Asymmetric Catalysis

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Chemoenzymatic Synthesis and Application of Bicyclo[2.2.2]octadiene Ligands: Increased Efficiency in Rhodium-Catalyzed Asymmetric Conjugate Additions by Electronic Tuning**

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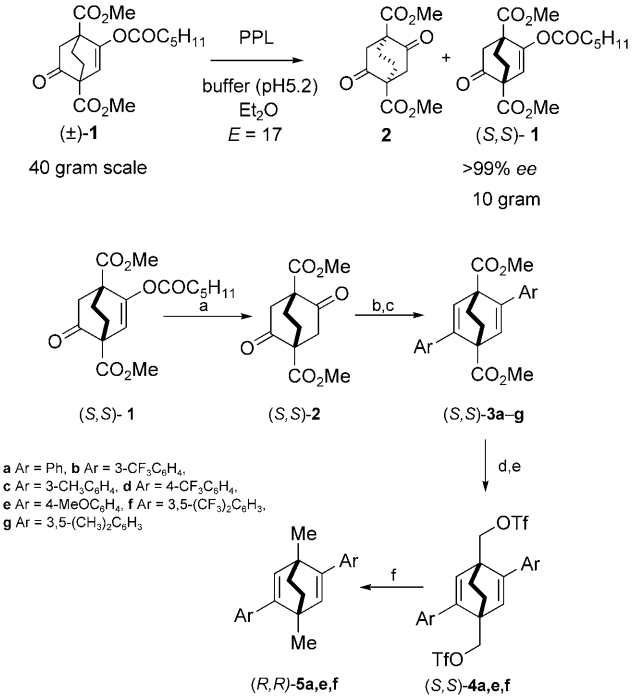
Chiral dienes are a new class of highly effective ligands, developed independently by Hayashi and Carriera et al., that have shown great promise in the field of asymmetric catalysis for reactions catalysed by rhodium and iridium.[1] A range of synthetically useful transformations have been realized in excellent yield and enantiomeric excess using C_1-symmetric and C_2-symmetric dienes.[2–10]

However, compared with phosphine ligands and C_1-symmetric dienes, the accessibility and structural variation in the most widely employed C_2-symmetric [2.2.2] diene ligands has been limited by inflexible synthetic routes and, most notably, the difficulty in resolution of the dienes or their synthetic precursors, which is currently achieved using chiral HPLC separation of the diene or a late-stage intermediate.[1b,2,11–14] As a result, the electronic effects on activity and enantioselectivity in these ligands have not been well studied. Although structural modifications including both electronic and steric changes have been made with the current bicyclic frameworks,[2b,c,5,6d,7] the results have shown that steric factors are dominant. Hayashi et al. have shown that C_1-symmetric [2.2.2] dienes in which one alkene was conjugated with an ester group gave a remarkable rate increase in arylation of imines.[6d] In this example it is believed that an electron withdrawing naphthyl ester substituent on one of the alkenes accelerates transmetallation to form a *trans* aryl–rhodium bond.

Although the chiral diene–Rh catalyst allows reactions to be conducted at lower temperatures compared with phosphine ligands, in diene–rhodium-catalyzed arylations with aryl boronic acids generally more than two equivalents of the arylboronic acid are necessary in order to achieve a high yield, and for particularly inactive substrates as many as 5 equivalents.[2h,15,16] This is attributed to the competing protodeboronation side-reaction[17] and indicates that reaction temperature is not the only factor responsible for the low atom efficiency.

Herein we report a chemoenzymatic approach giving access to a new series of chiral 1,4-disubstituted C_2-symmetric [2.2.2] diene ligands (Scheme 1).



Scheme 1. Biotransformation of (±)-enol ester **1** with PPL and preparation of 1,4-disubstituted bicyclo[2.2.2] ligands from (*S*,*S*)-enol ester **1**: a) Na_2CO_3, MeOH (99%); b) LHMDS, Tf_2O, THF, −78°C (70%); c) $ArB(OH)_2$, $[Pd(PPh_3)_4]$, Tol/EtOH/aq, Na_2CO_3, RT (80–95%); d) $LiAlH_4$, THF, (99%); e) Tf_2O, CH_2Cl_2/pyridine, −78°C→RT (99%); f) $LiHBEt_3$, THF, 0°C→RT (93–99%). LHMDS = lithium hexamethyldisilazide, Tf = trifluoromethanesulfonyl.

The scalability and ease of operation of the key enzyme resolution step, in addition to high yielding chemical transformations, provides a highly practical route that could quickly satisfy demands for greater quantities. Moreover, a significant electronic effect was observed in the diene ligands for rhodium-catalyzed arylation reactions. Both catalytic activity and, more interestingly from a mechanistic perspective, enantioselectivity depend on the electronic properties of the ligands. In addition, atom efficiency for the aryl boronic acids was correlated.

The key step in the route is a reliable and scalable lipase-catalysed chiral resolution of the (±)-enol ester **1**, derived

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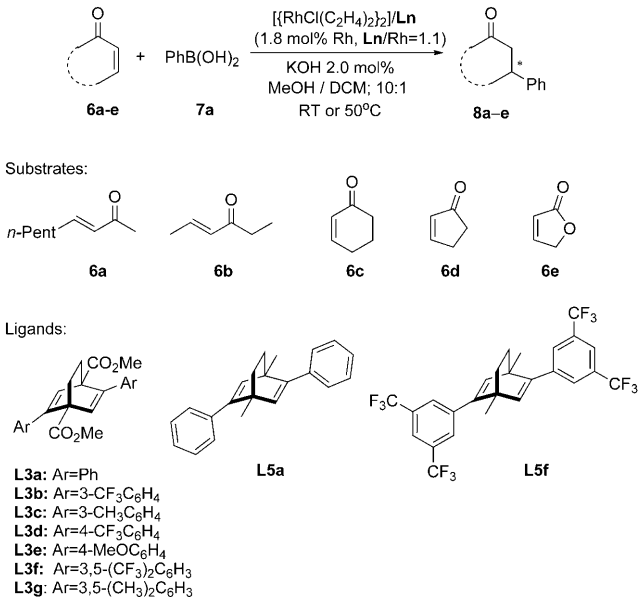
from the (±)-diketone **2**, which is made from commercially available succinate dimer.[18] After substrate and enzyme screening we found that porcine pancreatic lipase (PPL) in a biphasic system comprising Et_2O/citrate buffer (2:1; 100 mM, pH 5.2) gave reasonable selectivity ($E = 17$). The reaction was carried out on 40 g of substrate to afford 10 g of enantiopure enol ester (*S*,*S*)-**1**,[19] after purification by crystallisation. The crystals were found to be racemic enol ester, with enantiopure (*S*,*S*)-enol ester **1** remaining in solution, greatly facilitating isolation of the homochiral product. We found that enol ester of lower *ee* can also be purified to homochirality in a single crystallization.[20] Although the *E* value for this enzyme reaction is modest, the scalability and ease of purification make it an extremely attractive method to obtain quantities of the chiral dione (*S*,*S*)-**2** for our diene ligand synthesis. The antipodal (*R*,*R*)-**2** can be recovered and crystallized to optical purity through the (*R*,*R*)-enol ester **1**.[20]

The enantiopure (*S*,*S*)-dione **2** was obtained in near quantitative yield by methanolysis of the biotransformation product (*S*,*S*)-enol ester **1**. Formation of the bis-enol triflate was followed by introduction of the aryl substituents by palladium-catalysed cross-coupling to give ligands (*S*,*S*)-**L3a–g**.[2c,7,21] Lithium aluminum hydride reduction, activation as the ditriflate **4a**,**e**,**f** and displacement by superhydride gave (*R*,*R*)-ligands **L5a,e,f**.

The 1,4-diester ligands (*S*,*S*)-**L3a–g** (Scheme 1), were evaluated for the asymmetric conjugate addition of phenylboronic acid **7a** to 3-nonen-2-one **6a** using previously reported conditions (Scheme 2, Table 1).[2a,5]

The results for enantioselectivity were not encouraging compared to other [2.2.2] bicyclic ligands.[2j] From a purely structural perspective, it was logical that the substituent ester groups at the 1 and 4-positions may be giving a detrimental effect on the enantioselectivity. However, we also noted an interesting trend that for substrate **6a**, ligands with electron-withdrawing aryl substituents gave better enantioselectivities



Scheme 2. Asymmetric conjugate addition to substrates **6a–e**.

Table 1: Ligand screen for the asymmetric conjugate addition to **6a**.

Entry[a]	Ligand Ln	2,5-Aryl	Yield[b]	*ee* **8a**[c]
1	**L3a**	Ph	95	75
2	**L3b**	3-$CF_3C_6H_4$	93	83
3	**L3c**	3-$CH_3C_6H_4$	98	73
4	**L3d**	4-$CF_3C_6H_4$	95	82
5	**L3e**	4-$MeOC_6H_4$	99	74
6	**L3f**	3,5-$(CF_3)_2C_6H_3$	43	89
7	**L3g**	3,5-$(CH_3)_2C_6H_3$	96	70

than those with electron-donating groups, (e.g. comparing entry 2 with 3, entry 4 with 5 and entry 6 with 7 in Table 1).

The methyl ester groups were converted into methyl groups, and ligands **L5a** and **L5f** were evaluated for a range of acyclic and cyclic enones **6a–e** (Scheme 2, Table 2). For

Table 2: Comparison between **L5a** and **L5b** with various substrates.

Entry[a]	6	Prod. 8	Yield (%)[b] [*ee* (%)][c] **L5a**	**L5b**	Config.
1	**6a**	**8a**	99 [52]	99 [97]	*S*
2	**6b**	**8b**	99 [67]	99 [95]	*S*
3	**6c**	**8c**	98 [99]	92 [98]	*R*
4	**6d**	**8d**	100 [99]	80 [96]	*R*
5	**6e**	**8e**	95 [98]	76 [92][d]	*R*

[a] Reaction conditions: **6a** (0.5 mmol), **7a** (0.6 mmol for **L5a**, 1.0 mmol for **L3a–g** and **L5f**), [{$Rh(C_2H_4)_2Cl$}$_2$] (1.8 mol% Rh), Ligand **Ln** (2 mol%), MeOH/CH_2Cl_2; 10:1 (2.3 mL), KOH (2 mol%) (2.3 mL), RT, 1 h for **L5a** and 3 h at 30°C for **L5f** and **L3a–g**. [b] Yield of isolated product. [c] *Ee* values were determined by chiral HPLC (see Supporting Information). [d] 3.0 equiv of phenylboronic acid used.

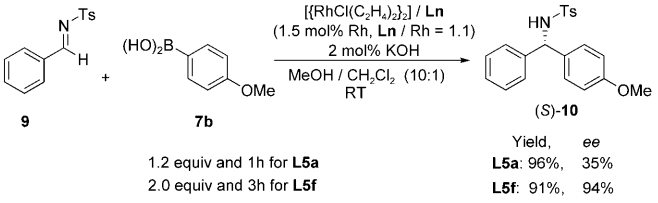
substrate **6a**, we were surprised to find a more pronounced difference in enantioselectivity between ligands **L5a** (52% *ee*) and **L5f** (97% *ee*) than between **L3a** (75% *ee*) and **L3f** (89% *ee*) (Table 1). The enantioselectivity improvement between **L3f** (89% *ee*) and **L5f** (97% *ee*) may result from removing a detrimental effect of 1,4-ester groups whilst maintaining the electron withdrawing aryl substituents. However, comparison of the results for **L3a** and **L5a** contradict this, where the 1,4-diester ligand **L5a** out-performs the 1,4-dimethyl ligand **L3a**. Similar results were obtained with substrate **6b** (Table 2, entry 2). Nevertheless, ligand **L5a** gave excellent yields and selectivity for enones **6c–e** affording (*R*)-configured products **8c–e**. Results for cyclohexanone **6c** are similar to those obtained by Hayashi with diene ligand **L5g**.[2c] For the lactone **6e** both yield and *ee* were improved (95%, 98% *ee*) compared with Carreira's carvone derived ligand (80%, 90% *ee*)[3b] and Darses' ligand (56%, 90% *ee*).[5] Unlike **L5a**, ligand **L5f** gives excellent *ee* for both acyclic and cyclic enones in the expected product configuration, which is consistent with the space differentiation model for chiral C_2-symmetric diene ligands developed by Hayashi.[2a,c,j,6a,15]

Despite the discrepancy between acyclic and cyclic enones for **L5a** in terms of enantioselectivity, we were pleased to find that the reactions completed smoothly at room temperature

in 1 h with only 1.2 equivalents of phenyl boronic acid, compared with at least 2 equivalents for current diene ligands. The requirement for use of excess arylboronic acid is thought to arise as a result of the competing rhodium-catalysed protodeboronation.[17] This significant and unexpected advantage can reasonably be attributed to the 1,4-dimethyl substitution in ligand **L5a** as compared to Hayashi's ligand **L5g** and other ligands. On the other hand, in order obtain a high yield when using our ligand **L5f**, more than 2 equivalents of phenyl boronic acid was required. For example, the yield of **8e** when using ligand **L5f** was only 76% although 3 equivalents phenyl boronic acid were used (Table 2, entry 5).

The only major difference between ligands **L5a** and **L5f** is that **L5a** is more electron rich. These results suggest that the electronic properties of diene ligands are associated with activity, enantioselectivty (for linear substrates) as well as the productivity (ability to avoid the protodeboronation of aryl boronic acid). Increasing the electron density of the ligand benefits the reactivity and suppresses the protodeboronation reaction, but can undermine the enantioselectivity for linear substrates, as for **L5a**. To retain the high enantioselectivity for the linear substrates requires the ligand not be too electron rich. However, this can sacrifice some reactivity and allow the side reaction, as for **L5f**.

In order to further test this electronic effect, ligands **L5a** and **L5f** were examined for the 1,2-addition to tosyl imine **9**, which can be categorized as a linear substrate (Scheme 3).

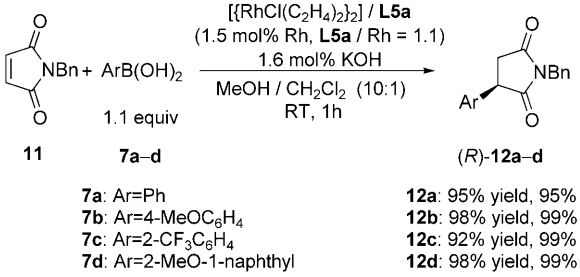


Scheme 3. Asymmetric arylation of *N*-tosyl benzylimine **9**.

The results were as expected; as with the 1,4-addition to linear enones, **L5a** gave much higher reactivity but lower *ee* with less arylboronic acid, while **L5f** gave excellent enantioselectivity but lower reactivity and some protodeboronation side-reaction. To the best of our knowledge, this is the first time that such a unique electronic effect has been observed in diene ligands closely linking reactivity, enantioselectivity and productivity.

The asymmetric conjugate addition of aryl boronic acids to *N*-benzyl maleimide (**11**) is known to be a challenging reaction, and the products are synthetically useful.[22] The chiral phosphine ligand, binap, gave only 70% yield and 58% *ee*, while a chiral norbornadiene diene ligand gave 88% yield and 69% *ee*.[2b] The phosphine–alkene hybrid ligands developed by Grützmacher and Hayashi et al. both gave the desired product in high yield with Hayashi's hybrid ligand giving 89–95% *ee*.[15,23] However, multiple equivalents (3 equiv) of arylboronic acid were required to ensure a high yield. Again it was found that ligand **L5a** achieves both high activity and enantioselectivity for the formation of (*R*)-**12a–d** using only 1.1 equivalents of $ArB(OH)_2$ (**7a–d**) at room temperature in 1 h (Scheme 4). This is the most efficient ligand for this transformation to date.

The product resulting from the conjugate addition of phenyl boronic acid to 6-methylcoumarin (**13**) has been used

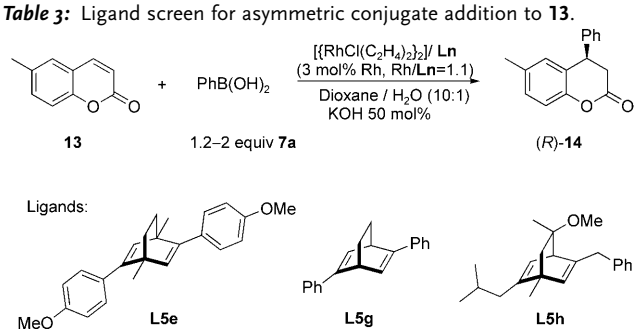


Scheme 4. Asymmetric conjugate addition to *N*-benzyl maleimide **11**.

in a synthesis of the urological drug tolterodine.[24] Examples reported by the Hayashi group show that phosphine ligands can give excellent *ee* (>99%), however 10 equivalents of phenylboronic acid were necessary to achieve a high yield.[24] Only one example using a chiral diene for this reaction has been reported by Carreira et al., where 43% yield and 98% *ee* were obtained in the addition of phenylboronic acid to the coumarin at 50 °C using his carvone derived ligand.[3b] We tested our ligands **L5a**, **L5e** and **L5f** and also ran comparative reactions with Hayashi's ligand **L5g** and Carreira's ligand **L5h** (Table 3).

The enantioselectivity for all ligands was uniformly high (98% *ee*). However, a remarkable difference in reaction rate and yield was found between the ligands when comparing conversion and isolated yield at 30 °C and 50 °C after 6 h. and

Table 3: Ligand screen for asymmetric conjugate addition to **13**.



Entry[a]	Ligand	*T* [°C]	*t* [h]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	**L5g**	30	24	<5	–	n.d.
2	**L5g**	50	6	40	32	98
3	**L5h**	30	24	22	20	98
4	**L5h**	50	6	48	39	98
5	**L5a**	30	24	66	63	98
6	**L5a**	50	6	85	72	98
7	**L5f**	50	24	0	0	–
8	**L5e**[e]	30	3	100	95	98

[a] Reaction conditions: Ref. [2c]. [b] Conversion determined by GC (EC-1 column; calibrated with standard **10** and **11**). [c] Yield of isolated product. [d] *Ee* values determined by chiral HPLC. [e] As footnote [a] except 25 mol% KOH and 1.2 equiv $PhB(OH)_2$ were used.

24 h. Hayashi's ligand **L5g** gave the lowest rate of conversion, Carreira's ligand **L5h** gave increased conversion, our **L5a** gave a further increase but the most active ligand for this reaction was ligand **L5e**, containing the 4-methoxyphenyl groups. This gradual increase in reactivity may be attributed to an increase in electron density in the ligand system; Hayashi's diene **L5g** contains no bridge substituents, Carreira's diene **L5h** contains one methyl substituent (but the 2,5-positions are alkyl-substituted rather than aryl), ligand **L5a** has two bridge methyl groups and **L5e** has two bridge methyl groups and electron donating 4-methoxyphenyl substituents. This is corroborated by the fact that our electron-deficient ligand **L5f** gave no reaction for this substrate.

In summary, we have developed an efficient synthesis of the chiral C_2-symmetric bicyclic [2.2.2] diene ligand system that enables flexible substitution at the 1- and 4-positions. The synthesis is short, high yielding and includes a practical lipase resolution as a key step that can be done on scale and provides an attractive alternative to resolution by chiral preparative HPLC. We have assessed a new series of 1,4-dimethyl 2,5-diaryl bicyclo [2.2.2] octadiene ligands for rhodium-catalysed asymmetric conjugate addition to a range of cyclic and acyclic enones. The addition of 1,4-methyl substituent groups in the ligands enabled us for the first time to observe a significant electronic effect which affects catalytic performance. The catalysts with electron rich ligands gave excellent activity for all substrates and excellent enantioselectivity for cyclic enones with high atom efficiency (only 1.1–1.2 equiv arylboronic acid), even for a challenging substrate such as 6-methylcoumarin. However, this advantage was not shared by linear enones as far as enantioselectivity is concerned. This problem could be abrogated by introducing electron-withdrawing groups on the ligand to achieve high *ee* for all type substrates, although 2-3 equivalents of arylboronic acid are required to compensate for protodeboronation and to achieve high yield. Mechanistic studies to gain a deeper understanding into this phenomenon are ongoing.

Experimental Section

General procedure for the Rh–diene-catalyzed asymmetric conjugate addition: To a Schlenk reaction tube $[\{RhCl(C_2H_4)_2\}_2]$ (1.8 mg, 9 μmol of Rh) and diene ligand (10 μmol) in DCM (0.3 mL) were added under a nitrogen atmosphere. The solution was stirred for 5 min followed by addition of 0.2 M KOH/methanol solution (50 μL, 10 μmol). The resultant mixture was stirred for 15 min before addition of methanol (2 mL), arylboronic acid (0.6–1.5 mmol) and enone (0.5 mmol). The reaction mixture was stirred at the required temperature for 1–3 h, then filtered through a silica pad and purified with preparative TLC to give pure product.

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[19] The absolute configuration of the (*S*,*S*)-enol ester **1** was established by X-ray crystallographic analysis of a bis-ketal bis-triflate derivative (see Supporting Information).

[20] In a non-optimised biotransformation, where the aim was to isolate the unreacted enol ester in high *ee*, the (*R*,*R*)- dione product **2** (2.5 g, 40 % *ee*) was isolated, converted to the enol hexanoate and crystallised to give the single enantiomer (0.84 g, 99.9 % *ee* (48 % of theory)).

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