

First Examples of Improved Catalytic Asymmetric C–C Bond Formation Using the Monodentate Ligand Combination Approach

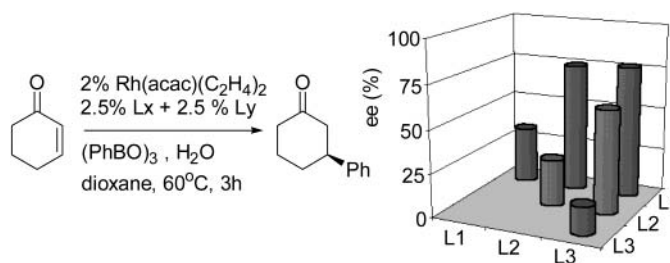
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ABSTRACT



Using a combination of chiral monodentate phosphoramidite ligands in the rhodium-catalyzed conjugate addition of boronic acids to three different substrates, we have shown for the first time that the ligand combination approach is applicable for C–C bond formation. Chiral catalysts based on hetero-combinations of ligands are found to be more effective than the homo-combinations. ^{31}P NMR experiments show that the hetero-combinations are formed in excess over the homo-combinations.

The asymmetric rhodium-catalyzed conjugate addition of boronic acids, developed by Miyaura and Hayashi,¹ is a highly convenient method for introducing an $\text{sp}^2\text{--}\text{sp}^3$ C–C bond with simultaneous formation of a new stereogenic center. The reaction is applicable to a broad range of substrates such as enones,^{1c} α,β -unsaturated esters,² α,β -unsaturated amides,³ 1-alkenylphosphonates,⁴ and 1-nitroal-

kenes.⁵ Excellent levels of enantioselectivity have been reached using BINAP,¹ phosphonites,⁶ and amidophosphines⁷ as chiral ligands. We have recently shown that chiral monodentate phosphoramidites are versatile ligands for this reaction,⁸ thereby introducing a class of cheap and easily tunable ligands that have already proven to be highly successful in the copper-catalyzed asymmetric conjugate addition of diorganozinc reagents⁹ and rhodium-catalyzed asymmetric hydrogenations.¹⁰ The monodentate nature of these phosphoramidite ligands allows us to apply the recently

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introduced ligand combination approach in asymmetric catalysis.¹¹ Since the catalytically active species contains two monodentate ligands, a mixture of two different phosphoramidites (Lx and Ly) will lead to the formation of two homo-complexes, Rh(Lx)₂ and Rh(Ly)₂, and the hetero-complex Rh(LxLy) simultaneously.¹² The hetero-complex represents a new catalyst, and if it shows higher activity and selectivity than the two homo-complexes simultaneously present in the reaction mixture, it will not only lead to better results but offer an easy combinatorial method for screening for effective chiral catalysts. This principle has been successful for asymmetric hydrogenations but so far has not been demonstrated for asymmetric C–C bond formation (Figure 1).¹¹

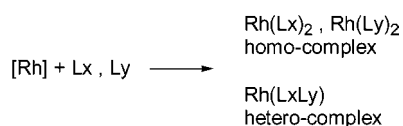


Figure 1. Rh complexes with two monodentate ligands using the ligand combination approach.

As the first substrate, we used 4-methyl-nitrostyrene (**1**) (Scheme 1), a nitroalkene lacking α -substituents, which has until now resisted a highly enantioselective conjugate addition of boronic acids and is therefore a good candidate for the mixed ligand approach.

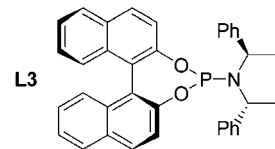
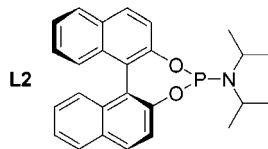
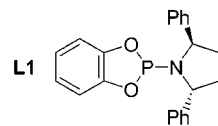
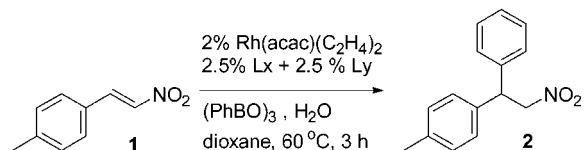
The reaction conditions have been slightly modified with respect to those in previous reports on the arylboronic acid coupling.^{5,8} Since it was found that large amounts of water can lead to catalyst deactivation, arylboroxines in combination with 1 equiv of water with respect to boron were used,⁴ leading to in situ arylboronic acid formation. From the data in Scheme 1, it follows that for homo-combinations of chiral ligands **L1**–**L3**, with an increase of steric bulk going from **L1** to **L3**, the conversion decreases but the enantioselectivity increases. Making hetero-combinations of a bulky ligand (**L2** or **L3**) and the relatively small **L1** combines the best properties of both ligands. With the hetero-combination **L1/L2**, a higher conversion as well as a higher ee is obtained compared to their homo-combinations. For the other two combinations, the effect on the enantioselectivity is even stronger. Not only the small size of **L1** is important,¹³ but

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Scheme 1. Conjugate Addition to 4-Methyl-nitrostyrene

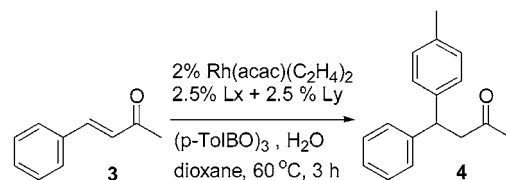


Lx/Lx	conv. %	ee %	Lx/Ly	conv %	ee %
L1/L1	69	-7	L1/L2	92	31
L2/L2	11	23	L1/L3	45	37
L3/L3	4	28	L2/L3	4	47

the configuration also plays a role because a strong mismatched effect is found when *ent*-**L3** is used in combination with **L1** (18% conversion, –23% ee).

On the basis of these encouraging preliminary results, the use of ligand combinations in arylboronic acid addition to enones was investigated. Benzylidene acetone (**3**) was considered to be an attractive substrate (Scheme 2). β -Aryl-

Scheme 2. Conjugate Addition to Benzylidene Acetone



Lx/Lx	conv %	ee %	Lx/Ly	conv %	ee %
L1/L1	27	33	L1/L2	33	-36
L2/L2	23	-30	L1/L3	30	12
L3/L3	0	-	L2/L3	15	-45

substituted enones have not been used before as substrates in the asymmetric conjugate addition of arylboronic acids and offer the attractive feature that they lead to a benzhydrylic stereogenic center.¹⁴ As in the case of nitrostyrenes, this is a frequent motif in natural products and pharmaceuticals.¹⁵

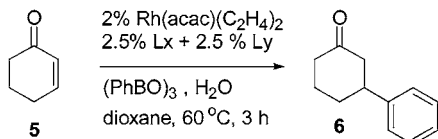
(12) It should be noted that the use of equal amounts of Lx and Ly does not necessarily have to result in a statistical mixture of the homo- and hetero-complex.

(13) The use of the small achiral ligand triphenyl phosphite in homo- and hetero-combinations gives almost complete conversions to racemic products, but the fact that this ligand is stable under these reaction conditions is remarkable.

Also with benzylidene acetone, using hetero-combinations of ligands has a beneficial effect on the enantioselectivity, although the conversion does not improve as much as in the previous case. Again a mismatched effect is found by using the **L1/ent-L2** combination (25% conversion, 0% ee).

Cyclic enones such as cyclohexenone (**5**) have been extensively studied as substrates in the rhodium-catalyzed asymmetric conjugate addition of arylboronic acids and their derivatives and can be seen as benchmark substrates (Scheme 3).¹

Scheme 3. Conjugate Addition to Cyclohexenone



Lx/Lx	conv %	ee %	Lx/Ly	conv %	ee %
L1/L1	26	33	L1/L2	93	75
L2/L2	22	-27	L1/L3	40	77
L3/L3	18	-16	L2/L3	16	-60

For this substrate, the trend of decreased conversion with increasing steric bulk is also present, although even the catalyst based on the homo-combination of the small ligand **L1** leads to a low conversion of 26%. Here the advantage of using hetero-combinations of monodentate ligands is considerably more pronounced. In the case of the **L1/L2** combination, the conversion almost quadruples to 93% due to a higher catalyst activity and the ee more than doubles to 75% (this also holds for the **L1/L3** and **L2/L3** combination).

Additional evidence for the formation of hetero-complexes of chiral monodentate phosphoramidite ligands with Rh(acac)(C₂H₄)₂ is obtained from their ³¹P NMR spectra. In the case of the homo-combination of ligands **L1–L3**, one doublet is observed showing the formation of a single Rh complex with two monodentate phosphoramidite ligands.¹⁶ The spectra of the three hetero-combinations show only

(14) For a racemic example, see: Itooka, R.; Iguchi, Y.; Miyaura, N. *Chem. Lett.* **2001**, 722–723.

minor signals for the doublets of the homo-complexes, and two new doublets from the hetero-complex appear as the major signals. By integration, the ratios between homo- and hetero-complexes are readily determined (Table 1).¹⁷

Table 1. Ratios of Homo- and Hetero-Complexes

Lx/Lx	Rh(Lx) ₂	Rh(Lx)(Ly)	Rh(Ly) ₂
L1/L2	17	78	5
L1/L3	5	91	4
L2/L3	27	54	19

It should be emphasized that for the two combinations where a small and a bulky phosphoramidite are used, **L1/L2** and **L1/L3**, the hetero-complex is clearly the most abundant one, while the mixture of the two bulky ligands **L2/L3** gives the expected statistical distribution.¹⁸

From these results, it can be concluded that for the first time, more effective catalysts for asymmetric C–C bond formation are obtained by combining chiral monodentate ligands, compared to catalysts based on single chiral ligands. The data for the three substrates and the ³¹P NMR spectra of the rhodium–phosphoramidite complexes obtained using ligand combinations suggest that the homo-combinations of bulky phosphoramidites are less active and selective because the steric hindrance prevents them from functioning properly. In contrast, an equimolar mixture, employing a small chiral phosphoramidite, leads to hetero-complexes with less steric hindrance that are more active and selective catalysts. Work to optimize the catalysts and the application to other reactions is currently in progress.

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Supporting Information Available: Selected experimental procedures and NMR data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Doublet due to Rh–P coupling.

(17) See Supporting Information for details.

(18) Imbalance in homo-complex ratios is due to errors in weighing.