

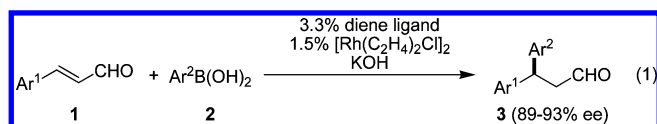
Asymmetric Synthesis of 3,3-Diarylpropanals with Chiral Diene–Rhodium Catalysts

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Compounds incorporating diarylmethine stereogenic centers are found in natural products¹ and a number of notable pharmaceuticals, such as tolterodine and sertraline.² However, the stereoselective preparation of building blocks leading to these is challenging, particularly when little differentiates the two arenes electronically or sterically. This is especially problematic in cases where the only differentiation occurs at the para position of the aromatic groups. The current state of the art for the preparation of nonracemic 3,3-diarylpropanals is the amine-catalyzed addition of aromatic nucleophiles to 3-substituted acrolein derivatives (74–92% ee).³ While this approach performs well with electron-rich nucleophiles, electron-poor aromatics do not furnish 1,4-addition products because they are insufficiently reactive. The Rh(I)-catalyzed conjugate addition of arylboronic acids⁴ offers the promise of a general solution for the synthesis of this important class of compounds⁵ and is less sensitive to the electronic nature of the arene nucleophile. We envisioned that the 1,4-addition to cinnamaldehydes with both electron-rich and -poor arylboronic acids would provide facile access to valuable intermediates, such as **3** (eq 1). Herein, we



document the asymmetric addition of arylboronic acids to cinnamaldehyde derivatives to give optically active 3,3-diaryl-substituted aldehydes. The method is noteworthy on a number of grounds: it provides access to building blocks that are otherwise not readily accessible; the process is both chemo- and regioselective wherein conjugate addition is preferred over 1,2-addition, and in doing so, expands the use of chiral dienes as ligands for transition metals.⁶

The use of chiral dienes as ligands has recently been applied to the asymmetric conjugate addition of arylboronic acids to a selection of electron-poor olefins.^{7,8} This follows in the footsteps of the excellent work involving conjugate addition reactions of boronic acids to unsaturated esters, ketones, and lactones using Rh(I)–phosphine complexes.⁴ The general, reliable conjugate addition to unsaturated aldehydes is notably absent from this listing. In fact, there have been only two reports of additions of arylboronic acids to unsaturated aldehydes by Miyaura; however, the products are either achiral⁹ or obtained in modest yield (3-alkyl-3-arylpropanal).¹⁰ In contrast, the Rh(I)-catalyzed 1,2-addition of arylboronic acids to aldehydes to give benzylic alcohols has been studied extensively.^{9,11,12} This precedence indicates that a serious complication could arise in developing a general conjugate addition reaction to unsaturated aldehydes (Figure 1). Any effort could be thwarted by 1,2-addition either in competition with 1,4-addition (*a* vs *b*) or after the formation of **3** (*a* then *c*) to give **5**.

The addition of 4-methoxybenzeneboronic acid to cinnamaldehyde was used as a test reaction to optimize enantioselectivity via systematic variation of the pseudo-C₂ symmetric ligand scaffold (Table 1).^{7a} In the presence of the parent ligand **6**, adduct **10** was

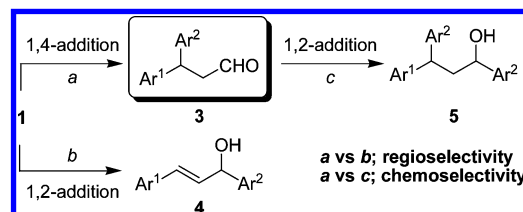
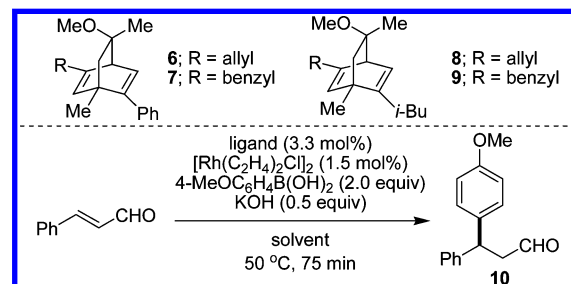


Figure 1. Possible reaction pathways.

Table 1. Ligand Screening and Reaction Optimization



entry	ligand	solvent	yield (%) ^a	ee (%) ^b
1	6	dioxane/H ₂ O (10:1)	43	47
2	7	dioxane/H ₂ O (10:1)	45	60
3	8	dioxane/H ₂ O (10:1)	50	83
4	9	dioxane/H ₂ O (10:1)	43	92
5	9	EtOH/H ₂ O (10:1)	68	92
6	9	MeOH/H ₂ O (10:1)	80	92
7	phosphoramidite ^c	MeOH/H ₂ O (10:1)	19	56
8	(<i>R</i>)-BINAP	MeOH/H ₂ O (10:1)	33	–89

^a Isolated yield after chromatography on SiO₂. ^b Determined by chiral HPLC after reduction of the aldehyde (see SI for details). ^c *O*,*O'*-(*R*)-(1,1'-Dinaphthyl-2,2'-diyl)-*N,N*-di-*i*-propylphosphoramidite.

isolated in 43% yield and 47% ee along with <5% of the product resulting from 1,2-addition (path *b*) (Table 1, entry 1). A modest increase to 60% ee was observed with Bn-substituted ligand **7** (entry 2). When phenyl was replaced with isobutyl, a significant amplification in the enantioselectivity to 83% ee was observed with ligand **8** (entry 3). The use of ligand **9**,¹³ a hybrid of **7** and **8**, afforded the desired product in 92% ee. In each case (entries 1–4), we were able to recover approximately 10% of cinnamaldehyde along with 20–25% of the corresponding double addition product (*a* then *c*). This observation is consistent with the greater propensity of the system to undergo conjugate addition than 1,2-addition. It also provided us with further impetus to study the reaction with the aim of precluding 1,2-addition to **10**.

In further investigations to optimize yield which had at this point been in the range of 43–50%, we observed that the use of alcohol solvents had a dramatic influence on the outcome of the reaction. Thus, in a mixture of 10:1 MeOH/H₂O when the reaction was conducted with ligand **9**, the desired aldehyde **10** could be isolated in 80% yield and 92% ee (entry 6).¹⁴ It is worthy of note that phosphorus-based ligands such as a phosphoramidite¹⁵ and BINAP

Table 2. Conjugate Addition Reactions Catalyzed by Rh(I)-**9**

$\text{Ar}^1\text{-CH=CH-CHO} \xrightarrow[\text{MeOH/H}_2\text{O (10:1), 50 }^\circ\text{C, 75 min}]{\begin{array}{l} \textbf{9 (3.3 mol\%)} \\ [\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2 \text{ (3.0 mol\% Rh)} \\ \text{Ar}^2\text{B(OH)}_2 \text{ (1.2-2 equiv)} \\ \text{KOH (0.5 equiv)} \end{array}} \text{Ar}^1\text{-CH(Ar}^2\text{)-CH}_2\text{-CHO}$				
entry	enal	Ar ² B(OH) ₂	yield (%) ^a	ee (%) ^{b,c}
1			80	92
2			90	93
3 ^d			78	92
4 ^e			70	89
5 ^f			85	90
6			78	93
7		PhB(OH) ₂	70	92
8		PhB(OH) ₂	87	91
9 ^g		PhB(OH) ₂	76	91
10		PhB(OH) ₂	78	90
11		PhB(OH) ₂	63	93

^a Isolated yield after chromatography on SiO₂. ^b Determined by chiral HPLC after reduction of the aldehyde. ^c The absolute configuration was assigned by correlation to earlier work with related acceptors. In entry 9, the adduct of conjugate addition was converted to the known TBDMS *O*-silyl ether³ of the corresponding primary alcohol, accessed by reduction of the aldehyde (NaBH₄) and silylation (TBDMSCl) (see SI for details). ^d Rxn *t* (time) = 2 h. ^e Rxn *t* = 22 h. ^f Rxn *t* = 2.5 h. ^g Rxn *t* = 4 h.

furnished adduct **10** in 19% yield/56% ee and 33% yield/89% ee, respectively.

While examining the scope of this transformation, the addition of both electron-rich (entry 1) as well as electron-poor boronic acids (Table 2, entries 2–6) proceeded smoothly with various enals in 63–90% yield with insignificant variation in the enantioselectivity (89–93% ee). Both enantiomers of a given building block can be obtained by varying the donor and acceptor (cf. Table 2, entries 1 and 7, and entries 2 and 8) for a single enantiomer of the ligand. In addition, the functional group tolerance on both donor and acceptor leads to a wide range of substitutions which could be used subsequently in the diversity-oriented synthesis of pharmaceutically interesting libraries.

In summary, the application of Rh(I)–diene complexes provides access to valuable, optically enriched 3,3-diarylpropanals in 63–

90% yield and 89–93% ee from readily available arylboronic acids and substituted cinnamaldehydes. The successful fine-tuning of the enantioselectivity in this process was made possible by our modular synthesis of bicyclo[2.2.2]octadiene ligands beginning with natural carvone. In addition, this approach offers a tactical advantage over existing methodology in that electron-poor nucleophiles function with efficiency equal to that of their electron-rich counterparts. In a broader sense, the study demonstrates the ability to tune reaction parameters such as chemo- (unsaturated versus saturated aldehyde) and regioselectivity (1,4 versus 1,2) by diene ligands in conjunction with reaction media, which may have additional wide applications in other processes involving this novel class of catalysts.

Acknowledgment. This research is supported by a Swiss National Science Foundation Grant and by the ETHZ. J.-F.P. is grateful to the National Sciences and Engineering Research Council of Canada (NSERC) for a postdoctoral fellowship.

Supporting Information Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the new compounds prepared. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA053270W