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Asymmetric palladium-catalyzed hydroarylation of styrenes and dienes

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Abstract

Alkenes are desirable and highly versatile starting materials for organic transformations, and wellknown substrates for palladium catalysis. Typically, these reactions result in the formation of a new alkene product via β -hydride elimination. In contrast to this scenario, our laboratory has been involved in the development of alkene hydro- and difunctionalization reactions, where β -hydride elimination can be controlled. We report herein the development of an asymmetric palladiumcatalyzed hydroarylation, which yields diarylmethine products in up to 75% ee. Interestingly, a linear free energy relationship is observed between the steric bulk of the ligand within a certain range and the enantiomeric excess of the reaction.

Keywords

Alkenes; Asymmetric Catalysis; Hydroarylation; Palladium-Catalyzed

1. Introduction

Alkenes are attractive starting materials for organic synthesis, since they can be easily functionalized using a plethora of both oxidative and reductive mono- and difunctionalization methods.¹ A subset of these methods have center around Pd-catalyzed olefin functionalization processes highlighted by the Wacker and Heck reactions.² Mechanistically, in both process, initial alkene attack is followed by β -hydride elimination and product release (Scheme 1).^{3,2} Unfortunately, the chiral information present in the Pd-alkyl intermediate is generally lost in the β -hydride elimination step. Several methods to avoid this process have been reported,^{4,5} both to retain stereochemical information and to achieve further functionalization. These include the use of substrates set up to form a quaternary chiral center, where β -hydride elimination is not possible,^{6–10} formation of a stabilized intermediate, such as a Pd π -allyl complex,^{11–18} or rapid conversion of the Pd alkyl complex to a different intermediate to effectively outcompete β -hydride elimination.^{19–21}

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In our laboratory, we have been interested in the functionalization of styrenes and dienes, which can form Pd π -benzyl or π -allyl intermediates to undergo further functionalization. We have been able to successfully develop both alkene hydro-^{11,12,15} and difunctionalization reactions^{13,14} using this approach. To access the hydrofunctionalized products, we have utilized a unique mechanistic manifold (Scheme 2), wherein a Pd-hydride **B** is formed via oxidation of the alcohol solvent, followed by insertion of the alkene into the Pd-hydride and reaction of the resulting Pd π -benzyl or π -allyl intermediate **D** with an exogenous reagent.

Using this manifold, we have developed a Pd-catalyzed hydrochlorination/ hydroalkoxylation of styrenes¹¹ as well as two distinct hydroarylation procedures for styrenes using aryl stannanes and aryl boronic esters, respectively (Scheme 3).^{22,23} While the stannane procedure works moderately well for dienes, the boronic ester method does not give significant amounts of diene hydroarylation products. Therefore, we developed an additional method using boronic esters, optimized specifically for dienes.¹⁵ It should be noted that even though all of the hydroarylation methods utilize (–)-sparteine either as a ligand on Pd or as a base, the products are generally formed in <5% enantiomeric excess. Of note, several diene substrates gave approximately 10% ee.

Considering the diarylmethine moiety is of biological interest to our laboratory²⁴ and difficult to prepare in an enantiomeric enriched form,^{25–29} we became interested in the development of an enantioselective variant of the Pd-catalyzed conjugated alkene hydroarylation reaction. Herein, we report our progress toward the development of such a reaction.

2. Results and Discussion

The boronic ester method was initially selected as a starting point for the development of an asymmetric hydroarylation reaction due to the lower toxicity and easier handling of boronic esters compared to tin reagents. Additionally, it was thought that carbenes are modular in nature and therefore a chiral N-heterocyclic carbene (NHC) ligand could be found to promote the reaction effectively. (–)-Sparteine, on the other hand, is notoriously difficult to modify, and it had been previously shown that it cannot generally be simply replaced with other bidentate amine ligands.^{30–33}

2.1. Chiral NHC ligands

Thus, several NHC's were prepared with chiral backbones as well as chiral substituents on nitrogen (Scheme 4). While all of these successfully promote the reaction, the product was essentially racemic in all cases. When studying Biox-derived carbenes, a low ee (6%) was found for the *i*PrBiox-derived NHC, and a 32% ee was observed with the menthol-derived NHC introduced by Glorius and coworkers.³⁴ Unfortunately, this was accompanied by a significant loss in catalyst activity, and since this ligand could not be easily modified, this result was not pursued further.

We hypothesized that the generally low enantioselectivity may be due to the chiral information being too far removed from the catalytic center, and therefore decided to investigate bidentate ligands, since they should provide a more rigid steric environment, and potentially place the chiral substituents closer to Pd.

2.2. Initial Study of Bidentate Ligand

Since phosphine-based ligands are known to be oxidatively unstable, we decided to evaluate several classes of bidentate nitrogen ligands initially. Different combinations of oxazoline and pyridine or quinoline moieties were synthesized and tested. Of these ligands, BINAM

(L10) and the valinol-derived bioxazoline L5 were the only ligands that did not promote the reaction at all. While menthol-derived bioxazoline L6 as well as pyridine-oxazoline L7 and quinoline-oxazoline L8 gave some product with 10–14% ee, bisoxazoline L11a gave by far the highest yield and ee (52% yield, 45% ee). Somewhat surprisingly, when bridged pyridine-oxazoline L9 was tested, a racemic product was observed.

2.3. Bisoxazoline ligands

A systematic study of bisoxazoline ligands was carried out in order to optimize the ligand, varying the substituent off the oxazoline ring. Interestingly, a linear free energy relationship between the sterics of the oxazoline substituent as defined by the Charton parameter^{35–37} and the log of the enantiomeric ratio of the product (corresponding to a relative rate of product formation for the two enantiomers) was observed up to a certain point (Figure 1). While substituents with a tertiary carbon (such as (*S*)-*i*PrBox **L11a**, (*S*)-diEtBox **L11e**) gave the predicted enantioselectivities, rapid precipitation of Pd metal along with diminished product formation and ee was observed with (*S*)-*t*BuBox (**L11g**) (vide infra). Moreover, when the dicyclohexyl-substituted Box ((*S*)-diCyBox **L11f**) was synthesized and tested, the ee of the hydroarylation product was found to be 63%, even though this substituent would be expected to give a higher ee than the diethyl one.³⁸ Overall, this implies that over a certain range the enantioselectivity is dictated by the size of the oxazoline substituent, as would be expected. However, when the substituent is too large, there is a change, possibly in the overall catalyst structure or reaction mechanism, which perturbs the enantioselectivity.

2.4. Optimization using organostannanes

Interestingly, it was observed that when using an organostannane instead of a boronic ester as the transmetallating agent, a nearly identical ee was observed (Figure 2, entry 1 vs. Figure 1). Additionally, changing from PhSnBu₃ (**4a**) to an enol ether (**4b**) did not affect the enantioselectivity substantially (entry 2). This seemed to indicate that the enantiodetermining step occurred before transmetallation, and, excitingly, gave us an opportunity to develop a set of reaction conditions that could be potentially used with a wide variety of reagents. It was also observed that base was not required for the reaction when using an organostannane, as similar results were obtained with and without KOtBu (entry 3).

Since variation of the ligand substituents alone did not provide sufficiently high enantioselectivity, it was decided to further explore the reaction conditions. For these studies, 4-methylstyrene (1c) and an enol ether stannane (4b) were used, since both reaction progress and ee could be conveniently monitored by GC.

The reaction was evaluated at different temperatures (Figure 3). It was found to be extremely slow at room temperature, but somewhat more efficient at elevated temperatures (65 °C). Interestingly, temperature only had a modest effect on enantioselectivity, and thus further optimization was performed at 65 °C.³⁹

Next, different counterions on Pd were evaluated. However, the use of non-coordinating anions (OTf, OTs, BF₄) led to <5% product in each case, while acetate provided the product in 8% GC yield and 28% ee. The use of 1:1 mixtures of IPA and other cosolvents also did not lead to any improvements. DCE, *t*BuOH, and PhMe led to extremely slow reactions, while DMA provided the product in comparable yield (39%), but diminished ee (37%). It was also observed that Pd(MeCN)₂Cl₂ was not completely soluble in IPA at room temperature, and small amounts of Pd metal precipitate were typically observed during the reaction. By preforming the Pd(*i*PrBox)Cl₂ catalyst and using it in place of Pd(MeCN)₂Cl₂, these issues could be avoided and slight increases in yield and ee were observed (34% yield, 51% ee). The reaction was also performed with Pd(MeCN)₂Cl₂ and no added ligand, which

The effect of excess ligand was then studied in more detail (Table 1). It was found that at <5 mol% of exogenous *i*PrBox the yield deteriorated, and at very low excess ligand loadings no reaction was observed. Since copper additives are known to promote Stille couplings, several different copper salts were added to the reaction mixture.^{40,41} As bisoxazolines are known to bind to copper, and decreased ee's have been observed by our group in reactions that contain "ligandless" copper,¹⁹ enough ligand was added to ligate both Pd and Cu (Table 1, entries 5 – 9). It was found that CuCl₂ gave the best result, furnishing product in 47% yield and 59% ee. Using 10 instead of 5 mol% CuCl₂ improved the yield slightly, and interestingly, with CuCl₂ present, excess ligand was not required for the reaction (Entries 10-11).

2.5. Other bisoxazoline ligand

Since optimization of the reaction conditions led to only modest improvements, other bisoxazoline derivatives were evaluated. Thus, (*S*)-*t*BuBox was tested again at lower temperatures and found to be a viable ligand at room temperature, providing the product in a rather low 18% yield, but in 75% ee, a best achieved thus far. It should be noted that the (*S*)*i*PrBox catalyst is not active under these conditions (see Figure 3). This showcases the fact that (*S*)-*t*BuBox not only forms an active catalyst, but one that is significantly more active than the (*S*)-*i*PrBox-derived one. The most likely reason for the formation of Pd metal with (*S*)-*t*BuBox at 55 °C is that the hydroarylation is proceeding rapidly, but reoxidation of Pd⁰ is slow, potentially due to lower concentration of O₂ in solution.⁴² At lower temperatures, the rate of hydroarylation decreases, while the solubility of O₂ increases, leading to a more robust catalytic system. However, even at room temperature, small amounts of Pd metal precipitate were observed. Unfortunately, lowering the temperature to 0 °C led to only a trace of product.

At this point, the $Pd((S)-tBuBox)Cl_2$ -catalyzed hydroarylation was also tested using boronic esters. Unfortunately, while ee's of up to 56% were observed for substrate **1b** with phenyl boronic ester, these results were found to be irreproducible.

Since formation of Pd black was observed with $Pd((S)-tBuBox)Cl_2$, several bisoxazoline derivatives were synthesized and tested in hopes of discovering a ligand that would provide both good enantioselectivity and a robust catalyst. Ligand **L12** was synthesized following a report by Paquin and coworkers, where a dimethyl-substituted valinol-derived oxazoline was found to be a good substitute for a *t*-butyl oxazoline.⁴³ This ligand was tested using boronic esters, and found to be slightly more selective than (*S*)-*i*PrBox (eq. 1). However, the increase in ee was not substantial enough to warrant further optimization for this ligand.



(eq.1)

With the idea in mind that a catalyst just slightly less sterically bulky than *t*BuBox was needed, ligand **L13** was synthesized, featuring a *t*-butyl-substituted oxazoline ring and an unsubstituted oxazoline. Unfortunately, this ligand gave rather poor results. Next, the bridging carbon was modified. It has been observed by Denmark and coworkers⁴⁴ that placing rings of different sizes at this position alters the angle between the two oxazoline rings, resulting in a subtle change in the bite angle of the ligand. Ligands **L14** and **L15** were synthesized and tested to evaluate the effect of this on our reaction. While this modification did result in improved ee's compared to *i*PrBox, the enantioselectivity was lower than that of *t*BuBox. Interestingly, the reactivity of the catalyst derived from ligand **L14** was found to be slightly lower compared to its "parent" ligand *t*BuBox, suggesting that a slightly larger bite angle alleviated the steric crowding in this catalyst, leading to both lower reactivity and enantioselectivity. Additionally, ligand **L16** was synthesized, with an unsubstituted bridging carbon. Ligands of this type have been found to be deprotonated upon binding to metals,^{45,46} and are therefore fundamentally different from typical Box ligands. Unfortunately, this ligand did not provide a particularly active or enantioselective catalyst.

2.6. Scope

Since it seemed the reaction for organostannanes had been optimized as far as possible, we chose to evaluate different substrates to probe the generality of the reaction (Table 2). In addition to the substrates used for ligand optimization with boron, styrene was found to be a viable substrate in combination with an electron poor aryl boronic ester. Furthermore, since π -allyl and π -benzyl Pd complexes can be accessed with this method, a diene was tested and indeed found to give the expected product, albeit in low yield. Unfortunately, when attempting to isolate the product derived from enol ether stannane **4b**, it was found to be inseparable from the starting material, and therefore, styrene **1b** was instead reacted with PhSnBu₃ (**4a**) (eq. 2).



(eq.2)

3. Conclusion

To summarize, we have made progress toward the development of a Pd-catalyzed asymmetric hydroarylation of styrenes and dienes. Unfortunately, the use of O_2 as the terminal oxidant restricts the potential types of ligands to those stable to oxidative conditions, precluding the use of typical phosphorus-based ligands. We believe that this limitation is the main obstacle that needs to be overcome to develop this reaction more fully. With this in mind, we are currently pursuing the further advancement of this reaction in two directions: by exploring new types of ligands, as well as new mechanistic scenarios involving different oxidants and hydride sources in order to remove oxygen.

4. Experimental

General Information

*i*PrOH (IPA) was distilled from CaH₂; CDCl₃ was dried by passing through a plug of activated neutral alumina. Liquid styrene substrates were purified by passing through a small

plug of activated neutral alumina before use. PhSnBu₃ was purchased from Gelest Inc. NaOtBu was stored in a glove box, and removed immediately prior to use. Unless otherwise noted, reactions were performed under an atmosphere of N2 using standard Schlenk techniques. Flash column chromatography was performed using EM Reagent silica 60 (230-400 mesh). ¹H NMR were obtained at 300 MHz and referenced to the residual CHCl₃ singlet at 7.26 ppm. ¹³C NMR were obtained at 75 MHz and referenced to the center line of the CDCl₃ triplet at 77.16 ppm. GC/MS were obtained on Agilent 6890 (EI) 20:1 split. IR spectra were recorded using a Nicolate FTIR instrument. HRMS (high resolution mass spectrometry) analysis was performed using Waters LCP Premier XE. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. Chiral GC (gas chromatography) analysis was performed using a Hewlett Packard HP 6890 Series GC system fitted with a HP-Chiral permethylated β -cyclodextrin column. SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with a chiral stationary phase (as indicated). Caution should be taken when heating flammable solvents in the presence of O_2 .

4.1. Scope using boronic ester

t-Butyl (4-(1-phenylethyl)phenyl)carbamate (3a)-Into a dry 100 mL Schlenk flask were added 6.7 mg $Pd((S)-iPrbox)Cl_2$ (0.015 mmol, 2.5 mol%), followed by 12.0 mg (S)iPrbox (0.045 mmol, 7.5 mol%), and 9.00 mL IPA. A condenser and 3-way adapter fitted with a balloon of O2 were added, and the flask was evacuated via water aspiration and refilled with O₂ three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 132 mg 1a (0.6 mmol, 1.00 equiv.), 266 mg 2a (1.8 mmol, 3.00 equiv.), and 3.4 mg KOtBu (0.03 mmol, 5.0 mol%) were added into a vial and dissolved in 2 mL IPA, and the solution was added to the Schlenk flask dropwise via syringe. The remaining 1 mL IPA was used to rinse the vial, and added to the flask. The resulting mixture was heated to 55 °C for 24 h. It was then cooled to room temperature, and the solvent was removed under reduced pressure. The residue was partitioned between $H_2O(10 \text{ mL})$ and Et₂O (20 mL), and the layers were separated. The organic layer was washed with 1 M NaOH (1 \times 10 mL), and the combined aqueous layers were extracted with Et₂O (3 \times 10 mL), and dried over a 1:1 mixture of $MgSO_4$ and silica gel. They were then filtered, and the solvent was removed in vacuo. The product was purified by flash column chromatography eluting with 5% acetone/hexanes, to give the product as a clear oil. Its spectral properties matched those of the previously published compound.²³ Yield: 94.1 mg (0.316 mmol, 53%, average of two experiments); 59% ee (average of two experiments); $[\alpha]_D^{20} = -6.8$ (c 1.0, CHCl₃).

N-(4-(1-Phenylethyl)phenyl)acetamide (3b)—The same procedure as for 3a was followed, except 96.7 mg 1b (0.600 mmol, 1.00 equiv.) was used. The product was purified by flash column chromatography eluting with 18% acetone/hexanes. At this stage, it was found to contain small amounts of starting material (1b). It was therefore crystallized from DCM/hexanes, which yielded pure product as a white solid. Yield: 41.6 mg (0.174 mmol, 29%, average of two experiments); 27% ee (average of two experiments); $R_f: 0.63 \text{ w}/50\%$ acetone/hexanes; $[\alpha]_D^{20} = -5.0 \text{ (c } 1.0 \text{ CHCl}_3)$; ¹H NMR (300 MHz, CDCl₃) δ 1.61 (d, J = 7.32 Hz, 3 H), 2.16 (s, 3 H), 4.12 (q, J = 7.32 Hz, 1 H), 7.10 (bs, 1 H), 7.12 – 7.23 (m, 5 H), 7.24 – 7.32 (m, 2 H), 7.39 (m, 2 H); ¹³C NMR {¹H} (75 MHz, CDCl₃) δ 21.99, 24.68, 44.35, 120.18, 126.18, 127.70, 128.26, 128.51, 135.92, 142.62, 146.43, 168.34; IR 3294, 2966, 1660, 1601, 1535, 1512, 1409, 1370, 1317, 1268 cm⁻¹; HRMS: (m/z) calcd. 262.1208 obsd. 262.1213 [M+H] +; mp 93–96 °C.

Methyl 4-(1-phenylethyl)benzoate (3d)—The same procedure as for **3a** was followed, except 62.5 mg **1d** (0.600 mmol, 1.00 equiv.) was used. The product was purified by flash column chromatography eluting with 3% acetone/hexanes. Its spectral properties matched those of the previously published compound.²³ Yield: 66.4 mg (0.276 mmol, 46%, average of two experiments); [α]_D²⁰ = 3.7 (c 1.0, CHCl₃).

(*E*)-1,3-Dimethoxy-5-(4-phenylbut-3-en-2-yl)benzene (3e)—The same procedure as for 3a was followed, except 78.1 mg 1d (0.600 mmol, 1.00 equiv.) was used. The product was purified by flash column chromatography eluting with 2% acetone/hexanes. Its spectral properties matched those of the previously published compound.¹⁵ Yield: 45.7 mg (0.170 mmol, 28%, average of two experiments); 45% ee (average of two experiments); $[\alpha]_D^{20} = -14.5$ (c 1.0, CHCl₃).

4.2. Procedure for hydroarylation using PhSnBu₃ (4a)

t-Butyl (4-(1-phenylethyl)phenyl)carbamate (3a)—Into a dry 100 mL Schlenk flask were added 6.7 mg Pd((S)-iPrbox)Cl₂ (0.015 mmol, 2.5 mol%), followed by 6.7 mg CuCl₂ (0.06 mmol, 10 mol%), 16.0 mg (S)-iPrbox (0.06 mmol, 10 mol%), and 9.00 mL IPA. A condenser and 3-way adapter fitted with a balloon of O₂ were added, and the flask was evacuated via water aspiration and refilled with O2 three times while stirring. The resulting mixture was stirred for 30 min at room temperature. Then, 132 mg 1a (0.6 mmol, 1.00 equiv.), and 330 mg PhSnBu₃ 4a (0.9 mmol, 1.50 equiv.) were added into a vial and dissolved in 2 mL IPA, and the solution was added to the Schlenk flask dropwise via syringe. The remaining 1 mL IPA was used to rinse the vial, and added to the flask. The resulting mixture was heated to 65 °C for 24 h. It was then cooled to room temperature, and stirred with 5 mL 1 M NaOH for 1 h. The resulting mixture was transferred to a separatory funnel and diluted with Et₂O. This was washed with a 1:1 mixture of brine and H₂O (1×10 mL), and the aqueous layer was extracted with Et₂O (3×10 mL). The combined organic layers were washed with brine $(1 \times 20 \text{ mL})$, dried over MgSO₄, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with 4% acetone/hexanes, which yielded a clear oil containing product and a small amount of tin byproduct. This was therefore purified again by flash column chromatography eluting with 4% EtOAc/hexanes. The pure product's spectral properties matched those of the previously published compound.²³ Yield: 65.6 mg (0.221 mmol, 37%, average of two experiments); 36% ee (average of two experiments); $[\alpha]_D^{20} = -4.5$ (c 1.0, CHCl₃).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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^a determined by chiral HPLC analysis. ^b No Charton value available.







chiral stationary phase. ^b no KOtBu.

Figure 2. Initial results using organostannanes.



entry	temp.	time	% yield ^a	% ee ^b
1	rt	25 h	8	nd
2	rt	4 d	31	49
3	55 °C	19 h	22	48
4	65 °C	22 h	31	46

^a GC yied, determined using an internal standard and response factor. ^b determined by GC using a chiral stationary phase.

Figure 3.

Temperature optimization for organostannes.



Figure 4.

Hydroarylation using (S)-tBuBox at lower temperatures.

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Scheme 1. Wacker- and Heck-type alkene functionalization.











Scheme 4.

Asymmetric hydroarylation using chiral carbenes. ^a The Pd carbene complex was formed *in situ* before addition of the remaining reagents (see SI for details).



Scheme 5.

Asymmetric hydroarylation using bidentate nitrogen ligands. ^a 3 mol% ligand were used. ^b 5 mol% Pd(MeCN)₂Cl₂, 20 mol% ligand and 10 mol% KOtBu were used, and the reaction was performed at room temperature. ^c 2.5 mol% Pd((*S*)-*i*PrBox)Cl₂ was used along with 7.5 mol% (*S*)-*i*PrBox.





Table 1

Optimization for organostannes.

	2.5 mol% Pd(iPrBox)Cl	2	
O SnBu ₃ 1.5 equiv.	<i>i</i> PrOH, 65 °C, O ₂		

entry	mol% <i>i</i> PrBox	mol% CuX ₂	% yield ^a	% ee ^b
1	1.25	-	0	NA
2	2.5	-	15	50
3	5	-	34	54
4	7.5	-	34	51
5	7.5	$5 \text{ mol} \% \text{ CuCl}_2$	47	59
6	7.5	5 mol % CuCl	27	56
7	7.5	$5 \text{ mol} \% \text{ CuF}_2$	45	55
8	7.5	5 mol % Cu(OTf) ₂	11	8
9	7.5	5 mol % Cu(OAc) ₂	26	57
10	10	10 mol % CuCl ₂	50	58
11	15	10 mol % CuCl ₂	46	56

 $^{a}\mathrm{GC}$ yield, determined using an internal standard and response factor.

^b determined by GC using a chiral stationary phase.

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Scope using boronic esters.

