Polyhedron 198 (2021) 115070

Contents lists available at ScienceDirect

Polyhedron

journal homepage: www.elsevier.com/locate/poly

Intramolecular hydroamination of trisubstituted aminoallenes catalyzed by titanium complexes of diaryl substituted tridentate imine-diols

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ARTICLE INFO

Article history:
Received 30 November 2020
Accepted 26 January 2021
Available online 9 February 2021

Keywords:
Asymmetric hydroamination
Titanium complex
Amino alcohol
Schiff base

ABSTRACT

Our laboratory has developed catalysts based on earth abundant titanium for asymmetric reactions including intramolecular hydroamination. Previously, we showed that titanium complexes of imine diol ligands showed improved enantioselectivity relative to complexes with bidentate amino alcohol ligands. As the catalyst with the highest selectivity had di-*tert*-butyl substitution, we sought to increase the steric protection by preparing three new ligands with diaryl substitution. These ligands were readily prepared in two steps: first, synthesis of diaryl substituted salicylaldehydes by a Suzuki coupling and second, a Schiff base condensation with a chiral amino alcohol. After characterizing the ligands, *in situ* hydroamination/cyclization with 6-methyl-hepta-4,5-dienylamine was carried out at temperatures ranging from 105 °C to 135 °C to give exclusively 2-(2-methyl-propenyl)-pyrrolidine with enantioselectivity up to 22 %ee. Unexpected dimerization of the catalyst resulted in reduced activity, so the reaction required a catalyst loading of 10–20%.

1. Introduction

Hydroamination is the addition of an N—H bond across an unsaturated C—C bond of an alkene, allene, or alkyne to synthesize amine or imine derivatives [1–5]. This reaction has garnered much interest as it is 100% atom economical and the nitrogen-containing products can be further used in organic synthesis, pharmaceuticals, and other industrial applications [2,6–8]. However, practical application of hydroamination still has many challenges including a high reaction barrier, and difficulty controlling the regio- or stereoselectivity of the resulting products. The reaction barrier can be overcome through use of a catalyst, while a well-designed catalyst is needed to control the regio- and/or stereoselectivity.

Over the past 30 years, many research groups have studied this reaction. Catalysts from across the periodic table have been developed including those based on transition metals, main group metals, lanthanides, actinides, and Brønsted acids [7,9,10]. Intramolecular hydroamination of aminoallenes has been studied extensively since the early mechanistic work of Bergman [11,12] and Marks [13,14] as these reactions can lead to chiral heterocycles with an alkene retained in the product (Scheme 1) [5,15]. The reaction proceeds first by protonolysis of NMe_2 groups by the incoming substrate to form the active catalyst followed by a [2 + 2] cycloaddition to form the metallaazacyclobutane. Protonolysis by another incoming substrate molecule regenerates the catalyst. Metal catalysts from across the periodic table have been studied [3,16–20]. In 2007, the Toste group reported enantiomeric excesses above 99% for gold(I) catalyzed intramolecular hydroamination of allenes [21]. However, there are aspects of this work that could be improved upon. First, as is typical for late metal catalyzed hydroamination reactions, the gold reaction requires the use of protected amine substrates, leading to additional steps in protecting the substrates and deprotecting the products [5,15,22]. Second, the preparation of ligands such as (R)-3,5-xylyl-BINAP requires multistep synthesis as well as expensive chiral resolving agents making the process time consuming and costly [23,24].

Group IV complexes show great potential for hydroamination and other reactions [1,25–33]. These metals are an especially attractive choice due to their low cost and toxicity, and while generally considered to be not functional group compatible, appropriate catalyst design can lead to tolerance of oxygen- and nitrogen-containing functional groups [34]. Titanium, in particular, is attractive because of its high earth abundance. Catalytic alkene hydroamination with other first row transition metals has been recently reviewed [35], and the development of earth-abundant catalysts has become an important goal for the organometallic community [36,37]. While these high oxidation state early metal complexes have been studied immensely over the years due to their practicality and usefulness, challenges come from the

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https://doi.org/10.1016/j.poly.2021.115070
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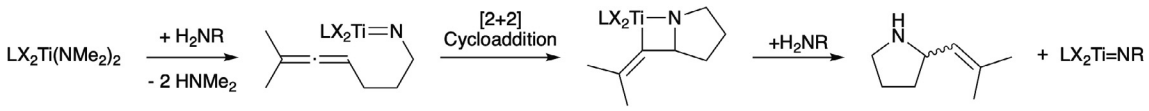


Scheme 1. The generally accepted mechanism for the titanium catalyzed hydroamination of aminoallenes (R = $CH_2CH_2CH_2CH$ = C = CMe_2).

propensity of these species to dimerize, undergo ligand exchange, or experience other processes that reduce catalytic reactivity [38]. Titanium catalyzed hydroamination has been studied by groups such as Schafer [9,39–41], Odom [38,42], and Doye [43–46]. Our group has carried out extensive research on titanium catalysts with bidentate nitrogen–oxygen chelating ligands [47,48]. Our early work suggested that the titanium complexes were dimeric complexes with bridging alkoxide oxygens in the solid state [49]. Our corresponding Tantalum complexes, however, appear to be monomeric and also tend to give higher enantioselectivities [50]. We hypothesized that the reduction in enantioselectivity for our Titanium complexes may be due to their dimeric nature relative to the corresponding Tantalum complexes. To address this hypothesis, we prepared ligands that contain an additional neutral donor atom to form a tridentate ligand in order to prevent dimerization of the titanium complex [51]. In this prior work, the di-*tert*-butyl substituted ligand (Fig. 1a) gave the highest stereoselectivity then reported for a titanium catalyzed hydroamination reaction at 17 %ee. Since the 3,5 di-*tert*-butyl substituted ligand was the best performing ligand, we sought to prepare other ligands with differing steric bulk on the phenol ring (Fig. 1b–d). Substituted aryl rings could be readily attached to these positions by a Suzuki coupling on the starting halogenated salicylaldehyde. Substitution of *tert*-butyl by phenyl would also result in a different electronic environment, albeit modest. We anticipated that phenyl rather than *tert*-butyl substitution in these new ligands would enhance the enantioselectivity of the reaction.

2. Experimental section

2.1. General

All reagents were obtained from commercial suppliers and purified by standard methods [52] or used as received. Ligand precursor (*S*)-2-amino-1,1,3-triphenylpropanol was prepared by literature procedures [53,54]. Aldehydes (**A1**) and (**A3**) have been reported previously [55,56], and were prepared analogously to aldehyde (**A2**); our spectra are consistent with the literature. The purity of compounds was established by ^{1}H NMR spectroscopy and elemental analysis. Solvents were dried by vacuum transfer from sodium/benzophenone (C_6D_6) or by passage through a column of activated alumina (Innovative Technology PS-400–5-MD) and stored under nitrogen (diethyl ether and toluene). Column chromatography was carried out using a CombiFlash NextGen 300 + system (Teledyne ISCO). Solutions of ligands (ca. 0.05 M in C_6D_6) and substrates (ca. 1.5 M in C_6D_6) for catalysis were dried over molecular sieves overnight and stored at −35 °C. All air and/or moisture sensitive compounds were manipulated under an atmosphere of nitrogen using standard Schlenk techniques, or in a glovebox (MBraun Unilab). ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on a Brüker Avance NEO 400 spectrometer and referenced to internal tetramethylsilane or residual solvent peaks. Carbon assignments were made using DEPT experiments. Coupling constants (*J* values) are given in Hz. Polarimetry was carried out using a JASCO P1010 instrument. IR spectroscopy was carried out using a Thermo-Nicolet iS5 FTIR using a diamond anvil ATR accessory. GC-MS analysis was carried out using a Hewlett Packard 5890 Series II Gas Chromatograph. Mass spectra were obtained using an Advion expression^L APCI Mass Spectrometer with quadrupole mass analyzer. Specific rotation values $[\alpha]_D$, are given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

2.2. Synthesis of aldehydes by Suzuki coupling

2-Hydroxy-3,5-di-4-(trifluoromethyl)phenylbenzaldehyde (**A2**).

3,5-dibromosalicylaldehyde (1.1757 g, 4.20 mmol), 4-(trifluoromethyl)phenylboronic acid (2.00 g, 10.5 mmol, 2.5 equiv.), [Pd(dba)$_2$] (0.1657 g, 0.263 mmol, 6.2 mol%), and PPh_3 (0.1314 g, 0.501 mmol, 11.9 mol%) were combined with toluene (100 mL), ethanol (25 mL), and aqueous Na_2CO_3 (2 M, 50 mL) under an atmosphere of N_2. The reaction mixture was stirred overnight in an oil bath at 90 °C. The reaction was cooled to room temperature under air for 30 min. The aqueous phase was extracted with ether (2 × 25 mL). The combined organic phase was washed twice with brine, dried ($MgSO_4$), and filtered to remove palladium black. Crude products were purified by flash column chromatography to yield a white solid (1.2854 g, 3.13 mmol, 75%). The product could also be purified by recrystallization from ethanol. Mp:143.0–144.6 °C. *Anal.* Calc. for $C_{21}H_{12}F_6O_2$: C, 61.47; H, 2.95. Found: C, 61.38; H, 3.04. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.65 (s, 1H, ArO*H*), 10.07 (s, 1H, *H*C = O), 7.85–7.72 (m, 10*H*, Ar*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.82 (H*C* = O), 158.94 (4°), 142.64 (4°),

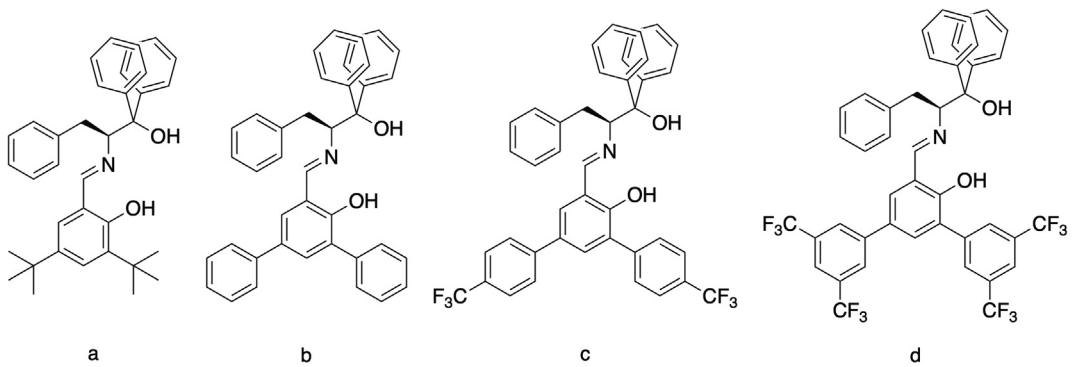


Fig. 1. a) 3,5-di-*tert*-butyl substituted ligand [51], b–d) the ligands used in this study.

139.70 (4°), 136.42 (CH), 132.31 (CH), 132.20 (4°), 130.21 (q, $^{2}J_{CF}$ = 33 Hz), 130.10 (4°), 129.98 (q, $^{2}J_{CF}$ = 32 Hz), 129.82 (CH), 127.10 (CH), 126.22 (q, $^{3}J_{CF}$ = 3.7 Hz), 125.50 (q, $^{3}J_{CF}$ = 3.7 Hz), 124.26 (q, $^{1}J_{CF}$ = 271 Hz), 124.14 (q, $^{1}J_{CF}$ = 271 Hz), 121.33 (4°). ^{19}F NMR (376 MHz, $CDCl_3$): δ − 62.46 (CF_3), − 62.58 (CF_3). MS (APCI): *m*/*z* 411[M + H]$^+$. IR (ATR, diamond): (HC = O) = 1660 cm^{-1}.

2.3. Synthesis of ligands by Schiff base condensation

2-Hydroxy-3,5-diphenyl-benzaldehyde 2-*S*-(1,1,3-triphenyl-propanol)imine (**L1**).

Diphenyl substituted aldehyde **A1** (0.8132 g, 2.96 mmol) and (S)-2-amino-1,1,3-triphenylpropanol (0.8994 g, 2.96 mmol, 1 equiv.) were each dissolved in ethanol (25 mL) in a flask with a reflux condenser open to air. The aldehyde solution was added to the amine solution and the reaction mixture was heated at reflux overnight. The solvent was removed *in vacuo*. The crude product was purified by flash column chromatography to give a bright yellow solid (2.51 mmol, 1.4030 g, 85%). The product could also be purified by recrystallization from hexane. Mp: 97.6–99.0 °C. [α]$_D$: −158° (*c* = 0.006 g/mL, EtOAc). *Anal*. Calcd for $C_{40}H_{33}NO_2$: C, 85.84; H, 5.94; N, 2.50. Calcd for $C_{40}H_{33}NO_2{\cdot}1/2\ H_2O$: C, 84.48; H, 6.03; N, 2.46. Found: C, 84.49; H, 6.22; N, 2.47. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.4 (s, 1H, ArO*H*), 7.74–7.01 (m, 28H, Ar*H*, *H*C = N) , 4.45 (dd, 1H, *J* = 10.0, 1.6 Hz, C*H*CH$_a$H$_b$Ph), 3.22 (br s, 1H, OH), 3.04 (apparent d, 1H, *J* = 12.6, CHC*H$_a$*H$_b$Ph), 2.95 (dd, 1H, *J* = 13.8, 10.1, CHCH$_a$*H$_b$*Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.01 (H*C* = N), 157.68 (4°), 145.63 (4°), 144.19 (4°), 140.24 (4°), 139.04 (4°), 137.63 (4°), 132.42 (CH), 132.01 (4°), 130.15 (4°), 129.88 (CH), 129.50 (CH), 128.95 (CH), 128.66 (CH), 128.58 (CH), 128.53 (CH), 128.39 (CH), 127.52 (CH), 127.22 (CH), 127.10 (CH), 127.05 (CH), 126.70 (CH), 126.56 (CH), 126.23 (CH), 126.00 (CH), 118.81 (4°) , 79.87 (4°, C18), 78.96 (CHCH$_2$Ph), 37.55 (CH_2, C16). One aromatic CH was not observed. MS (APCI): *m*/*z* 559 [M + H]$^+$. IR (ATR, diamond): (C═N) = 1624 cm^{-1}.

2-Hydroxy-3,5-di-4-(trifluoromethyl)phenylbenzaldehyde 2S-(1,1,3- triphenylpropanol)imine (**L2**).

L2 was prepared analogously to **L1** starting from the mono-CF_3 substituted aldehyde **A2** (2.0595 g, 5.02 mmol) and (S)-2-amino-1,1,3-triphenylpropanol (1.5228 g, 5.02 mmol, 1 equiv.) to yield a cream solid that is bright yellow in solution (2.3568 g, 3.39 mmol, 68%). Mp: 84.4–84.5 °C. [α]$_D$: −143° (0.006 g / mL, EtOAc). *Anal*. Calcd for $C_{42}H_{31}F_6NO_2$: C, 72.51; H, 4.49; N, 2.01. Found: C, 72.14; H, 4.71; N, 1.95. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.67 (br s, 1H, ArO*H*), 7.68–6.91 (m, 26H, Ar*H*, *H*C = N), 4.36 (dd, 1H, *J* = 10.2, 1.6 Hz, C*H*CH$_a$H$_b$Ph), 2.98 (apparent d, 1H, *J* = 12.7 Hz, CHC*H$_a$*H$_b$Ph), 2.87 (s, 1H, O*H*), 2.82 (dd, 1H, *J* = 13.8, 10.3 Hz, CHCH$_a$*H$_b$*Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.45 (H*C* = N), 158.90 (4°), 145.36 (4°), 144.03 (4°), 143.45 (4°), 141.01 (4°), 138.85 (4°), 132.24 (CH), 130.48 (4°), 130.28 (CH), 129.85 (CH), 129.81 (CH), 129.32 (4°, CCF_3, q, $^{2}J_{CF}$ = 33 Hz), 129.27 (4°, CCF_3, q, $^{2}J_{CF}$ = 32 Hz), 129.15 (4°), 128.72 (CH). 128.64 (CH), 128.57 (CH), 127.40 (CH), 127.23 (CH), 126.88 (CH), 126.66 (CH), 126.25 (CH), 126.06 (CH), 125.96 (CH, q, $^{3}J_{CF}$ = 3.7 Hz), 125.35 (CH, q, $^{3}J_{CF}$ = 3.8-Hz), 124.40 (CF_3, q, $^{1}J_{CF}$ = 270 Hz), 124.37 (CF_3, q, $^{1}J_{CF}$ = 270 Hz), 118.96 (4°), 79.88 (4°), 78.71 (CH). 37.53 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): δ − 62.39 (CF_3), − 62.51 (CF_3). MS (APCI): *m*/*z* 696 [M + H]$^+$. IR (ATR, diamond): (C═N) = 1616 cm^{-1}.

2-Hydroxy-3,5-di-(3,5-di(trifluoromethyl))phenylbenzaldehyde 2S-(1,1,3- triphenylpropanol)imine (**L3**).

L3 was prepared analogously to **L1** starting from di-CF_3 substituted aldehyde **A3** (0.8368 g, 1.53 mmol) and (S)-2-amino-1,1,3-triphenylpropanol (0.4644 g, 1.53 mmol, 1 equiv.) to yield a yellow solid (1.531 g, 1.84 mmol, 91%). Mp: 99.6–102.8 °C. [α]$_D$: −69.08° (*c* = 0.006 g / mL, EtOAc). *Anal*. Calcd for $C_{44}H_{29}F_{12}NO_2$: C, 63.54; H, 3.51; N, 1.68. Found: C, 63.44; H, 3.73; N, 1.76. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.97 (s, 1H, ArO*H*), 8.02–6.92 (m, 24H, Ar*H*, *H*C = N), 4.37 (apparent d, 1H, *J* = 9.8 Hz, C*H*CH$_a$H$_b$Ph), 3.04 (apparent d, 1H, *J* = 13.5 Hz, CHC*H$_a$*H$_b$Ph), 2.80 (m, 2H, O*H*, CHCH$_a$*H$_b$*Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.88 (H*C* = N), 159.66 (4°), 145.03 (4°), 143.90 (4°), 141.98 (4°), 139.08 (4°), 138.69 (4°), 132.46 (4°, q, ^{2}J = 33 Hz), 131.76 (4°, q, ^{2}J = 33 Hz), 131.81 (CH), 130.86 (CH), 129.82 (CH), 129.75 (CH), 129.12 (4°), 128.76 (CH), 128.71 (CH), 128.61 (CH), 128.05 (4°), 127.56 (CH), 127.40 (CH), 126.78 (CH, shoulder), 126.76 (CH), 126.40 (CH), 126.23 (CH), 123.59 (CF_3, q, ^{1}J = 273 Hz), 123.43 ((CF_3, q, ^{1}J = 273 Hz), 121.45 (CH, septet, ^{3}J = 3 Hz, para), 120.91 (CH, septet, ^{3}J = 3 Hz), 119.17 (4°), 79.92 (4°), 78.61(CH), 37.50 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$): − 62.66 (CF_3), − 62.80 (CF_3). MS (APCI): *m*/*z* 831 [M + H]$^+$. IR (ATR, diamond): (C═N) = 1633 cm^{-1}.

2.4. In situ catalysis

Hydroamination was carried out using a slight modification to our previous *in situ* catalysis procedures [47,51,57]. Inside the glovebox, deuterated benzene (212.5 μL), Ti(NMe$_2$)$_4$ (100 μL of a 0.0375 M solution, $3.75{\cdot}10^{-3}$ mmol), and ligand (75 μL of a 0.05 M solution, $3.75{\cdot}10^{-3}$ mmol) were combined in a medium-walled J. Young NMR tube. The solution was heated at 100 °C for 2 h. Then, 6-methyl-hepta-4,5-dienylamine (12.5 μL of a 1.5 M solution, 0.019 mmol 5 equiv.) was added and the J. Young NMR tube was heated at 105–135 °C. Reactions were monitored periodically by ^{1}H NMR spectroscopy until completed or when conversion stalled. Percent conversion of products were determined by ^{1}H NMR spectroscopy (allene hydrogen is a pseudo-nonet at 5.02 ppm, while the pyrrolidine hydrogen is a doublet of septets at 5.19 ppm).

Enantiomeric excesses of the products were determined of their benzyl derivatives. Benzyl bromide (2.25 μL, 0.02 mmol) and triethylamine (5.25 μL, 0.04 mmol) were added to the J. Young NMR tube of a completed hydroamination reaction. The tube was left to sit overnight and a crystalline solid precipitated out of solution. Isopropanol (100 μL) was added to the solution which was then filtered through glass fibers in a pipette filter to remove any residual TiO_2 . The clear solution was diluted to a total volume of 4 mL with ether. The crude solution (0.2–0.5 μL) was injected onto the chiral GC capillary column (Chiraldex B-DM, 30 m × 0.25 μm, split ratio 400, flow rate 41 cm s-1, 100 °C, 8 min, 1 °C min^{-1}to 136 °C, 10 °C min^{-1}to 180 °C, hold 20 min). The two enantiomers of 2-(2-methyl- propenyl)-pyrrolidine (2a) were separated with retention time at approximately 41.5 min and 42.2 min.

3. Results & discussion

3.1. Design and synthesis of ligands

In our prior study we found that bulky ligands with 3,5-di-*tert*-butyl substitution gave the highest enantioselectivity for the intramolecular hydroamination of aminoallenes [51]. A similar zirconium catalyzed intramolecular hydroamination of aminoalkenes has been reported [32]. We designed new ligands that could be readily prepared that had differing steric protection at the 3,5-positions (Fig. 1). The three aldehydes differ in the substitution of the 3,5-diaryl rings, being phenyl (unsubstituted), or containing CF_3 groups, attached at either the 4- or 3,5-positions of the phenyl ring.

The three aldehydes used in this study were prepared via a Suzuki coupling using two different procedures. Procedure 1 used Pd(dba)$_2$, 2.5 equiv. of boronic acid, 3,5-dibromosalicylaldehyde and PPh_3 [56]. Procedure 2 used Pd(PPh_3)$_4$, 3,5-diiodosalicylalde-

hyde, and 3 equiv. of boronic acid [58]. Either haloaldehyde could be used in either synthesis, but procedure 1 gave higher yields and was therefore adopted for the synthesis of all three aldehydes.

The resulting aldehydes were purified by recrystallization or chromatography, and were isolated as white or yellow solids. **A2** was fully characterized by melting point, ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy, mass spectrometry, and infrared spectroscopy. All three aldehydes exhibited an OH and a C(O)H peak in the ^{1}H NMR spectra near 12 and 10 ppm respectively, and **A2** exhibited CF_3 peaks in the ^{19}F NMR spectra near – 62 ppm. All aldehydes exhibited a C=O stretch in the IR spectrum at near 1650 cm^{-1}.

The synthesis of the ligands **L1**, **L2** and **L3** was carried out by combining the salicylaldehyde derivatives with the chiral amino alcohol derived from phenylalanine (*S*)-2-amino-1,1,3-triphenylpropanol (Scheme 2). After an overnight reflux in ethanol, the crude material was obtained simply by removing solvent. Ligands could be purified either by recrystallization or by chromatography. Similar imine-diol ligands we have prepared have been bright canary yellow in the solid state, and all three were this color in solution. However, **L2** was a cream color in the solid state following chromatography. Multiple attempts were made to obtain X-ray quality crystals of the three ligands but they have thus far been unsuccessful. The X-ray crystal structure of a related ligand (4-CH_3 substituted) was obtained and published recently [59].

Ligands **L1**, **L2**, and **L3** were completely characterized by melting point, optical rotation, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and infrared spectroscopy. Ligands **L2** and **L3** were also characterized by ^{19}F NMR spectroscopy. Each ligand exhibited three doublets of doublets corresponding to the ligand backbone in their ^{1}H NMR spectra between 2 and 5 ppm, and **L2** and **L3** also exhibited CF_3 peaks at around -62 ppm in their ^{19}F NMR spectra. All ligands contained a C=N stretch in the IR spectrum near 1620–1630 cm^{-1}. Although one aromatic CH was not observed for **L1**, the ^{1}H, ^{19}F and ^{13}C NMR spectra otherwise were consistent with the proposed structures. Long range CF coupling ($^{1}J_{CF}$, $^{2}J_{CF}$ and $^{3}J_{CF}$) was observed in both **L2** and **L3**, although the quartet due to the 2,6-carbons was not definitively located in **L3**.

3.2. Intramolecular hydroamination of aminoallenes

Hydroamination of aminoallene substrates was carried out *in situ*. Titanium precatalyst complexes were prepared by mixing a solution of the desired ligand with $Ti(NMe_2)_4$ in benzened_6 in a J. Young NMR tube and heated at 100 °C for 2 h. Catalysis was initiated by the addition of a solution of 6-methyl-hepta-4,5-dienylamine in benzened_6 followed by heating to 135 °C, 125 °C, 115 °C, or 105 °C overnight (Scheme 3). Our established procedures for hydroamination using this ligand type do not include any preheating [51]. However, if we did not pre-form the complexes, no conversion was observed. We studied different pre-heating times of 1-, 2-, and 4-hours; 1 h of preheating resulted in no eventual conversion to product, but the 2- and 4-hour preheating times gave similar results so we adopted the 2-hour procedure for all subsequent studies.

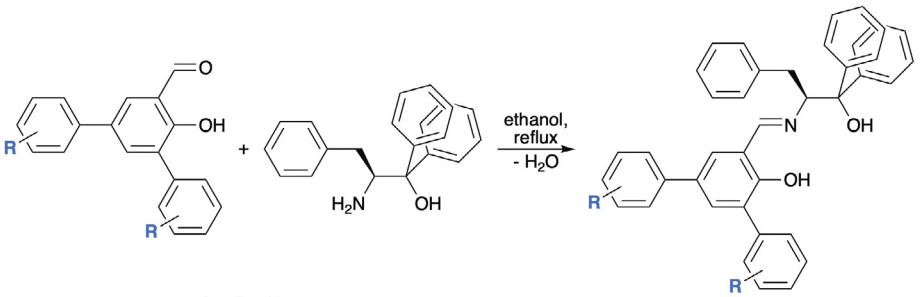
The hydroamination reactions were monitored by ^{1}H NMR spectroscopy and quenched when complete or when no additional reaction progress was observed after a 16–24 h period. The reactions proceeded to give only the desired pyrrolidine product, as we have previously observed with this substrate [47,50,51]. The time to reach conversion was usually around 18 h, though some reactions continued to progress for several days. The reaction reached 100% conversion at 20% catalyst loading for all ligands and temperatures. Lower conversion was observed at 10% catalyst loading, though some samples achieved 100% conversion. Essentially no conversion was observed at our typical catalyst loading of 5%. Enantioselectivities were determined by converting the pyrrolidine product to its benzyl derivative using benzyl bromide. Samples were injected onto the GC-MS instrument and enantioselectivities were determined using our established procedure [51]. The results of our study of temperature and catalyst loading on selectivity are found in Table 1.

At 135 °C, the observed enantioselectivities ranged from 6 to 8% at 20 mol% loading (entries 1, 6 and 11); the selectivity rose to 12–15 %ee for **TiL1** and **TiL3** at 10 mol% loading, though the conversions were low for both of these trials (entries 2 and 12). At 125 °C, the observed enantioselectivities were 21% for **TiL1** (entry 3) 6% for **TiL2** (entry 8) and 5% for **TiL3** (entry 13) rising to 18% for **TiL3** at 10 mol% loading (entry 14). At 115 °C, the observed enantioselectivities were 19% for **TiL1**, and 7% for both **TiL2** and **TiL3** (entries 4, 9 and 15). At 10 mol% loading, **TiL3** gave a 21 %ee (entry 16). Finally, at 105 °C, the observed enantioselectivities were 22% for **TiL1**, 8% for **TiL2**, and 6% for **TiL3** (entries 5, 10 and 17).

Although there was a slight increase in enantioselectivity as temperature dropped, the effect was not as substantial as observed in a similar study carried out with sulfonamide ligands on titanium and tantalum [48]. In addition, **TiL1** gave the best selectivity, which was unexpected as it was the least sterically crowded. Admittedly, the CF_3 substitution on ligands **L2** and **L3** are not much larger than a phenyl group, but we expected that the larger ligands would give higher selectivity. We cannot rule out a small inductive electronic effect on the selectivity of the reaction.

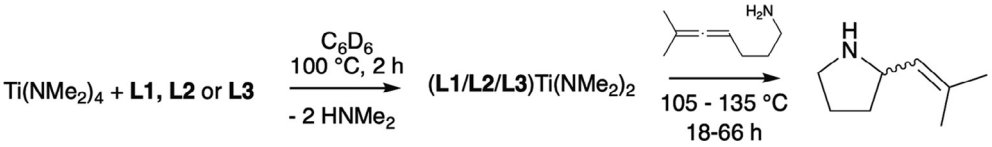
These results are a slight improvement on the imine-diol derived catalysts we have reported previously [51]. In that work, the highest enantioselectivity of 17 %ee was observed for the 3,5-di-*tert*-butyl substituted ligand (Fig. 1a). The **L1** ligand is more selective by about 5%. The highest enantioselectivity for the titanium catalyzed hydroamination of this dimethylaminoallene substrate was recently reported at 27 %ee [47].

The decrease in reactivity requiring increased catalyst loading is perhaps explained by the unexpected formation of 2:1 complexes.



L1: R = H, 85%
L2: R = 4-CF_3, 68%
L3: R = 3,5-$(CF_3)_2$, 91%

Scheme 2. Synthesis of ligands by Schiff base condensation.



Scheme 3. Hydroamination of trisubstituted aminoallenes.

Table 1
Hydroamination of 6-methyl-hetpa-4,5-dienylamine at various loadings and temperatures with *in situ* catalysts.

Entry	Catalyst	Catalyst Loading (%)	Temperature (°C)	Time (h)	NMR Yield (%)	% ee[a]
1	**TiL1**	20	135	18	100	8
2	**TiL1**	10	135	66	25	15
3	**TiL1**	20	125	18	100	21
4	**TiL1**	20	115	66	100	19
5	**TiL1**	20	105	18	100	22
6	**TiL2**	20	135	13	100	8
7	**TiL2**	10	135	13	100	6
8	**TiL2**	20	125	21	100	6
9	**TiL2**	20	115	19	100	7
10	**TiL2**	20	105	19	100	8
11	**TiL3**	20	135	18	100	6
12	**TiL3**	10	135	18	40	12
13	**TiL3**	20	125	18	100	5
14	**TiL3**	10	125	18	25	18
15	**TiL3**	20	115	18	100	7
16	**TiL3**	10	115	66	63	21
17	**TiL3**	20	105	18	100	6

[a]Of the benzyl derivative, determined by GC, ±2%. All reactions favored the formation of the *S*-(-) enantiomer as determined by comparison to literature values [50,60–62]. Data reported as the average of at least two individual runs.

During the preparation of the hydroamination solutions, we occasionally observed the formation of a yellow precipitate in the NMR tubes. This precipitate was not observed with the prior imine-diol ligands we have studied, though we did accidentally obtain a crystal structure of a pseudooctahedral 2:1 complex of a similar ligand on titanium [63], and structures of this type have been reported previously [64]. Other groups have reported the observation of isomers of complexes with imine-diol ligands on both copper [65] and molybdenum [66], and it is possible that these isomers may in fact be 2:1 complexes. The formation of this 2:1 complex would remove the reactive dimethylamide groups, preventing it from being a suitable precatalyst for the hydroamination reaction which requires the formation of the titanium imido complex (Scheme 1). Increasing the catalyst loading to 10–20 mol% allowed these complexes to serve as effective catalysts for the hydroamination, though the active catalyst concentration is surely lower.

The formation of the 2:1 structure could also account for the decrease in enantioselectivity. If the complex forms *in situ* by a disproportionation reaction, an equal amount of $Ti(NMe_2)_4$ would form according to Eq. (1). This titanium complex is competent for the catalytic hydroamination reaction, albeit at a lower rate (100% conversion at 135 °C in 67 h) and with no selectivity [57]. Although drawn as an equilibrium, precipitation of the $Ti(X_2L)_2$ complex would drive the reaction to the right, reducing the concentration of the active, chiral, catalyst. It is unclear why these ligands favored the formation of the 2:1 complex so strongly but clearly the steric protection afforded by the 3,5-diaryl substitution does not prevent the formation of this complex.

$$2\ Ti(X_2L)(NMe_2)_2 \rightleftharpoons Ti(X_2L)_2 + Ti(NMe_2)_4 \quad (1)$$

4. Conclusion

A series of imine-diol ligands with differently substituted aryl groups was prepared, and intramolecular hydroamination of aminoallenes was studied using their titanium complexes. The *S*-(-)-enantiomer of the pyrrolidine product was favored in enantiomeric excesses of up to 22%. This selectivity is the second highest observed, and is an improvement by about 5% from our previous ligands of similar design. There is not a substantial difference in stereoselectivity at different temperatures, and the least sterically encumbered ligand was found to give the highest selectivity. Catalysis was carried out at 10–20 mol% loading due to the formation of an unreactive 2:1 complex. Further investigation in this area should focus on looking at steric *width* at the 3,5 positions on the phenol ring to prevent the formation of the undesired complex. It may be worthwhile to incorporate substitutions with a more three-dimensional shape rather than planar rings.

CRediT authorship contribution statement

Emily Y. Fok: Investigation, Writing - original draft, Writing - review & editing. **Veronica L. Show:** Investigation, Writing - review & editing. **Adam R. Johnson:** Conceptualization, Methodology, Writing - review & editing, Data curation, Resources, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Financial support for this project was provided by the John Stauffer Fund for Summer Research in Chemistry and Harvey Mudd College. The authors thank Ty G. Waggener for providing artwork. This paper is dedicated to the memory of RJC.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.poly.2021.115070.

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