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Asymmetric catalytic arylation of ethyl glyoxylate using organoboron reagents and Rh(I)–phosphane and phosphane–phosphite catalysts†

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Herein we report the first application of Rh(I)–phosphane and phosphane–phosphite catalysts in the enantioselective catalytic arylation of ethyl glyoxylate with organoboron reagents, providing access to ethyl mandelate derivatives in high yield (up to 99%) and moderate to very good enantioselectivities (up to 75% ee). Commercial phosphane ligands, such as (*R*)-MonoPhos and (*R*)-Phanephos were tested, as well as non-commercial (*R*,*R*)-TADDOL-derived phosphane–phosphite ligands. Those ligands containing bulky substituents in the *ortho*-and *para*-positions of the chiral phosphite moiety were found to be the most selective.

Introduction

The formation of C–C bonds, despite its long history and interest to organic chemists, still remains a challenge. Our group has worked exhaustively on this transformation as a means to easily access important key structural units, present in biologically active compounds, such as chiral amines,[1a–c] α-hydroxyesters,[1d,e] and α-amino acids.[1f] With regard to the synthesis of α-hydroxyesters – which are structural moieties widespread in natural products[2] – our group has been a pioneer in the implementation of the catalytic arylation of glyoxylates with Rh(I)–NHC catalysts giving mandelate derivatives in excellent yields. Unfortunately, the principle downside was the moderate enantioselectivities that were achieved (up to 34% ee).[1e]

There is still an ever increasing demand for single enantiomer products. Over the past few decades, phosphorous-based ligands, which are almost indispensable in asymmetric organometallic catalysis,[3] have been used with much success in a plethora of transformations, including the catalytic addition of the phenyl group to activated imine substrates[1b] and aldehydes[4] with the aid of organoboron reagents. Phosphite ligands are a very important class of phosphorous ligands, which were successfully applied in the Rh-catalyzed hydroformylation of aldehydes[5] and in Cu-catalysed 1,4-additions[6] as well as in several other asymmetric catalytic transformations.[7] Some of us have recently developed a class of modular chiral phosphane–phosphite ligands (Schmalz ligands), prepared from TADDOL[8] and TARTROL[9] building blocks (Fig. 1), and which have been used in several transition metal-catalysed reactions.[10] We decided to test these ligands for the first time, in the transition metal-catalysed arylation of ethyl glyoxylate, using organoboron reagents and Rh(I) pre-catalysts.

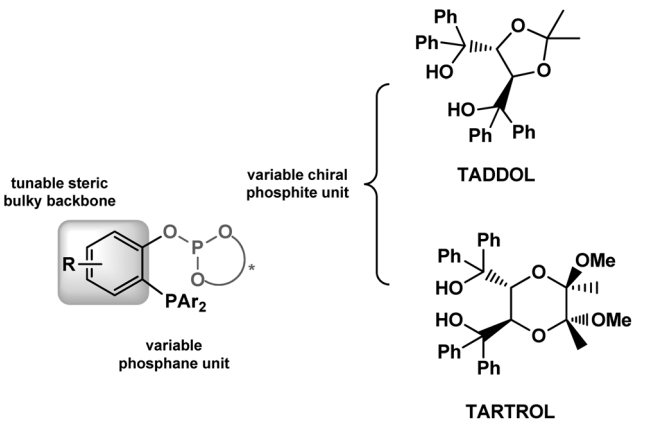

Fig. 1 General structure of the modular phosphane–phosphite ligands introduced by Schmalz's group.[10]

Results and discussion

Miyaura and co-workers already reported a non-asymmetric rhodium-catalysed addition of organoboronic acids to aldehydes using several racemic phosphane ligands.[11a,b] With regard to the synthesis of mandelate derivatives, Francesco and co-workers reported a non-asymmetric Suzuki–Miyaura coupling

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reaction of organoboronic acids and ethyl glyoxylate using Pd(0) catalysts.[12] In 2012, Yamamoto and co-workers reported the addition of arylboronic acids to ethyl glyoxylate catalysed by a Ru/Me–BIPAM complex, giving mandelate derivatives in high yields and enantioselectivities.[13]

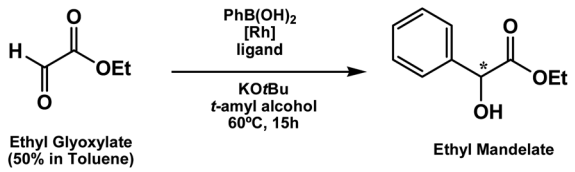
Based on our previous work on the synthesis of ethyl mandelate derivatives using Rh(I)–NHC catalysts,[1d,e] and our unsuccessful attempts at obtaining high enantioselectivities, we initiated a focused program at screening various chiral phosphorous ligands in an attempt at increasing the enantioselectivities. The study was based on the same methodology previously employed[1d,e] and besides the commercial bidentate phosphane ligands (Fig. 2): (*R*)-Phanephos (**1**), commonly used for asymmetric hydrogenations,[14] (*R*,*R*)-Chiraphos (**2**), (*R*)-MonoPhos (**3**) and other phosphoramidite type derivatives (**4**) and (**5**) were also employed. The results can be seen in Table 1. In the case of (*R*)-Phanephos (**1**) (Fig. 2), full conversion into ethyl mandelate was observed (Table 1, entry 1) but with poor enantiocontrol (<5% ee). $Rh(acac)(C_2H_4)_2$ is a pre-catalyst, which was already applied with success by Hayashi's group in the rhodium-catalyzed asymmetric 1,4-addition of aryl- and alkenylboronic acids to enones.[15a] When we used this pre-catalyst, only a moderate yield and a poor enantioselectivity was obtained (Table 1, entry 2). By testing the same reaction conditions at room temperature in an attempt to improve the enantioselectivity, a good enantioselectivity of 75% ee was obtained, unfortunately with a low yield (see Table 1, entry 3). We decided to test the less bulkier commercial (*R*,*R*)-Chiraphos (**2**) ligand (Fig. 2) using the same reaction conditions, since it was successfully applied by Miyaura's group for the conjugate addition of organoboron, organosilicon, and organobismuth reagents to α,β-unsaturated ketones.[11c] The reaction was non-enantioselective, and the racemic ethyl mandelate product was obtained, with moderate yield (48% yield) (see Table 1, entry 4).

Inspired by the work developed by Yamamoto and co-workers,[13] we decided to use the chiral commercial phosphoramidite ligand (*R*)-MonoPhos (**3**) (Fig. 2) under these reaction conditions. These ligands reported by Feringa's group were shown to be privileged in several asymmetric catalytic reactions.[16] Excellent yields were obtained with this ligand, using several Rh(I) pre-catalysts (see Table 1, entries 5 to 8), but only low enantioselectivities were observed. Since this reaction appeared to be highly dependent on the rhodium complex, the bulky Rh(I) pre-catalyst $[Rh(nbd)Cl]_2$ was tested with this ligand (Table 1, entry 9), but only a 33% yield was obtained and an enantioselectivity of only 28% ee with (*R*)-MonoPhos (**3**). In a final attempt to improve the enantioselectivity, we decided to test the commercial chiral MonoPhos derivatives (**4**) and (**5**) (Fig. 2). Full conversion to the ethyl mandelate product was obtained, but the enantioselectivity was poor (see Table 1, entries 10 and 11).

Recently we have successfully developed a family of phosphane–phosphite chiral ligands containing the TADDOL backbone, which were evaluated in this work in catalytic arylation reactions with organoboron reagents and transition metal catalysts. The ligands are schematized in Fig. 3.[10]

Zhou and co-workers reported the first asymmetric Rh spirophosphite-catalysed addition of arylboronic acids to α-ketoesters in aqueous media.[17] At this point, we decided to use our TADDOL-phosphane–phosphite ligands (see Fig. 3),

Table 1 Rh(I) catalysed enantioselective arylation of ethyl glyoxylate with phenylboronic acid



Entry[a]	Rh(I)	Ligand	Yield[b]/%	ee[c]/%
1	$[Rh(COD)OH]_2$	**1**	>99	<5
2	$Rh(acac)(C_2H_4)_2$		66	<10 (*R*)
3[d]	$Rh(acac)(C_2H_4)_2$		12	75 (*R*)
4	$[Rh(COD)OH]_2$	**2**	48	<5
5	$[Rh(COD)OH]_2$	**3**	>99	19 (*S*)
6	$Rh(COD)_2BF_4$		>99	10 (*S*)
7	$[Rh(COD)Cl]_2$		>99	<10 (*S*)
8	$Rh(acac)(C_2H_4)_2$		>99	26 (*S*)
9	$[Rh(nbd)Cl]_2$		33	28 (*S*)
10	$[Rh(COD)OH]_2$	**4**	>99	23 (*S*)
11	$[Rh(COD)OH]_2$	**5**	>99	19 (*S*)

[a] *Reaction conditions*: 1.5 mol% $[Rh(I)]_2$ or 3 mol% [Rh(I)], 3.3 mol% Ligand, 2 equivalents $PhB(OH)_2$, 2 equivalents KO*t*Bu, 1 ml *t*-amyl alcohol, 100 μl ethyl glyoxylate. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral stationary phase HPLC. [d] Reaction run at room temperature.

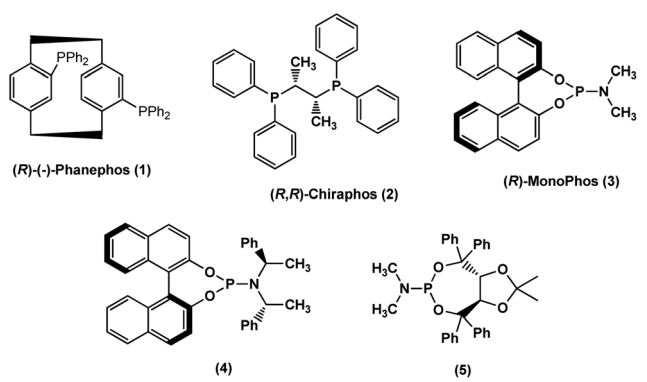


Fig. 2 Commercial phosphorous containing ligands.

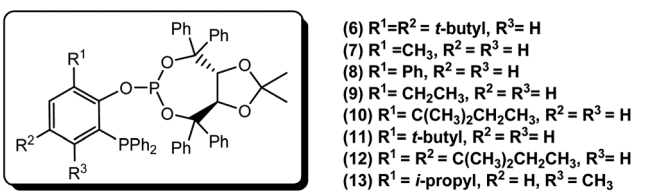


Fig. 3 (*R*,*R*)-TADDOL-derived chiral phosphane–phosphite ligands.[10]

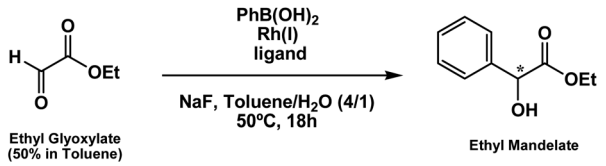
along with $[RhCl(C_2H_4)_2]_2$ and $Rh(acac)(C_2H_4)_2$ pre-catalysts and NaF as additive, in toluene and water. The application of inorganic fluorinated bases seemed to improve significantly the yield.[1f,17] The results are shown in Table 2. Generally, moderate to excellent yields were obtained with $[RhCl(C_2H_4)_2]_2$ (see Table 2, entries 3, 4, 8, 10 and 12). This Rh pre-catalyst type has already been used successfully in several catalytic reactions.[18] Despite its successful application in several other catalytic reactions,[15] the use of $Rh(acac)(C_2H_4)_2$ leads to a significant decrease in the reaction yield (see Table 2, entries 2, 11, 13 and 15). Apparently, the substitution pattern on the aromatic moiety of the TADDOL-derived phosphane–phosphite ligand backbone (see Fig. 3) doesn't seem to have a pronounced influence on the efficiency of the reaction. A maximum enantioselectivity of 69% ee was obtained for the arylation of ethyl glyoxylate with $Rh(acac)(C_2H_4)_2$ and the TADDOL-phosphane–phosphite ligand (**10**) (Table 2, entry 17). It seems that there is a slight temperature effect on the reaction enantioselectivity, since on conducting the experiment at 50 °C and room temperature no significant difference was noted (Table 2, compared entries 9 and 17), but when the experiment was conducted at 0 °C there was a significant difference in the enantioselectivity and in the yield (Table 2, compare entries 9 and 17 with entry 18). In general, the use $[RhCl(C_2H_4)_2]_2$ afforded the highest enantioselectivities (Table 2, entries 1, 4, 6, 10, 12 and 14, ranging from 44–61% ee). The lowest enantioselectivity value obtained with the use of this Rh-pre-catalyst and the less bulky TADDOL-phosphane–phosphite ligand (**7**) was 23% ee (Table 2, entry 3). So, it seems that the size of the substituents on the phenyl ring in the ligand backbone has an effect on the reaction enantioselectivity.

No big difference between aliphatic and aromatic substituents was observed, for example compare ligand (**8**) with (**10**) (Table 2, entries 4 and 8), where the enantioselectivities obtained were practically the same. The (*S*)-enantiomer of the ethyl mandelate product was the major isomer obtained in most of the reactions.

After these preliminary test studies, we decided to select $[RhCl(C_2H_4)_2]_2$ as the pre-catalyst and the TADDOL-phosphane–phosphite ligands (**8**) and (**12**) (see Fig. 3) for further studies. The use of different phenyl-organoboron sources and bases was evaluated. The results can be seen in Table 3.

The highest obtained enantioselectivity was 56% ee with $C_9H_{11}BO_2$. It was observed that the yields for the ethyl mandelate product decreased significantly (Table 3). In fact, the more anhydrous arylboron reagents, like potassium trifluoro(phenyl)borate ($PhBF_3K$), triphenylborane (Ph_3B), sodium tetraphenylborate (Ph_4BNa) and 1,3-propanediol boronic ester ($C_9H_{11}BO_2$) (Table 3, entries 1 to 4, respectively), previously evaluated in the enantioselective arylation of activated imines with Ru catalysts,[1c] gave poorer results than phenylboronic acid, and thus phenylboronic acid was identified as the organoboron reagent of choice in this reaction (compare Table 2 with Table

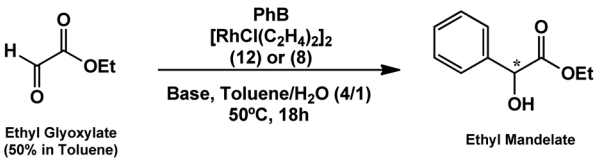
Table 2 Rh(I)–phosphane–phosphite enantioselective catalytic arylation of ethyl glyoxylate with phenylboronic acid



Entry[a]	Rh(I)	Ligand (Fig. 3)	Yield[b]/%	ee[c]/%
1	$[RhCl(C_2H_4)_2]_2$	**6**	88	51 (*S*)
2	$Rh(acac)(C_2H_4)_2$		26	14 (*S*)
3	$[RhCl(C_2H_4)_2]_2$	**7**	93	23 (*S*)
4	$[RhCl(C_2H_4)_2]_2$	**8**	>99	60 (*S*)
5	$Rh(acac)(C_2H_4)_2$		79	60 (*S*)
6	$[RhCl(C_2H_4)_2]_2$	**9**	36	49 (*S*)
7	$Rh(acac)(C_2H_4)_2$		92	30 (*S*)
8	$[RhCl(C_2H_4)_2]_2$	**10**	>99	57 (*S*)
9	$Rh(acac)(C_2H_4)_2$		90	67 (*S*)
10	$[RhCl(C_2H_4)_2]_2$	**11**	89	61 (*S*)
11	$Rh(acac)(C_2H_4)_2$		33	15 (*S*)
12	$[RhCl(C_2H_4)_2]_2$	**12**	>99	56 (*S*)
13	$Rh(acac)(C_2H_4)_2$		23	33 (*R*)
14	$[RhCl(C_2H_4)_2]_2$	**13**	43	44 (*S*)
15	$Rh(acac)(C_2H_4)_2$		17	26 (*R*)
16[d]	$[RhCl(C_2H_4)_2]_2$	**10**	57	10 (*S*)
17[d]	$Rh(acac)(C_2H_4)_2$		>99	69 (*S*)
18[e]	$Rh(acac)(C_2H_4)_2$		18	51 (*S*)

[a] *Reaction conditions*: 1.5 mol% $[RhCl(C_2H_4)_2]_2$ or 3 mol% $Rh(acac)(C_2H_4)_2$, 6 mol% Ligand, 2 equivalents $PhB(OH)_2$, 2 equivalents NaF, 2 ml solvent, 100 μl ethyl glyoxylate. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral stationary phase HPLC. [d] Reaction run at room temperature. [e] Reaction run at 0 °C.

Table 3 Screening of different phenyl-organoboron reagents and bases in the Rh(I)–phosphane–phosphite enantioselective arylation of ethyl glyoxylate



Entry[a]	Ligand (Fig. 3)	PhB	Base	Yield[b]/%	ee[c]/%
1	**12**	$PhBF_3K$	NaF	12	50 (*S*)
2		Ph_3B	NaF	35	40 (*S*)
3		Ph_4BNa	NaF	36	<5
4		$C_9H_{11}BO_2$	NaF	38	56 (*S*)
5		$PhB(OH)_2$	KF	18	15 (*S*)
6		$PhB(OH)_2$	CsF	25	24 (*R*)
7		$PhB(OH)_2$	KHF_2	<10	<5
8		$PhB(OH)_2$	KPF_6	33	32 (*R*)
9		$PhB(OH)_2$	ZnF_2	70	23 (*R*)
10		$PhB(OH)_2$	LiF	45	11 (*R*)
11	**8**	$PhB(OH)_2$	NaOH	14	43 (*S*)
12		$PhB(OH)_2$	K_3PO_4	17	47 (*S*)
13		$PhB(OH)_2$	K_2CO_3	26	52 (*S*)
14		$PhB(OH)_2$	KHF_2	11	28 (*S*)

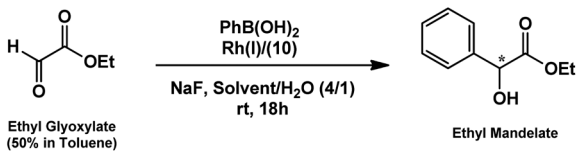
[a] *Reaction conditions*: 1.5 mol% $[RhCl(C_2H_4)_2]_2$, 6 mol% Ligand, 2 equivalents phenyl-organoboron reagent, 2 equivalents base, 2 ml solvent, 100 μl ethyl glyoxylate. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral stationary phase HPLC.

3). In the case of the base, NaF was undoubtedly the right choice (compare Table 2, entry 12 with Table 3, entries 5 to 10 and Table 2, entry 4 with Table 3, entries 11 to 14). Curiously, when other fluoride derivatives like CsF, ZnF_2 or LiF where used, the major enantiomer of ethyl mandelate was determined to have the (*R*) absolute configuration, contrary to when NaF was used (see Table 2). At this juncture, we do not have a plausible explanation to account for these facts. We decided to screen other commercially available Rh(I) pre-catalysts, including screening various solvents, using our optimized procedure (see Table 2, entry 17). The results are given in Table 4.

The results were quite disappointing, since in general both yield and enantioselectivity decreased significantly (compare Table 2, entry 17 with Table 4, entries 1 to 5). Curiously, upon using acetone as solvent, the absolute configuration of the major product enantiomer switched from (*S*) to (*R*) (Table 4, entry 4, last column). Toluene was undoubtedly the solvent of choice for this transformation. We decided to evaluate the effect of silver salts on this transformation, since we already reported their success in similar arylation reactions using organoboron reagents.[1c] In fact, a pronounced counter-ion effect was noted since there was an increase in both the yield and the enantioselectivity (Table 4, compare entries 5 and 6). To evaluate the effect of $AgBF_4$ on the reaction, we decided to test it using all the Rh pre-catalysts and ligand (**8**) (Fig. 3). $[Rh(nbd)Cl]_2$ gave the best balanced overall results.

In order to probe the reaction scope, we decided to screen several arylboronic acids bearing electron-donating and electron-withdrawing substituents in the *ortho*, *meta* and *para*-positions of the phenyl ring (Table 5). Two methods (A and B) were evaluated. Method A consisted in the use of Rh(acac)$(C_2H_4)_2$ along with (*R*)-MonoPhos ligand (**3**) (Fig. 2), KO*t*Bu as base and *t*-amyl-alcohol as solvent (optimized conditions from Table 1). Method B consisted in the use of $[RhCl(C_2H_4)_2]_2$ along with (*R*,*R*)-TADDOL-phosphane–phosphite ligands (**8**) and (**11**) (Fig. 3), with NaF as base in toluene and water (4/1) (optimized conditions from Table 2). In general, method A afforded the best results (Table 5, entries 5, 7, 11, 13, 15 and 16). With the exception of 2-naphthylboronic acid and 4-fluorophenylboronic acid, which worked better in the case of method B (Table 5, entries 4 and 10). As regards electronic effects, apparently no significant differences were found when electron-withdrawing or electron-donating substituents were present in the phenyl ring of the organoboron reagent (see Table 5, compare for instance entry 8 with entry 12, and entry 1 with entry 3). On the other hand, the reaction seems to suffer from steric hindrance. For instance, in the case of 1 or 2-naphthylboronic acid method A worked best for the former and method B for the latter (Table 5, compare entries 4 and 12 (method B)). The reaction enantioselectivity was generally poor,

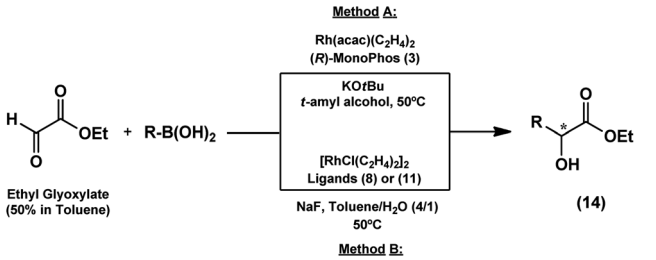
Table 4 Solvent and catalyst screening study for the Rh(I)-catalysed enantioselective arylation of ethyl glyoxylate



Entry[a]	Rh(I)	Solvent	Yield[b]/%	ee[c]/%
1	Rh(acac)$(C_2H_4)_2$	THF	27	54 (*S*)
2	Rh(acac)$(C_2H_4)_2$	1,4-Dioxane	25	37 (*S*)
3	Rh(acac)$(C_2H_4)_2$	DME	0	—
4	Rh(acac)$(C_2H_4)_2$	Acetone	14	35 (*R*)
5	$[RhCl(COD)]_2$	Toluene	46	<5
6[e]	$[RhCl(COD)]_2$	Toluene	70	37 (*R*)
7[d,e,f]	Rh(acac)$(C_2H_4)_2$	Toluene	9	41 (*S*)
8[d,e,f]	$[RhCl(C_2H_4)_2]_2$	Toluene	16	60 (*S*)
9[d,f]	$[Rh(nbd)Cl]_2$	Toluene	24	54 (*S*)
10[d,e,f]	$[Rh(nbd)Cl]_2$	Toluene	43	61 (*S*)

[a] *Reaction conditions*: 1.5 mol% $[Rh(I)]_2$ or 3 mol% [Rh(I)], 6 mol% Schmalz Ligand (**10**), 2 equivalents $PhB(OH)_2$, 2 equivalents NaF, 2 ml solvent, 100 μl ethyl glyoxylate. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral stationary phase HPLC. [d] Reaction run at 50 °C. [e] 3.3 mol% $AgBF_4$ was added to the reaction vessel. [f] Ligand (**8**) was used.

Table 5 Reaction scope for the Rh(I)-catalytic arylation of ethyl glyoxylate with various arylboronic acids[a]



Entry[a]	R	(**14**)	Method	Yield[b]/%	ee[c]/%
1	3-AcC_6H_4	**a**	A	16	<10
2[d]			B	<10	13
3	2-Naphthyl	**b**	A	16	<5
4[d]			B	82	35
5	4-ClC_6H_4	**c**	A	23	32 (*S*)
6[d]			B	13	12 (*S*)
7	3-MeOC_6H_4	**d**	A	32	<5
8[d]			B	11	29
9	4-FC_6H_4	**e**	A	18	<5
10[e]			B	50	28 (*R*)
11	1-Naphthyl	**f**	A	76	14
12[e]			B	12	55
13	2-Furyl	**g**	A	71	<10
14[e]			B	39	<10
15	2-MeOC_6H_4	**h**	A	30	n.d.
16	4-MeOC_6H_4	**i**	A	18	15
17	3-$NH_2C_6H_4$	**j**	A	Traces	n.d.

[a] *Reaction conditions*: Method A: 3 mol% Rh(acac)$(C_2H_4)_2$, 3.3 mol% (*R*)-MonoPhos (**3**), 2 equivalents R–$B(OH)_2$, 2 equivalents KO*t*Bu, 1 ml *t*-amyl alcohol, 100 μl ethyl glyoxylate. Method B: 1.5 mol% $[RhCl(C_2H_4)_2]_2$, 6 mol% Ligand (**8**) or (**11**), 2 equivalents R–$B(OH)_2$, 2 equivalents NaF, 2 ml solvent, 100 μl ethyl glyoxylate. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral stationary phase HPLC. [d] Ligand (**8**) was used. [e] Ligand (**11**) was used. n.d. = not determined.

(Table 5, last column), but the highest enantioselectivity (55% ee) was obtained with the 1-naphthylboronic acid reagent (Table 5, entry 12).

Conclusions

We have developed an efficient Rh(I)-catalysed glyoxylate arylation reaction allowing the synthesis of mandelate derivatives in excellent yields and good enantioselectivities (up to 75% ee for a virtually unexplored reaction). This procedure was applied for the first time with chiral phosphorous-containing Rh(I) catalysts. Several ethyl mandelate derivatives were synthesized, using two different catalytic protocols. We are currently developing an intra-molecular version of this reaction in order to access families of very interesting pharmacologically active chiral cyclo-alkanol compounds for HTS studies.

Experimental

General procedures

All the reagents were obtained from Aldrich, Fluka, Acros and Alfa Aeser. The solvents used were dried using current laboratory techniques.[19] All the reagents applied in this work were used as received. All reactions were conducted under a nitrogen atmosphere. Column chromatography was carried out on silica gel (sds, 70–200 μm). Thin layer chromatography (TLC) was carried out on aluminium backed Kiselgel 60 F254 plates (Merck). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. The NMR analyses were recorded on a Bruker Avance instrument (400 MHz) using $CDCl_3$ as solvent and the signal from the residual $CHCl_3$ as an internal standard. Mass spectra were recorded on a Waters-Micromass instrument (MaldiTOF, MicroTOF, ESI). High performance liquid chromatographic (HPLC) analyses were performed with an Agilent 1100 series instrument. The conditions used were, flux = 1 ml min^{-1}, detector = wavelength light (λ = 210 nm), eluent = hexane/2-propanol (90/10), and column = Chiralcel OD-H (0.46 cm × 25 cm) fitted with a guard column composed of the same stationary phase. Racemic mixtures were prepared using the followed procedure: $[RhCl(COD)]_2$ (1.5 mol%, 7.34 × 10^{-3} mmol) was added to a round bottom flask, under an inert atmosphere. PPh_3 (3.3 mol%, 0.015 mmol), arylboronic acid (2 equiv., 0.98 mmol), KO*t*Bu (1 equiv., 0.49 mmol) and *t*-amyl alcohol (1 ml) were added sequentially. Finally, ethyl glyoxylate (50% in toluene, 0.49 mmol, 100 μl) was added and the reaction was stirred at 60 °C, and monitored by TLC. The crude mixture was passed through a porous ceramic glass filter and eluted with CH_2Cl_2. The solvents were concentrated under reduced pressure and the residue purified by liquid chromatography (SiO_2 gel, hexane/AcOEt (5/1)), yielding the desired racemic ethyl mandelate derivative product.

Catalytic reactions

Method A. $[Rh(I)]_2$ (1.5 mol%, 7.34 × 10^{-3} mmol) or [Rh(I)] (3 mol%, 0.015 mmol) was added to a round bottom flask, under an inert atmosphere. Commercial phosphane ligand (3.3 mol%, 0.015 mmol), arylboronic acid or derivative (2 equiv., 0.98 mmol), KO*t*Bu (1 equiv., 0.49 mmol), and *t*-amyl alcohol (1 ml) were added sequentially. Finally, ethyl glyoxylate (50% in toluene, 0.49 mmol, 100 μl) was added and the reaction was stirred at the desired temperature, and monitored by TLC. The crude mixture was passed through a porous ceramic glass filter and eluted with CH_2Cl_2. The solvents were concentrated under reduced pressure and the residue purified by liquid chromatography (SiO_2 gel, hexane/AcOEt (5/1)), yielding the desired ethyl mandelate derivative product.

Method B. $[RhCl(C_2H_4)_2]_2$ (1.5 mol%, 7.34 × 10^{-3} mmol) or $Rh(acac)(C_2H_4)_2$ (3 mol%, 0.015 mmol) was added to a round bottom flask, under a nitrogen atmosphere. The chiral TADDOL-phosphane–phosphite ligands (6 mol%, 0.030 mmol) and toluene (1.6 ml) were added to the reaction vessel. The mixture was stirred at 50 °C during 30 minutes, which was followed by the sequential addition of the arylboronic acid or derivative (2 equiv., 0.98 mmol), NaF (2 equiv., 0.98 mmol), and water (0.4 ml). Finally, ethyl glyoxylate (50% in toluene, 0.49 mmol, 100 μl) was added and the reaction was stirred at the desired temperature, and monitored by TLC. The reaction was quenched with water (10 ml) and extracted with AcOEt (3 × 10 ml). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by liquid chromatography (SiO_2 gel, hexane/AcOEt (5/1)), yielding the desired ethyl mandelate derivative product.

Ethyl mandelate:.[1d,e] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.21 (m, 3H, CH_3), 3.56 (br s, 1H, OH), 4.17–4.26 (m, 2H, CH_2), 5.16 (s, 1H, CH), 7.34–7.42 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 14.14, 62.33, 73.01, 126.63, 128.49, 128.66, 138.53, 173.76. HPLC: t_R: 7.4 min (*S*) and 12.1 min (*R*).

Ethyl 2-(3-acetylphenyl)-2-hydroxyacetate (12a):.[1d,e] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (m, 3H, CH_3), 2.62 (s, 3H, CH_3 (Ac)), 4.19–4.41 (m, 2H, CH_2), 5.35 (s, 1H, CH), 7.32–7.66 (m, 2H, Ar), 7.69–8.04 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 Hz) δ: 14.03, 22.62, 62.83, 72.39, 128.41, 128.66, 129.01, 131.30, 137.55, 139.17, 173.06, 198.14. ESI-TOF MS (*m*/*z*) 223.10 (M + 1). HPLC: t_R: 18.5 min and 20.9 min.

Ethyl 2-hydroxy-2-(naphthalen-2-yl)acetate (12b):.[1d,e] White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (m, 3H,CH_3), 3.71 (br s, 1H, OH), 4.13–4.19 (m, 1H, CH_2), 4.21–4.30 (m, 1H, CH_2), 5.33 (s, 1H, CH), 7.47–7.54 (m, 3H, Ar), 7.83–7.85 (m, 3H, Ar), 7.91 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.45, 62.40, 73.08, 124.17, 125.90, 126.06, 126.33, 127.91, 128.34, 128.62, 133.28, 133.38, 135.89, 173.84. ESI-TOF MS (*m*/*z*): 213.10 (–OH), 231.10 (M + 1). HPLC: t_R: 11.0 min and 13.5 min.

Ethyl 2-(4-chlorophenyl)-2-hydroxyacetate (12c):.[1d,e] Light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.06 (m, 3H, CH_3), 4.00–4.05 (m, 2H, CH_2), 4.99 (s, 1H, CH), 7.15–7.25 (m, 2H, Ar), 7.63–7.65 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.12, 64.06, 71.82, 128.02, 128.36, 129.18, 129.55, 137.11, 137.14, 169.66. ESI-TOF MS (*m*/*z*): 213.11. HPLC: t_R: 7.1 min (*S*) and 8.1 min (*R*).

Ethyl 2-hydroxy-2-(3-methoxyphenyl)acetate (12d):.[1d,e] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.21 (m, 3H, CH_3), 3.63 (br s, 1H, OH), 3.78 (s, 3H, OCH_3), 4.14–4.19 (m, 1H, CH_2), 4.20–4.28 (m, 1H, CH_2), 5.12 (s, 1H, CH), 6.83–6.85 (m, 1H, Ar), 6.96–6.98

(m, 2H, Ar), 7.23–7.27 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.96, 55.29, 62.14, 72.61, 111.85, 114.32, 118.92, 129.46, 140.23, 159.73, 173.97. ESI-TOF MS (*m*/*z*): 193.09 (–OH), 211.10 (M + 1). HPLC: t_R: 14.3 min and 17.6 min.

Ethyl 2-(4-fluorophenyl)-2-hydroxyacetate (12e):.[1d,e] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (m, 3H, CH_3), 3.88 (br s, 1H, OH), 4.12–4.18 (m, 1H, CH_2), 4.20–4.24 (m, 1H, CH_2), 5.11 (s, 1H, CH), 6.99–7.03 (m, 2H, Ar), 7.36–7.40 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.15, 62.36, 71.47, 115.49, 115.61, 128.24, 134.37, 161.42, 164.06, 173.67. ESI-TOF MS (*m*/*z*): 181.07 (–OH), 199.08 (M + 1). HPLC: t_R: 6.9 min (*S*) and 8.2 min (*R*).

Ethyl 2-hydroxy-2-(naphthalen-1-yl)acetate (12f):.[1d,e] White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (m, 3H, CH_3), 4.12–4.32 (m, 2H, CH_2), 5.81 (s, 1H, CH), 7.44–7.70 (m, 4H, Ar), 7.84–7.96 (m, 2H, Ar), 8.11–8.18 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.17, 62.06, 71.33, 123.46, 123.70, 125.13, 125.68, 125.78, 126.48, 127.84, 128.80, 129.36, 134.07, 174.48. ESI-TOF MS (*m*/*z*): 233.08 (M + 2). HPLC: t_R: 55.8 min and 36.2 min. (HPLC eluent: hexane/2-propanol (98/2)).

Ethyl 2-(furan-2-yl)-2-hydroxyacetate (12g):.[1d,e] Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (m, 3H, CH_3), 4.27–4.30 (m, 2H, CH_2), 5.18 (s, 1H, CH), 6.37 (m, 2H, CH–CH), 7.40 (m, 1H, OCH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.10, 62.60, 67.03, 108.45, 110.55, 143.09, 151.05, 171.47. ESI-TOF MS (*m*/*z*): 153.05 (–OH), 171.06 (M + 1). HPLC: t_R: 8.9 min and 10.8 min.

Ethyl 2-hydroxy-2-(2-methoxyphenyl)acetate (12h):.[1d] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (m, 3H, CH_3), 3.91 (s, 3H, OCH_3), 4.17–4.26 (m, 2H, CH_2), 5.28 (s, 1H, CH), 6.89–6.96 (m, 2H, Ar), 7.01–7.05 (m, 1H, Ar), 7.42–7.47 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.31, 55.64, 61.52, 71.45, 110.01, 121.46, 129.51, 132.60, 137.17, 164.75, 174.01. ESI-TOF MS (*m*/*z*): 193.10 (–OH), 211.10 (M + 1). HPLC: not determined.

Ethyl 2-hydroxy-2-(4-methoxyphenyl)acetate (12i):.[12] Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (m, 3H, CH_3), 3.39 (br s, 1H, OH), 3.81 (s, 3H, OCH_3), 4.15–4.28 (m, 2H, CH_2), 5.10 (s, 1H, CH), 6.88–6.90 (m, 2H, Ar), 7.32–7.34 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.10, 55.53, 62.36, 72.39, 114.13, 127.70, 130.36, 159.95, 173.82. ESI-TOF MS (*m*/*z*): 193.08 (–OH), 233.08 (M + 1 plus Na). HPLC: t_R: 10.2 min and 14.4 min.

Ethyl 2-(3-aminophenyl)-2-hydroxyacetate (12j):.[1d] Obtained in vestigial quantities. Colorless oil.

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