\alpha]_D^{24°C}$**= -1.5 (c=0.894, $CHCl_3$) for 92% ee **8af obtained using ligand (S)-5: $[\alpha]_D^{24°C}$**= +1.5 (c=0.844, $CHCl_3$) for 94% ee

Ethyl 3-(Naphtalen-2-yl)-3-phenylpropanoate[14]

8ga with ligand **(R)-5** yield 90%, 274 mg; with ligand **(S)-5** yield 31%, 95 mg; **8ag** with ligand **(R)-5** yield 95%, 289 mg.**^{1}H NMR:**(400 MHz, $CDCl_3$, 25°C) δ=7.87-7.70 (m, 4H), 7.57-7.16 (m, 8H), 4.75 (t, *J*=7.9 Hz, 1H), 4.06 (q, *J*=7.1 Hz, 2H), 3.25-3.11 (m, 2H), 1.08 (td, *J*=7.1, 1.4 Hz, 3H). **^{13}C NMR:**(100 MHz, $CDCl_3$, 25°C) δ=171.8, 143.4, 140.9, 133.4, 132.3, 128.6, 128.3, 127.9, 127.8 (2 peaks), 127.6, 126.6 (2 peaks), 126.1, 125.7, 125.6, 112.4, 60.5, 47.1, 40.8, 14.1. **HPLC:** Lux 5µm Cellulose-1; 1.0mL/min; n-Hexane:2-Propanol 99:1; 230 nm. t_R(1)=15.0min, t_R(2)=24.7min. **8ga obtained using ligand (R)-5: $[\alpha]_D^{26°C}$**= -38.5 (c=1.200, $CHCl_3$) for 94% ee **8ga obtained using ligand (S)-5: $[\alpha]_D^{26°C}$**= +34.9 (c=0.980, $CHCl_3$) for 84% ee **8ag obtained using ligand (R)-5: $[\alpha]_D^{26°C}$**= +38.5 (c=0.770, $CHCl_3$) for 94% ee

Ethyl 3-(3-Fluoro, 4-Methylphenyl)-3-phenylpropanoate

8ha with ligand **(R)-5** yield 90%, 257 mg; with ligand **(S)-5** yield 85%, 243 mg; **8ah** with ligand **(R)-5** yield 99%, 283 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$, 25°C) δ=7.33-7.19 (m, 5H), 7.10 (t, *J*=7.9 Hz, 1H), 6.97-6.87 (m, 2H), 4.52 (t, *J*=8.0 Hz, 1H), 4.07 (q, *J*=7.1 Hz, 2H), 3.03 (d, *J*=8.0 Hz, 2H), 2.23 (s, 3H), 1.15 (t, *J*=7.1 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$, 25°C) δ=171.6, 143.1, 131.4 (two peaks), 128.6, 127.6, 126.7, 123.0, 114.4, 114.1, 60.5, 46.5, 40.7, 14.2, 14.1 (two peaks). **HPLC:** Lux 5µm Cellulose-1; 1.0mL/min; n-Hexane:2-Propanol 99:1; 230 nm. t_R(1)=8.7min, t_R(2)=15.4min. **Anal. Calcd. For $C_{18}H_{19}FO_2$:** C, 75.50; H, 6.69; F, 6.63; O, 11.17. **Found:** C, 75.55; H, 6.71. **8ha obtained using ligand (R)-5: $[\alpha]_D^{26°C}$**= -6.3 (c=0.940, $CHCl_3$) for 92% ee **8ha obtained using ligand (S)-5: $[\alpha]_D^{26°C}$**=+6.0 (c=0.800, $CHCl_3$) for 88% ee **8ah obtained using ligand (R)-5: $[\alpha]_D^{26°C}$**= +6.4 (c=0.970, $CHCl_3$) for 90% ee

Ehthyl 3-(3-Phenoxyphenyl)-3-phenylpropanoate

8ia with ligand **(R)-5** yield 99%, 342 mg; with ligand **(S)-5** yield 92%, 317 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$, 25°C) δ=7.40-7.19 (m, 8H), 7.13 (t, J=7.4 Hz, 1H), 7.06-6.97 (m, 4H), 6.86 (dd, J=8.1, 1.6 Hz, 1H), 4.58 (t, J=8.0 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.07 (d, J=8.0 Hz, 2H), 1.16 (t, J=7.1 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$, 25°C) δ=171.7, 157.3, 157.2,

145.7, 143.1, 129.8, 129.7, 128.6, 127.7, 126.7, 123.2, 122.7, 118.7, 118.4, 116.8, 60.5, 47.0, 40.8, 29.8, 14.1. **HPLC:** Lux 5µm Cellulose-1; 1.0mL/min; n-Hexane:2-Propanol 98:2; 230 nm. t_R(1)=16.7min, t_R(2)=28.7min. **Anal. Calcd. For: $C_{23}H_{22}O_3$:** C, 79.74; H, 6.40; O, 13.85; **Found:** C, 79.69; H, 6.41. **8ia obtained using ligand (R)-5: $[\alpha]_D^{25°C}$**= -4.3 (c=0.950, $CHCl_3$) for 90% ee **8ia obtained using ligand (S)-5: $[\alpha]_D^{25°C}$**= +4.5 (c=0.970, $CHCl_3$) for 94% ee

Ethyl 3-(3-Methoxyphenyl)-3-phenylpropanoate[14]

8aj with ligand **(R)-5** yield 90%, 256 mg; with ligand **(S)-5** yield 99%, 281 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$) δ=7.31-7.14 (m, 6H), 6.84 (d, J = 7.7 Hz, 1H), 6.78 (s, 1H), 6.75 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.52 (t, J = 8.0 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.03 (d, J = 8.0 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$) δ=171.8, 159.7, 145.1, 143.3, 129.5, 128.5, 127.7, 126.6, 120.1, 120.0, 113.8, 111.6, 60.5, 55.2, 47.1, 40.8, 14.1. **HPLC:** Lux 5µm Cellulose-2; 1.0 mL/min; n-Hexane:2-Propanol 99:1; 230 nm. t_R(1)=14.5min, t_R(2)=18.4 min. **8aj obtained using ligand (R)-5: $[\alpha]_D^{27°C}$**= -3.1 (c=0.845, $CHCl_3$) for 94% ee **8aj obtained using ligand (S)-5: $[\alpha]_D^{27°C}$**= +3.1 (c=0.720, $CHCl_3$) for 94% ee

Ethyl 3-(2-Methoxyphenyl)-3-phenylpropanoate[15]

8ka with ligand **(R)-5** yield 70%, 199 mg; with ligand **(S)-5** yield 60%, 171 mg; **8ak** with ligand **(S)-5** yield 45%, 128 mg. **^{1}H NMR:** (400 MHz, $CDCl_3$, 25°C) δ=7.40-7.17 (m, 7H), 6.96 (t, J=7.4 Hz, 1H), 6.89 (d, J=8.2 Hz, 1H), 5.02 (t, J=8.1 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 3.19-3.04 (m, 2H), 1.16 (t, J=7.1 Hz, 3H). **^{13}C NMR:** (100 MHz, $CDCl_3$, 25°C) δ=172.1, 157.0, 143.3, 132.0, 128.3, 128.0, 127.8, 127.7, 126.2, 120.5, 110.9, 60.3, 55.4, 40.5, 39.8, 14.1. **HPLC:** Lux 5µm Cellulose-1; 1.0 mL/min; n-Hexane:2-Propanol 98:2; 230 nm. t_R(1)=10.6min, t_R(2)=35.0min. **8ka obtained using ligand (R)-5: $[\alpha]_D^{28°C}$**= +15.5 (c=0.950, $CHCl_3$) for 92% ee **8ka obtained using ligand (S)-5: $[\alpha]_D^{28°C}$**= -16.2 (c=0.960, $CHCl_3$) for 96% ee **8ak obtained using ligand (S)-5: $[\alpha]_D^{28°C}$**= +16.9 (c=0.990, $CHCl_3$) for 99% ee

Ethyl 3-(2-Methylphenyl)-3-phenylpropanoate[14]

8la with ligand **(R)-5** yield 75%, 201 mg; with ligand **(S)-5** yield 99%, 265 mg; **8al** with ligand **(S)-5** yield 95%, 255 mg; **^{1}H NMR:** (400 MHz, $CDCl_3$, 25°C) δ=7.36-7.07 (m, 9H), 4.74 (t, J=8.0 Hz, 1H), 4.03 (q, J=7.1 Hz, 2H), 3.02 (dd, J=8.0, 1.2 Hz, 2H), 2.29 (s, 3H), 1.11 (t, J=7.1 Hz, 3H). **HPLC:** Lux 5µm Cellulose-1, 1.0mL/min; n-Hexane:2-Propanol 99.5:0.5; 230nm, t_R(1)=11,2min, t_R(2)=14.6min. **8la obtained using ligand (R)-5: $[\alpha]_D^{26°C}$**= -52.7 (c=0.990, $CHCl_3$) for 94% ee **8la obtained using ligand (S)-5: $[\alpha]_D^{26°C}$**= +53.9 (c=0.995, $CHCl_3$) for 96% ee **8al obtained using ligand (S)-5: $[\alpha]_D^{26°C}$**= -53.9 (c=0.980, $CHCl_3$) for 96% ee

Enantioselective Synthesis of (R)-Tolterodine

*2-benzyloxy-5-methylbenzaldheyde (**10**)*[16]

K_2CO_3 (2.11g, 15.3mmol) and 18-crown-6 ether (20.7mg, 0.08mmol) were added to a pale brown solution of 5-methylsalicylaldehyde (1.03g, 7.6mmol) in acetone (15mL) and the slurry was stirred for 30 minutes at room temperature. Benzyl bromide (1.4mL, 11.8mmol) was added dropwise and the yellow mixture was stirred under reflux. The reaction was monitored by TLC analysis (n-Hexane:Ethyl Acetate 10:1). After 3 hours the reaction mixture was cooled to room temperature, the solids were filtered off and the filtrate was concentrated under vacuum. The residue was purified by Biotage Isolera™ Chromatograph (n-Hexane:Ethyl Acetate 10:1) to give **10** as a white solid (1.41g, 6.2mmol, 82% yield). m.p. 57.8°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.54 (s, 1H), 7.66 (d, J=2.0 Hz, 1H), 7.47-7.30 (m, 6H), 6.95 (d, J=8.5 Hz, 1H), 5.16 (s, 2H), 2.31 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 189.9, 159.2, 136.6, 136.3, 130.5, 128.7, 128.5, 128.2, 127.3, 124.9, 113.2, 70.6, 20.3.

*(E)-Ethyl-3-(2'-benzyloxy-5'-methyl)phenyl-2-propenoate (**11**)*

Under nitrogen atmosphere, triethyl phosphonoacetate (1.4mL, 6.8mmol) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 369.7mg, 9.2mmol of NaH) in 30mL of dry THF at 0°C. The mixture was stirred for 20 minutes then a solution of **10** (1.41g, 6.2mmol) in 8mL of dry THF was added dropwise. The reaction was stirred at room temperature and was monitored by GC-FID analysis. After 2 hours the reaction was quenched with H_2O (30mL) and extracted with CH_2Cl_2 (3 x 30mL). The combined organic extracts were washed with H_2O (30mL), dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give **11** as a white solid (1.74g, 5.9mmoli, 95% yield). m.p. 58.1°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J=16.2 Hz, 1H), 7.46-7.28 (m, 6H), 7.10 (dd, J=8.4, 1.8 Hz, 1H), 6.84 (d, J=8.4 Hz, 1H), 6.53 (d, J=16.2 Hz, 1H), 5.14 (s, 2H), 4.25 (q, J=7.1 Hz, 2H), 2.29 (s, 3H), 1.33 (t, J=7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ=167.5, 155.4, 140.0, 136.9, 132.0, 130.3, 129.1, 128.6, 127.9, 127.1, 123.6, 118.6, 112.9, 70.5, 68.0, 60.3, 20.5, 14.4. **Anal. Calcd. For $C_{19}H_{20}O_3$:** C, 77.00; H, 6.80; O, 16.20. **Found:** C, 77.21; H, 6.79.

(±)-Ethyl-3-(2'-benzyloxy-5'-methylphenyl)phenylpropanoate

Under nitrogen atmosphere, phenilboronic acid (1.8mmol), **11** (148 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol) 2,2'-bipyridyl (17 mg, 0.11 mmol), disareated acetic acid (0.5 mL), dry THF (0.25mL) and disareated H_2O (0.2mL) were stirred at 50°C. The reaction was monitored by GC-FID analysis and after 76h was quenched with 5% NaOH solution (15mL) and extracted with Et_2O (3 x 8mL). The combined organic extracts were washed with brine (10mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by filtration on silica gel (n-Hexane:Ethyl Acetate 97:3) giving the pure product (97 mg, 0.26 mmol, 52% yield).

HPLC-FSC: Lux 3µm Amilose-2; 0.5mL/min; n-Hexane:2-Propanol 98:2; 230nm. t_R(1)=20.2min, t_R(2)=23.5min **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42-7.26 (m, 9H), 7.26-7.19 (m, 1H), 7.09 (s, 1H), 7.01 (d, J=8.3 Hz, 1H), 6.82 (d, J=8.3 Hz, 1H), 5.09-4.99 (m, 3H), 4.13-4.03 (m, 2H), 3.11 (qd, J=15.3, 8.1 Hz, 2H), 2.32 (s, 3H), 1.15 (t, J=7.1 Hz, 3H). **^{13}C NM**R (100 MHz, CDCl3) δ: 172.1, 153.9, 143.4, 137.4, 132.0, 129.9, 128.7, 128.4, 128.2, 128.1, 127.9, 127.7, 127.2, 126.2, 112.2, 70.2, 60.3, 40.8, 39.9, 20.8, 14.1. **Anal. Calcd. For $C_{25}H_{26}O_3$**: C, 80.18; H, 7.00; O, 12.82. **Found:** C, 80.68; H, 7.02.

*(R)-Ethyl-3-(2'-benzyloxy-5'-methylphenyl)phenylpropanoate (**12**)*

Under nitrogen atmosphere, freshly distilled 1,4-dioxane (12mL) was added to $[RhCl(C_2H_4)_2]_2$ (17.5mg, 0.045mmol, 1.5mol%) and the phosphite **(R)-5** (139.0mg, 0.18mmol, 6.0mol%). The mixture was stirred for 30 min at room temperature then disareated H_2O (6mL), disareated KOH solution (1M, 3mL), phenylboronic acid (758.1mg, 6.2mmol) and **11** (885.3mg, 3.0mmol) were added. The mixture was stirred at room temperature, and the reaction was monitored by GC-FID analysis. The reaction was quenched after 24h with 5% NaOH (45mL) and extracted with Et_2O (3 x 25mL). The combined organic extracts were washed with brine (30mL), dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude product, which was purified by Biotage Isolera™ Chromatograph (n-Hexane:Ethyl Acetate 10:1) to give a mixture of **11** and **12** (1.01g of mixture, 71% of **12** and 29% of **11** as showed by ^{1}H NMR analysis).

HPLC-FSC: Lux 3µm Amilose-2; 0.5mL/min; n-Hexane:2-Propanol 98:2; 230nm. t_R(1)=20.2min, t_R(2)=23.5min. ee 96%**^{1}H NMR** (400 MHz, $CDCl_3$) (**12**) δ:7.58-6.97 (m, 12H), 6.82 (d, J=8.3 Hz, 1H), 5.09-4.97 (m, 3H),

4.16-4.01 (m, 2H), 3.24-2.99 (m, 2H), 2.33 (s, 3H), 1.23-1.08 (m, 3H); (**11**) δ:8.13 (d, J=16.2 Hz, 1H), 7.58-6.97 (m, 7H), 6.91 (d, J=8.4 Hz, 1H), 6.59 (d, J=16.2 Hz, 1H), 5.21 (s, 2H), 4.32 (q, J=7.1 Hz, 2H), 2.36 (s, 3H), 1.40 (t, J=7.1 Hz, 3H).

*(R)-3-(2'-benzyloxy-5'-methyl)phenylpropanoic acid (**13**)*[3a, 17]

10mL of 10% NaOH solution were added to the mixture (1.01 g) of **11** and **12** and the suspension was stirred under reflux for 3 hours. 1M HCl solution was added until pH 1-2. The mixture was extracted with ethyl acetate (3 x 30mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude product as waxy solid. The crude product was a mixture (983.1mg) of **13** (71%) and (E)-3-(2'-benzyloxy, 5'-methylphenyl)-2-propenoic acid (29%), as showed by ^{1}H NMR analysis.

^{1}H NMR (200 MHz, $CDCl_3$) δ (**13**): 11.10-9.70 (bs, 1H), 7.45-6.95 (m, 12H), 6.80 (d, J=8.1 Hz, 1H), 5.03-4.95 (m, 3H), 3.23-3.01 (m, 2H), 2.29 (s, 3H); **(E)-3-(2'-benzyloxy, 5'-methylphenyl)-2-propenoic acid** δ: 11.10-9.70 (bs, 1H), 8.15 (d, J=16.1 Hz, 1H), 7.45-6.95 (m, 7H), 6.88 (d, J=8.5 Hz, 1H), 6.54 (d, J=16.1 Hz, 1H), 5.18 (s, 2H), 2.33 (s, 3H).

(R)-N,N-diisopropyl-3-(2'-benzyloxy-5'-methyl)-phenylpropanammide (**14**)[3a]

Under nitrogen atmosphere, 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC HCl, 697.8mg, 3.6mmol), 4-(dimethylamino)pyridine (DMAP, 96.3mg, 0.79mmol) and diisopropylamine (1.5mL, 10.5mmol) were added to a solution of the mixture of **13** and (E)-3-(2'-benzyloxy, 5'-methylphenyl)-2-propenoic acid (983.1mg) in dry CH_2Cl_2 (6mL). The yellow-green mixture was stirred at room temperature and the reaction was monitored by TLC analysis (n-Hexane:Ethyl Acetate 85:15). After 24h the mixture was diluted with CH_2Cl_2 (90mL) and washed with 1M HCl solution (2 x 90mL), saturated $NaHCO_3$ solution (2 x 45mL) and H_2O (2 x 45mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum to give the crude product as a white-yellow glue (1.02g), which was purified by Biotage Isolera™ Chromatograph (n-Hexane:Ethyl Acetate 85:15) to give **14** as a yellow glue (494.1mg, 1.2mmol, 40% yield calculated on **11**).

^{1}H NMR (400 MHz, CDCl3) δ: 7.34-7.13 (m, 10H), 7.04 (d, J=2.1 Hz, 1H), 6.97 (dd, J= 8.2, 2.2 Hz, 1H), 6.77 (d, J=8.3 Hz, 1H), 5.02-4.90 (m, 3H), 4.00 (qui, J=6.7 Hz 1H), 3.35 (bs, 1H), 3.07-2.97 (m, 2H), 2.29 (s, 3H), 1.28 (dd, J=15.5 6.8 Hz, 6H), 1.07 (d, J=6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H). **^{13}C NMR** (100 MHz, CDCl3) δ: 170.2, 154.0, 144.2, 137.3, 132.6, 129.6, 129.1, 128.3 (2 peaks), 128.0, 127.6, 127.4, 125.8, 111.9, 70.0, 45.7, 41.9, 39.6, 21.0, 20.8, 20.7, 20.6, 20.5. **$[\alpha]_D^{28}$** = -2.7 (c=0.70, CH_2Cl_2) for 96% ee.

*(R)-N,N-diisopropyl-3-(2'-benzyloxy-5'-methyl)phenylpropanammine (**15**)*[3g]

Under nitrogen atmosphere a solution of $BH_3{\cdot}Me_2S$ (10.0-10.2M, 0.5mL) was added dropwise to a solution of **14** (494.1mg, 1.2mmol) in dry THF (6mL). The clear solution was heated under reflux and the reaction was monitored by TLC analysis (n-Hexane:Ethyl Acetate 85:15). After 20h the reaction was quenched with MeOH (10mL) at 0°C, the mixture was stirred under reflux for one hour, then was concentrated under vacuum and water (15mL) was added. The mixture was extracted with Et_2O (3 x 15mL) and the combined organic extracts were dried over anhydrous Na_2SO_4. After removing the solvent under reduced pressure, **15** was obtained as withe glue (448.5 mg, 1.08 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.28 (m, 5H), 7.25–7.19 (m, 4H), 7.18–7.10 (m, 2H), 6.92 (dd, J=8.3, 2.2 Hz, 1H), 6.75 (d, J=8.3 Hz, 1H), 5.02–4.92 (m, 2H), 4.39 (t, J = 7.7 Hz, 1H), 2.96 (qui, J=6.5 Hz, 2H), 2.36-2.32 (m, 2H), 2.27 (s, 3H), 2.17-2.10 (m, 2H), 0.91 (d, J = 6.5 Hz, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 154.0, 145.1, 137.5, 133.6, 129.8, 128.5, 128.4, 128.3, 128.0, 127.6, 127.4, 127.2, 125.6, 111.8, 70.2, 48.9, 44.2, 41.6, 37.0, 20.8, 20.6, 20.5. **$[\alpha]_D^{25}$** = -2.9 (c=0.89, $CHCl_3$) for 96% ee.

(R)-N,N-diisopropyl-3-(2'-benzyloxy-5'-methyl)phenylpropanammine - (R)-Tolterodine (**1**)[2b]

Under a nitrogen atmosphere, Pd/C (10%, 90.4mg) was added to a solution of **15** (357.1mg, 0.86mmol) in disareated MeOH (6mL). The mixture was saturated with H_2 and was stirred for 24h under 1.5bar hydrogen pressure. The solid was filtered off and the solvent was removed under reduced pressure to give **1** as white glue-foam (257.4mg, 0.79mmol, 94% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) δ: 7.34–7.28 (m, 4H), 7.28–7.19 (m, 2H), 6.87–6.78 (m, 2H), 6.57 (s, 1H), 4.48 (dd, J = 11.1, 4.0 Hz, 1H), 3.26 (qui, J = 6.7 Hz, 2H), 2.80–2.67 (m, 1H), 2.48–2.33 (m, 2H), 2.21–2.06 (m, 4H), 1.13 (dd, J = 19.5, 6.7 Hz, 12H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 153.1, 144.6, 132.2, 129.4, 128.6, 128.5, 128.3, 128.10, 127.8, 126.2, 120.0, 118.1, 48.5, 42.5, 39.6, 33.1, 20.8, 19.8, 19.4. **$[\alpha]_D^{29}$** = +28.8 (c=1.67, MeOH) for 96% ee. **$[\alpha]_D^{20}$** = +24.9 (c=1.50, MeOH) for 96% ee.

[Lit. value:[2b] $[\alpha]_D^{20}$ = –23.0 (c 1.5, MeOH) for (S)-Tolterodine].

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Keywords: Asymmetric catalysis; P-ligands; Steroids; Chiral pool; Chiral auxiliaries; (R)-Tolterodine

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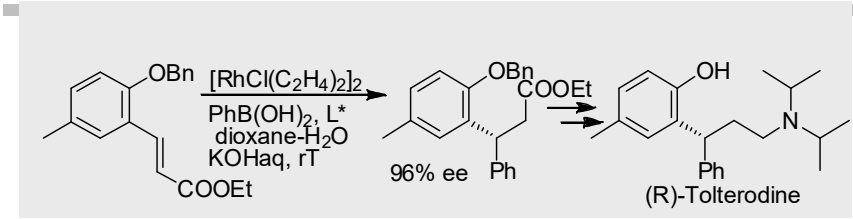

Deoxycholic acid derived binaphthyl phosphites promote a highly enantioselective Rh-catalyzed conjugate addition of arylboronic acids to 3-arylpropenoates, giving useful chiral building blocks for the synthesis of biologically active compounds. The protocol was successfully applied to the enantioselective synthesis of the antimuscarinic drug (R)-Tolterodine.

Key Topic* Enantioselective catalysis

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Rh-catalyzed enantioselective conjugate addition of arylboronic acids to 3-arylpropenoates: enantioselective synthesis of (R)-Tolterodine