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Highly Enantioselective Conjugate Additions of Potassium Organotrifluoroborates to Enones by Use of Monodentate Phosphoramidite Ligands

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The use of phosphoramidite ligands in the rhodium-catalyzed asymmetric conjugate addition of potassium organotrifluoroborates to various enones in the absence of water is described. A systematic search for effective catalysts has been performed by use of high-throughput screening methods. Initially, we have screened reaction conditions, catalyst precursors, and focused ligand libraries. In the next stage we have used the monodentate ligand combination approach, and finally we have made a library of 96 different phosphoramidites by parallel synthesis in the robot (instant ligand libraries) and have tested these in the vinylation of cyclohexenone (up to 88% enantiomeric excess, ee) and 4-phenyl-3-buten-2-one (up to 42% ee). Arylation of cyclohexenone by use of potassium phenyltrifluoroborate gave 3-phenylcyclohexanone with 99% ee.

Introduction

Since their original application as monodentate chiral ligands in the copper-catalyzed asymmetric conjugate addition of dialkylzinc reagents,¹ phosphoramidites have evolved into a class of privileged ligands that has been successfully applied in a large number of catalytic asymmetric transformations.² The facile synthesis and modular nature of these monodentate ligands makes a large variety of phosphoramidites readily available, enabling the finding of a tailored catalyst for a particular transformation. As part of our ongoing efforts to increase the scope of phosphoramidite-based catalysts, our attention was caught by the use of potassium organotrifluoroborates as reagents for the rhodium-catalyzed conjugate addition of alkenyl and aryl groups. Since their first practical synthesis in 1995 by Vedejs et al.,³ potassium

trifluoroborates have been used as an alternative for boronic acids in cross-coupling reactions.⁴ Shortly thereafter these ate complexes were applied in the rhodium-catalyzed conjugate addition,⁵ due to a number of advantages over the commonly used boronic acids.⁶ Potassium organotrifluoroborates have a higher stability toward moisture, are easier to purify, and lack trimer formation.⁷ Whereas current methods based on copper–phosphoramidite and rhodium–phosphoramidite catalysts are well suited to introduce alkyl and aryl groups, respectively, with excellent enantioselectivity,^{2e–h} a method for the catalytic asymmetric conjugate addition of alkenyl groups by phosphoramidite-based catalysts is still lacking. Herein we report the development of a highly selective rhodium–phosphoramidite catalyst for the asymmetric conjugate addition of alkenyl and aryl potassium trifluoroborates, using rational design and combinatorial techniques (Scheme 1).

The introduction of a vinyl group is especially appealing, since valuable building blocks are obtained that allow

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SCHEME 1

SCHEME 2

TABLE 1. Effect of Rhodium Sources^a

entry	[Rh]	conv ^b (%)	ee ^b (%)
1	Rh(acac)(eth) ₂	43	60
2	[Rh(cod)Cl] ₂	40	55
3	[Rh(eth) ₂ Cl] ₂	43	59
4	Rh(cod) ₂ BF ₄	33	44
5	Rh(cod) ₂ OTf	42	41

^a Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), 2 mL of dioxane/H₂O, N₂ atmosphere. ^b Determined by chiral GC.

further derivatization by, for example, ozonolysis, hydrogenation, hydroboration, or olefin cross-metathesis. To the best of our knowledge only two reports have appeared about the catalytic asymmetric conjugate addition of a vinyl group,^{5b,8} both of which used a rhodium–BINAP catalyst in an organic solvent/water mixture (Scheme 2).

Results and Discussion

Because preliminary experiments indicated that rhodium–phosphoramidite catalysts were unable to effect the conjugate addition of organosiloxanes, we turned our attention to organotrifluoroborates. Unlike vinylboronic acid, which cannot be isolated,⁹ potassium vinyltrifluoroborate (**2**) is readily available from the corresponding Grignard reagent.^{4a} Using the optimal conditions found for our conjugate addition of boronic acids,^{2g} we screened a number of commercially available rhodium complexes in the asymmetric conjugate addition of trifluoroborate **2** to cyclohexenone (**1**), by using MonoPhos (**L1A**) as a ligand (Table 1).

In contrast to previous findings,^{5b,10} neutral (entries 1–3) as well as cationic rhodium complexes (entries 4 and 5) are able to give product **3** with moderate conversion

TABLE 2. Effect of Solvent^a

solvent	conv ^b (%)	ee ^b (%)	solvent	conv ^b (%)	ee ^b (%)
heptane	30	50	DMF	15	32
toluene	12	60	DMSO	5	38
dioxane	43	60	MeCN	1	61
DME	24	61	iPrOH	70	59
THF	6	52	EtOH	74	60
CHCl ₃	1	52	MeOH	52	61
acetone	5	55	H ₂ O	0	

^a Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), Rh(acac)(eth)₂ (0.01 mmol), **L1A** (0.025 mmol), 2 mL of solvent/H₂O (10/1), 3 h reflux, N₂ atmosphere. ^b Determined by chiral GC.

TABLE 3. Effect of Water and Temperature^a

entry	equiv of H ₂ O ^b	conv ^c (%)	ee ^c (%)
1	22	74	60
2	10	85	60
3	4	92	62
4	1	97	63
5	0	99	63
6	0	60 ^d	63
7	0	5 ^e	63

^a Reaction conditions: **1** (0.5 mmol), **2** (2.0 mmol), Rh(acac)(eth)₂ (0.01 mmol), **L1A** (0.025 mmol), 2 mL of EtOH/H₂O, 3 h reflux, N₂ atmosphere. ^b Compared to **1**. ^c Determined by chiral GC. ^d At 70 °C. ^e At 50 °C.

and enantiomeric excess (ee), with Rh(acac)(eth)₂ being the most effective rhodium precursor.

To determine the effect of solvent on the yield and ee, dioxane was replaced by a broad range of solvents (Table 2).

Surprisingly the enantioselectivity obtained after 3 h at reflux temperature was nearly independent of the solvent; the lower values for *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) can be attributed to their high boiling points. Although acetone is the only solvent in which **2** is soluble at room temperature, its use does not lead to high conversions. In other solvents the reaction mixture needs to be heated in order to dissolve **2**. The best results are obtained with alcohols as solvents, and up to 74% conversion and 60% ee is reached in ethanol/water (10/1). Replacement of water with ethanol as the proton source in the case of dioxane led to identical results (40% conversion, 60% ee). This prompted us to investigate the role of water with ethanol as the solvent (Table 3).

The presence of water clearly has a detrimental effect upon the reaction and its role as proton source can be taken over by ethanol (entry 5), which is also the most effective solvent (Table 2). The ee is even slightly higher in the absence of water. The lower conversions obtained with the addition of water (entries 1–4) are not due to a lower reaction rate but probably to faster solvolysis of trifluoroborate **2** or decomposition of the catalyst. The reaction can also be run at lower temperatures, but a decrease in reaction rate leads to lower conversions (entries 6 and 7). The use of dried ethanol did not have an advantage over ordinary absolute ethanol, making it a mild and practical method for the asymmetric conjugate addition of potassium vinyltrifluoroborate.

Whereas MonoPhos (**L1A**) and its 8*H* analogue (**L1B**) were prepared from the corresponding diol and HMPT,¹¹ a number of other phosphoramidites based on (modified)

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SCHEME 3

TABLE 4. Ligand Screening^a

entry	ligand (L)	conv ^b (%)	ee ^b (%)
1	L1A	99	63
2	L1B	75	70
3	L2A	0	
4	L3D	18	13
5	L4A	27	50
6	L5A	76	84
7	L5B	98	88
8	L6A	100	62
9	L6B	76	66
10	L7A	86	66
11	L7B	100	76
12	L8A	38	75
13	L8B	90	79
14	L9A	32	80
15	L10B	100	70
16	L11B	99	86
17	L12A	27	79
18	L13A	26	32
19	L14A	5	47
20	L15A	76	75

^a Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC.

(*S*)-BINOL and catechol were synthesized according to Scheme 3.¹²

Via this efficient procedure, 300 mg each of two analytically pure ligands could be obtained per day in an average yield of 70%. These ligands were screened in the conjugate addition of potassium vinyltrifluoroborate under optimized conditions (Table 4).

From entries 3–5 it follows that bulky amine substituents on the ligand are not beneficial for the ee and

TABLE 5. Variation of Amine Substituents^a

entry	ligand (L)	R	R'	conv ^b (%)	ee ^b (%)
1	L1B	Me	Me	80	70
2	L16B	Me	Et	96	86
3	L5B	Et	Et	99	88
4	L17B	Me	Pr	99	83
5	L18B	Et	Pr	86	87
6	L19B	Pr	Pr	81	78
7	L1A	Me	Me	99	63
8	L5A	Et	Et	81	84
9	L18A	Et	Pr	86	86
10	L19A	Pr	Pr	77	88
11	L20A	Et	Bu	85	86
12	L21A	Pr	Bu	79	84
13	L22A	Bu	Bu	66	85
14	L23A	pentyl	pentyl	72	81

^a Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC.

conversion, not even when the small catechol moiety is used as a backbone (entry 4). In the case of ligands **L1** and **L5**, the use of 8*H*-BINOL as the backbone leads to higher ee values compared to their BINOL analogues (compare entries 1 and 2 and entries 6 and 7). This trend also holds for ligands **L6**–**L8**, based on cyclic amines, where in most cases the conversion is also improved by the use of 8*H*-BINOL as the backbone (entries 8–13). This might be due to the better solubility of these ligands. While the best results are obtained with ligand **L5B** (98% conversion, 88% ee), the azepane-based phosphoramidite **L11B** gives nearly identical results (entry 16). With the use of ligands based on (thio)morpholine, ee values of up to 80% can be reached (entries 10–14). Aromatic substituents, on the other hand, lead to lower conversions and ee values (entries 15, 18, and 19). The fact that unsymmetrical amines also give good results is proven by **L15A** (entry 20).

Since phosphoramidite ligands based on secondary amines with unbranched alkyl substituents gave the best results, a systematic screening was performed. According to the general route in Scheme 3, 14 ligands with substituents ranging from methyl to pentyl, with identical and different alkyl groups, were synthesized, and the effect of the chain length upon the yield and ee in the conjugate addition of **2** was tested (Table 5).

Several remarkable trends can be observed from the results of these “homologous series” of ligands. In the case of 8*H*-BINOL-based phosphoramidites (entries 1–6), the ee as well as the conversion increases with increasing length of the alkyl substituents until ligand **L5B** (diethyl), after which the ee and the conversion decrease when the substituents on the amine are longer. The same trend can be seen for phosphoramidites based on BINOL, where the optimal ligand requires a higher homologue in the series (**L19A**). Going from two methyl substituents (entry 7) to two propyl substituents (entry 10), the ee increases. For unknown reasons, the conversions for these two ligands do not follow the same trend. Further elongating the alkyl substituents leads again to lower conversions and ee values.

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TABLE 6. Enantiomeric Excess Values (%) for Monodentate Ligand Combinations^{a,b}

L_y	L_x					
	L1B	L16B	L5B	L18B	L17B	L19B
L1B	70					
L16B	77	86				
L5B	81	85	88			
L18B	80	83	86	87		
L17B	80	83	84	82	83	
L19B	78	84	81	80	83	78

^a Determined by chiral GC. ^b Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), 2 mL of EtOH, N₂ atmosphere.

TABLE 7. Conversions (%) for Monodentate Ligand Combinations^{a,b}

L_y	L_x					
	L1B	L16B	L5B	L18B	L17B	L19B
L1B	60					
L16B	60	75				
L5B	73	86	88			
L18B	69	81	79	38		
L17B	70	85	70	65	67	
L19B	61	72	53	55	64	59

^a Determined by chiral GC. ^b Reaction conditions: **1** (0.25 mmol), **2** (1.0 mmol), 2 mL of EtOH, N₂ atmosphere.

To have an even more comprehensive screening of the homologous series, the monodentate ligand combination approach was used.¹³ In this approach an equimolar mixture of two monodentate ligands is used, leading to the simultaneous formation of two homo complexes and one hetero complex. If this hetero complex is more active and selective than the homo complexes it will lead to better results, as has been demonstrated for enantioselective C–H and C–C bond formation.¹³ For the ligand combinations, the six phosphoramidites based on *8H*-BINOL of Table 5 were used (Table 6).

The use of ligand combinations where hetero complexes can be formed ($L_x \neq L_y$) does not lead to improved ee values compared to the homo complexes ($L_x = L_y$).¹⁴ Instead, a value close to the average of the two homo complexes is found, and ligand **L5B** remains the most optimal one. Interestingly, the general relationship between activity and selectivity also holds for the monodentate ligand combinations when the conversions after 1 h are measured (Table 7), which shows that the catalyst based on **L5B** is also the most active.

Following the optimization of the conditions and the ligand, two substituted potassium alkenyltrifluoroborates (**4** and **5**) as well as a potassium alkyl- (**6**)¹⁵ and

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TABLE 8. Other Potassium Organotrifluoroborates^a

entry	RBF ₃ K	product	conv ^b (%)	ee ^b (%)
1	4	8	71	72
2	5	9	74	71
3	6	10	0	
4	7	11	0	

^a Reaction conditions: **1** (0.25 mmol), **4–7** (1.0 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC.

TABLE 9. Optimization of Catalyst and Reagent Loading^a

entry	% catalyst	equiv of 2	time (h)	conv ^b (%)	ee ^b (%)
1	4	4	3	100	88
2	4	3	3	97	87
3	4	2	3	84	87
4	2	4	6	100	88
5	2	3	6	92	86
6	2	2	6	83	87
7	1	3	20	85	79

^a Reaction conditions: **1** (0.25 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC.

alkynyltrifluoroborate (**7**)^{4c} were used in the asymmetric conjugate addition to **1** (Table 8).

The introduction of *trans*-alkyl or aryl substituents at the 2-position of the vinyl group unfortunately leads to lower conversions and ee values (entries 1 and 2). Trifluoroborates **6** and **7** are unable to undergo conjugate addition to **1** (entries 3 and 4), and the use of other rhodium sources and solvents did not give any conversion either.

Since ligand **L5B** clearly leads to the most active and selective rhodium–phosphoramidite catalyst for the enantioselective conjugate addition of trifluoroborate **2**, an optimization of the catalyst loading and equivalents of **2** used was performed in order to downsize the amount of catalyst (Table 9).

As can be concluded from these results, the catalyst loading can be decreased to 2 mol %, leading to almost identical conversions and ee values (compare entries 1–3 and 4–6). A further decrease leads to a long reaction time and a lower ee (entry 7). At least 3 equiv of trifluoroborate **2** need to be employed to achieve high conversions (compare entries 2 and 3), presumably due to solvolysis of **2** during the reaction.

Since phosphoramidite ligands have proven to be very successful in the conjugate addition of aromatic boronic acids,^{2g,h} their application in the conjugate addition of potassium phenyltrifluoroborate (**12**) was investigated (Table 10).

TABLE 10. Addition of Phenyltrifluoroborate^a

entry	ligand (L)	conv ^b (%)	ee ^b (%)
1	L19A	75	96
2	L11B	81	95
3	L5B	99 ^c	99
4	<i>S</i> -BINAP (5%)	27	99

^a Reaction conditions: **1** (0.25 mmol), **12** (0.5 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC. ^c Reaction time 2 h.

TABLE 11. Potassium Aryltrifluoroborates^a

entry	ArBF ₃ K	conv of 1 ^b (%)	product	ee ^c (%)
1	14	99	18	98
2	15	98	19	99
3	16	100	20	98
4	17	68	21	99

^a Reaction conditions: **1** (0.25 mmol), **14–17** (0.5 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC. ^c Determined by chiral HPLC.

The three most successful ligands identified in the conjugate addition of **2** were used and compared to BINAP. All three phosphoramidites achieve excellent levels of enantioselectivity ($\geq 95\%$), with **L5B** being the most effective ligand, providing virtually enantiopure **13** with complete conversion (entry 3). Compared to vinyltrifluoroborate **2**, phenyltrifluoroborate **12** has a higher reactivity, which leads to shorter reaction times (2 h for **L5B**) and a reduction in the number of equivalents of trifluoroborate needed. Although BINAP also reaches this level of ee, the reaction rate is much lower (entry 4).

Encouraged by this success, we examined several other potassium aryltrifluoroborates in the asymmetric conjugate addition to cyclohexenone (Table 11).

The catalyst is tolerant of the use of functionalized potassium aryltrifluoroborates. Electron-withdrawing (entry 2) and electron-donating (entry 3) substituents both lead to high conversions and ee values. The advantage of the use of potassium trifluoroborates over boronic acids is illustrated by entry 4. Whereas 3-thiopheneboronic acid does not give any conjugate addition product due to rapid solvolysis, the corresponding trifluoroborate **17** gives **21** with excellent ee and a moderate conversion.

The scope with respect to the substrate was investigated by the use of various Michael acceptors (Table 12).

In all cases complete conversion to the corresponding product was observed, although the ee values obtained

TABLE 12. Scope of Michael Acceptor^a

entry	acceptor	conv ^b (%)	product	ee ^c (%)
1	22	100	25	84
2	1	100	13	99
3	23	100	26	91 ^c
4	24	100	27	87

^a Reaction conditions: **1**, **22–24** (0.25 mmol), **12** (0.5 mmol), 2 mL of EtOH, N₂ atmosphere. ^b Determined by chiral GC. ^c Determined by chiral HPLC.

for the other ring sizes (entries 1 and 3) and the lactone (entry 4) are slightly lower than for cyclohexenone (entry 2).

Although **L5B** proved to be a highly effective ligand for the addition of alkenyl trifluoroborates as well as aryltrifluoroborates, in the former case lower levels of enantioselectivity were obtained compared to the latter. Ligand **L5B** was found by an extensive screening of phosphoramidites based on secondary aliphatic amines (vide supra). A screening of phosphoramidites based on primary and/or aromatic amines still had to be performed. For this screening we made use of the recently developed instant ligand libraries.¹⁶

In this approach a solution-phase ligand library containing 96 different monodentate phosphoramidites is synthesized and screened by a fully automated parallel preparation (Figure 1).

The automation is based on the principle that all reagents are used as stock solutions, which are transferred by a liquid handling robot placed in a glovebox.¹⁷ The chromatography normally performed at the end of the phosphoramidite synthesis is replaced by a simple filtration, not only because it allows for a much more simple automated procedure but also because phosphoramidites based on primary and/or aromatic amines tend to decompose on a silica column.

For the parallel synthesis of the 96 ligand library according to Scheme 3 and Figure 1, stock solutions of the three (modified) (*R*)-BINOL phosphorochloridites **A**, **B**, and **C** in toluene were added to a 96-well oleophobic filter plate in three areas of 32 wells, respectively. The addition of a stoichiometric amount of triethylamine to each of the 96 wells was followed by the addition of a stoichiometric amount of 32 different amines (Table 13) to each area of phosphorochloridite, giving 96 different crude phosphoramidites (**L5A–L49C**) based on three diols and 32 amines.

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(17) See Supporting Information for details.

FIGURE 1. Procedure for ligand library synthesis and screening.

After 2 h of agitation at room temperature on an orbital shaker, the precipitated triethylamine hydrochloric acid salt was removed via parallel filtration. By placing the oleophobic filter plate on top of a 96-well microplate and applying vacuum, a library of 96 clear solutions of phosphoramidite ligands in toluene was obtained. To establish a good protocol for the screening of the entire library, four ligands out of the library were used in the conjugate addition of trifluoroborate **2** to cyclohexenone (**1**) and the results were compared with those obtained previously by purified phosphoramidite ligands synthesized on a larger scale (Table 14).

The results show that the use of phosphoramidite ligands synthesized by the automated parallel procedure leads to very similar ee values as for the purified ligands. More important, the trend in ee values remains intact, allowing comparison of the ligands within the library. The lower yield can be attributed to the 4-fold lower concentration and shorter reaction time of the automated experiments. To our delight, the presence of 5 vol % toluene, from the ligand stock solution, does not have a negative effect upon the ee.

After these encouraging results, the entire library was tested in the reaction of **1** with **2** (for details see Table 14 and Experimental Section) by an automated procedure (Figure 1). A part of the solution in each well of the entire library was transferred to 96 corresponding reaction vials, followed by an ethanol stock solution of the rhodium precursor and substrate **1**. After the addition of trifluoroborate **2**, the vials were sealed, placed in a

TABLE 13. Amines Used in Synthesis of the Ligand Library

	a	e	i	b	f	j	c	g	k	d	h	l
1												
2												
3												
4												
5												
6												
7												
8												

TABLE 14. Comparison of Selected Ligands^a

ligand (L)	automated		purified	
	conv ^b (%)	ee ^b (%)	conv ^b (%)	ee ^b (%)
L5B	55	86	99	88
L16B	72	83	96	86
L22A	25	77	66	85
L7A	35	64	86	66

^a Reaction conditions: **1** (0.06 mmol), **2** (0.25 mmol), 2 mL of EtOH, 0.1 mL of PhCH₃. ^b Determined by chiral GC.

Premex 96-multi reactor,¹⁸ and heated at reflux for 2 h. Analysis of the reaction mixture by chiral GC gave the results shown in Figure 2.

Phosphoramidite ligands based on 3,3'-dimethyl-BINOL (**C**) give poor results (up to 21% conversion, 51% ee for **L38C**). The BINOL- (**A**-) and 8*H*-BINOL- (**B**-) based ligands perform much better in most cases, the latter giving a slightly higher ee and about 30% more conversion than the former. Again this might be due to the better solubility of the catalyst. Ligands based on primary aromatic amines give low conversions (up to 39% for **L38B**) and ee values (up to 37% for **L25B**). Phosphoramidites based on primary aliphatic amines give

(18) This reactor was developed by Premex in cooperation with DSM; see www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten/.

FIGURE 2. Results of the library screening for **1**.

FIGURE 3. Results of the library screening for **28**.

higher ee values (up to 53% for **L42B**) but lower conversions (up to 19% for **L42C**). Secondary aromatic amines also lead to moderate ee values and low conversions (22% conversion, 48% ee for **L36B**). As expected, phosphoramidites based on secondary aliphatic amines lead to both high conversions and ee values, with **L5B** as the most effective ligand (81% conversion, 87% ee). Amines used for the synthesis of ligands **L31**, **L32**, and **L33** are used as mixtures of stereoisomers, leading to diastereomeric ligands and catalysts. The fact that **L33A** and **L33B** are still able to achieve high conversions (up to 62%) and ee values (up to 73%) suggests that screening of the individual stereoisomers could lead to more effective catalysts. This point is illustrated by phosphoramidites based

SCHEME 4

on **L29**, which give higher conversions and ee values than those based on **L30**.

In addition to cyclic enone **1**, the more challenging acyclic enone benzylidene acetone (**28**) was used in the screening of the library. This type of substrate has, to the best of our knowledge, never been used before in the asymmetric conjugate addition of alkenyl groups (Scheme 4).

The reaction was run overnight, and the conversion and ee were determined by chiral GC. The results are shown in Figure 3.

As in the case of cyclic enone **1**, phosphoramidites based on 3,3'-dimethyl-BINOL (**C**) give low conversions and ee values (22% and 29% for **L22C**) for acyclic enone **28**, even after 16 h. Ligands based on BINOL (**A**) and 8*H*-BINOL (**B**) are much more effective and able to reach full conversion, but in contrast to the previous case, the former gives slightly higher ee values. The most effective ligands, that give moderate ee values so far, are based on cyclic amines containing ester substituents such as **L32A** (42% ee) and **L34A** (40% ee). The screening of a more focused library based on this type of amine, including the single stereoisomers, is in progress.

Conclusion

The screening of various reaction parameters led to the identification of mild conditions for the asymmetric conjugate addition of potassium organotrifluoroborates to enones. The replacement of water by ethanol as the proton source, the use of a commercially available rhodium precursor, and the relatively short reaction times at moderate temperatures are advantageous compared to existing methods.⁵ The facile synthesis of the phosphoramidites allowed isolation and screening of a wide variety of structurally different ligands in the asymmetric conjugate addition of a vinyl group. Subsequent screening of a homologous series of ligands and use of the monodentate ligand combination approach¹³ resulted in a highly efficient catalyst for the asymmetric conjugate addition of alkenyltrifluoroborates (up to 88% ee) and aryltrifluoroborates (up to 99% ee) to enones. Furthermore, a solution-phase ligand library containing 96 different phosphoramidites was synthesized via an automated parallel protocol and used in the conjugate addition of potassium vinyltrifluoroborate to different enones. The results were in accordance with the results obtained by purified ligands and led to the identification of leads for selective catalysts in the asymmetric conjugate addition to acyclic enones.

Experimental Section

General Procedure for the Synthesis of Phosphoramidite Ligands: Preparation of *O,O'*-(*S*)-(1,1'-Dinaphth-2,2'-diyl)-*N,N*-dipropylphosphoramidite (L19A**).** To a Schlenk vessel containing 1.43 g (5.0 mmol) of (*S*)-BINOL was added 5 mL of PCl_3 . The resulting suspension was refluxed overnight and excess PCl_3 was removed in vacuo. Anhydrous toluene (5 mL) was added and the remaining PCl_3 was

removed by azeotropic distillation to give a white foam after thorough removal of all volatiles. The resulting phosphorochloridite was dissolved in 5 mL of anhydrous toluene and cooled to 0 °C. Triethylamine (0.70 mL, 5.05 mmol) was added, followed by 0.72 mL (5.25 mmol) of di-*n*-propylamine, and the solution was stirred for 1 h. Diethyl ether (10 mL) was added and the reaction mixture was filtered, concentrated under reduced pressure, and purified by column chromatography (heptanes/EtOAc 4/1) to give L19A as a white foam (1.88 g, 85%). ¹H NMR (200 MHz, CDCl₃) δ 0.81 (t, *J* = 7.0 Hz, 6H), 1.12–1.21 (m, 4H), 1.40–1.59 (m, 4H), 2.71–3.05 (m, 4H), 7.22–7.52 (m, 8H), and 7.93 (m, 4H) ppm. ¹³C NMR (50 MHz, CDCl₃) δ 13.7, 19.8, 30.5, 44.2 (d, *J* = 20.8 Hz), 122.1 (d, *J* = 9.1 Hz), 124.6 (d, *J* = 12.5 Hz), 125.9, 127.0 (d, *J* = 4.9 Hz), 128.2 (d, *J* = 6.0 Hz), 130.1 (d, *J* = 20.8 Hz), 131.2 (d, *J* = 33.8 Hz), 132.8 (d, *J* = 10.2 Hz), 149.5, and 150.1 (d, *J* = 5.3 Hz) ppm. ³¹P NMR (81 MHz, CDCl₃) δ 149.03 ppm. HRMS calcd for C₂₈H₃₀NO₂P, 443.201 40; found, 443.200 86. Anal. Calcd for C₂₈H₃₀NO₂P: C, 75.83; H, 6.82; N, 3.16. Found: C, 76.10; H, 7.09; N, 3.19. Mp 42 °C. [α]_D = + 399° (*c* = 1.0, CHCl₃).

General Procedure for Conjugate Addition of Potassium Organotrifluoroborates to Enones: Addition of Potassium Vinyltrifluoroborate (**2**) to Cyclohexenone (**1**). In a flame-dried Schlenk tube flushed with nitrogen, 1.3 mg (5 μmol, 2 mol %) of Rh(acac)(eth)₂ and 4.9 mg (13 μmol, 5 mol %) of phosphoramidite L5B were dissolved in 2 mL of absolute ethanol. After the solution was stirred for 15 min at room temperature, 24 μL (0.25 mmol) of **1** and 5 μL of tridecane were added, followed by 100 mg (0.75 mmol) of **2**. The resulting mixture was heated at reflux for 6 h, after which the solution was cooled to room temperature, quenched with saturated aqueous NaHCO₃, and extracted with diethyl ether. The organic phase was dried on sodium sulfate and the crude product **3** was subjected to chiral GC analysis (Chiraldex A-TA column, 30 m × 0.25 mm, 90 °C isothermic, 11.8/12.4 min).

Synthesis of the Solution-Phase Phosphoramidite Library. All stock solutions were prepared by dissolving the proper amount of reagent necessary for the library synthesis in dry toluene (by weight). Concentrations of 0.150 M for the

phosphorochloridites, 0.157 M for the amines, and 0.500 M for the triethylamine were used, respectively. By use of the liquid handling robot, 0.333 mL (1.00 equiv) of each of the three phosphorochloridite solutions was transferred into the corresponding 32 wells of the filter plate. Triethylamine solution (0.100 mL, 1.00 equiv) was added to each of the 96 wells. Each of the 32 amine solutions (0.333 mL, 1.05 equiv) was added to each of the three blocks of 32 wells. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed by application of the vacuum. The filtrates, that is, 96 solutions of different phosphoramidites in dry toluene (0.766 mL, 0.065 M), were collected and stored into a 96-well polypropylene microplate.

Screening of the Library for Enone 1. A stock solution containing Rh(acac)(eth)₂ at a concentration of 0.0012 M and enone **1** at a concentration of 0.0310 M in absolute ethanol was prepared. By use of the liquid handling robot, 0.100 mL portions (0.10 equiv) of the 96 ligand solutions were transferred from the microplate into 96 vials, equipped with stirring bars. Then 2.000 mL of the Rh(acac)(eth)₂ and enone stock solution (0.04 and 1.00 equiv, respectively) was added to each of the 96 vials. After the addition of 35 mg (4.00 equiv) of **2**, the vials were capped and transferred to the parallel reactor. The reactions were stirred at reflux for 2 h and then analyzed by chiral GC.

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Supporting Information Available: Detailed experimental procedures, quantitative results, and spectral and analytical data for reaction products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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