Tetrahedron 75 (2019) 3341–3347

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis of chiral titanium-containing phosphinoamide ligands for enantioselective heterobimetallic catalysis

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ARTICLE INFO

Article history:
Received 11 February 2019
Received in revised form
24 April 2019
Accepted 25 April 2019
Available online 4 May 2019

Keywords:
Phosphinoamide ligand
Heterobimetallic catalyst
Enantioselective
Allylic amination
Palladium

ABSTRACT

The synthesis of six chiral titanium-containing phosphinoamide ligands is discussed. These ligands assemble chiral heterobimetallic Pd–Ti complexes, enable enantioselective intramolecular allylic aminations with hindered amine nucleophiles and achieve selectivity up to 53% ee. Mechanistic studies demonstrate the reversibility of the enantio-determining C–N bond forming step, which leads to a gradual increase in the % ee of the reaction over time. These results represent a rare example of enantioselective heterobimetallic catalysis and suggest that these new ligands could find broad application in enantioselective transition metal catalysis.

1. Introduction

The field of bimetallic catalysis is an emerging and evolving area of transition metal catalysis that provides unique opportunities for reactivity and enables new types of cooperative reaction mechanisms [1]. Recent studies have suggested that bimetallic cooperativity may be a relatively common phenomenon and a significant contributor to catalysis in many transition metal-catalyzed reactions [2–4]. The development of bimetallic complexes that contain direct metal–metal bonds or through-space metal–metal interactions provides the opportunity to enhance the electronic properties of a transition metal catalyst without disturbing the influence of coordinated organic ligands [1,4]. Bimetallic catalysts have traditionally played an important role in organic synthesis, in particular through the development and application of dirhodium tetracarboxylate catalysts [5]. The unique reactivity of these bimetallic complexes in important reactions like cyclopropanations [6] and C–H activation reactions [7,8], including enantioselective catalysis [9,10], is intimately tied to the presence of two electronically-coupled rhodium centers within the catalyst [11].

Recently, a resurgence in the design of bimetallic complexes and their application to organic reactions has led to the report of various new catalysts that rely on the presence of two metal centers (Fig. 1a). For example, Uyeda and coworkers have used a homodinuclear nickel complex (**1**) for carbene formation [12], azoarene synthesis [13], strained ring activation [14], carbonylative rearrangements [15], and reductive vinylidine transfer reactions [16]. Mankad and coworkers demonstrated unique reactivity in C–H borylation reactions with Fe–Cu bimetallic complexes such as **2** [17]. Thomas and coworkers reported a catalytically active Co/Zr complex (**3**) that enables excellent reactivity in Kumada cross couplings with unactivated alkyl electrophiles [18,19]. The Lu laboratory has also demonstrated that a series of Ni–M (M = Al, Ga, In) catalysts (**4**) perform alkene and CO_2 hydrogenation with H_2 and that the nature of the Lewis acidic group 13 metal was essential for high reactivity [20,21]. The Nagashima [22] and Michaelis [23,24] groups have developed bis(phosphino)amide Ti–Pd (**5**) and Ti–Pt catalysts that facilitate highly efficient allylic amination and cycloisomerization reactions respectively. Each of these reported catalytic reactions relies on the communication between two metal centers to achieve the observed reactivity and selectivity.

What has not been accomplished to date is the development of chiral homo- and heterobimetallic complexes, outside of the known enantioselective dirhodium catalysts [9,10], that enable enantioselective catalysis across this broad range of reactions. Our

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https://doi.org/10.1016/j.tet.2019.04.063
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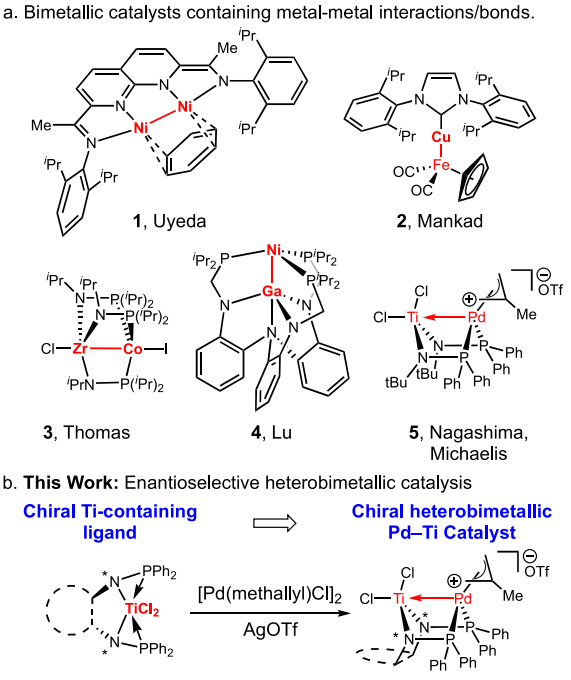


Fig. 1. Examples of bimetallic catalysts and the chiral heterobimetallic catalyst used in this work.

group is interested in developing new strategies for ligand design in heterobimetallic catalysis where chiral scaffolds can be used to enable enantioselective transformations. Our strategy involves the *in situ* generation of active heterobimetallic catalysts from transition metal precursors and metal-containing ligand frameworks (Fig. 1b) [24]. This approach enables the development of heterobimetallic catalyst systems via a ligand design approach that precludes the need to synthesize potentially sensitive bimetallic complexes. In this report, we synthesize a series of chiral titanium-containing phosphinoamide ligands, demonstrate that they assemble bimetallic Pd–Ti complexes *in situ*, and enable efficient and enantioselective allylic aminations with hindered amine nucleophiles via heterobimetallic catalysis.

Enantioenriched and sterically hindered alkylamines are valuable intermediates in the synthesis of many bioactive compounds. However, hindered trialkyl amines are challenging to access synthetically due to their high basicity and low nucleophilicity. The enantioselective allylic amination reaction is a highly versatile method for generating enantioenriched amines, yet few procedures tolerate steric hindrance at the amine nucleophile [25,26]. In fact, many recently developed transition metal catalyzed methods capitalize on the use of ammonia [27], monosubstituted, or cyclic disubstituted amines to achieve optimal reactivity [28–30]. Our group recently demonstrated that heterobimetallic Pd–Ti complexes enable highly efficient allylic aminations under mild conditions, even with highly hindered disubstituted amines [23]. As an extension of this work in allylic amination catalysis, we desired to enable enantioselective allylic aminations through the design and synthesis of chiral titanium-containing phosphinoamide ligands. The development of these chiral titanium ligands represents a rare example of enantioselective heterobimetallic catalysis where metal-metal interactions are key to reactivity [31–35].

2. Results and discussion

Our laboratory recently reported that heterobimetallic Pd–Ti complex **5**, originally developed by the Nagashima laboratory [22], enables exceptional reactivity in the amination of allylic chlorides (Fig. 2) [23]. Our results demonstrate that traditionally unreactive hindered amine nucleophiles react with ease using this heterobimetallic catalyst. We also showed that the active bimetallic Pd–Ti catalyst could assemble *in situ* from titanium-containing ligand **6** and enable the same level of reactivity as with the preformed complex **5** (Fig. 2a). In addition, we also confirmed the importance of the Pd–Ti interaction, which decreases the electron density around palladium due to the Lewis acidity of the titanium center [36]. For example, the free energy landscapes were computed and compared between a complex containing a Pd–Ti interaction and one in which the interaction had been severed. The intact Pd–Ti interaction was shown to lower the rate-limiting amine addition step by 4.5 kcal/mol. Experimentally, we also demonstrated that if the Ti-atom was removed from the ligand framework (complex **7** vs **5**), catalysis was greatly diminished in the amination reaction (TOF = >1200 with **5** and TOF = 17 for **7**). Therefore, in designing new chiral titanium-phosphinoamide ligands, a key factor was ensuring that the ligand structure did not prevent formation of the Pd–Ti interaction and that the rate of catalysis remained high.

In designing chiral phosphinoamine ligand structures that would assemble our Pd–Ti complexes, we considered both mono(aminophosphine) ligands and bis(aminophosphine) ligands due to the presence of two Pd-coordinated phosphines in complex **5**. Our synthetic strategy involves phosphinylation of the chiral amine or diamine precursor, followed by metallation of the aminophosphine intermediate (Fig. 3a). Each of these titanium-coordinated phosphinoamide ligands is a crystalline solid and can be obtained in pure form via recrystallization. Using this protocol, we successfully generated the four new chiral titanium phosphinoamide ligands (**8**–**11**) shown in Fig. 3b. X-ray quality crystals were grown for each ligand in order to confirm their structure. Of note, each complex contains a hexa-coordinate titanium center where the two phosphorous atoms are coordinated to the titanium center. Importantly, Nagashima demonstrated the dynamic nature of the Ti–P bond in complex **6**, which enables coordination of the Pd center to assemble the bimetallic catalyst [37]. Our previous studies also confirm that the dynamic nature of the Ti–P bond enables assembly of bimetallic complex **5** under the reaction conditions for allylic amination.

Our next goal was to ascertain whether these new ligand structures could coordinate palladium and assemble bimetallic catalysts. In our previous work, we demonstrated that when titanium ligand **6** is mixed with $[Pd(methallyl)Cl]_2$ in $CDCl_3$, a characteristic shift in the ^{31}P NMR was observed (from −15 ppm to 21 ppm), indicating that the phosphorous atoms had coordinated to the palladium. With our newly synthesized chiral titanium complexes, we also see a similar shift in the NMR spectrum upon

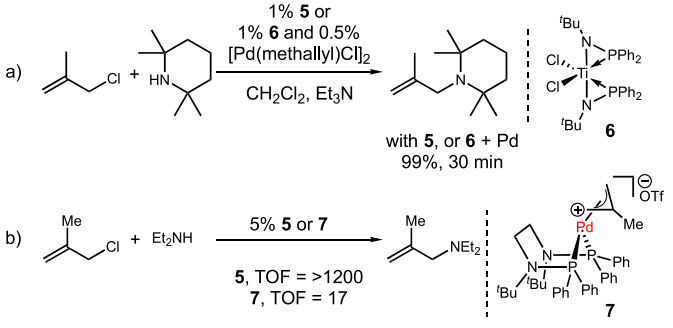


Fig. 2. Allylic amination with Ti-Pd catalysts.

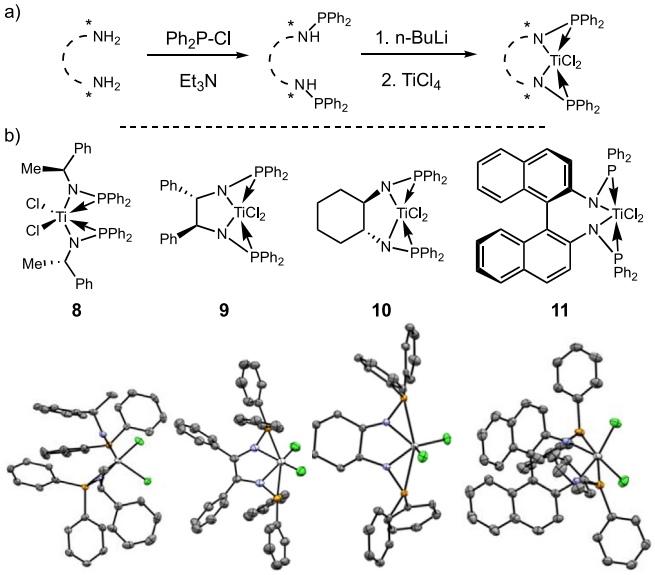


Fig. 3. a) Synthesis route for chiral titanium phosphinoamide ligands. b) Structure and X-ray structure of titanium ligands synthesized.

addition of palladium. For example, the phosphorous signal for ligand **10** shifts from −11 ppm to 17 ppm upon addition of palladium to the solution. Unfortunately, to date we have not been able to obtain X-ray quality crystals for any of the ligands shown in Fig. 3 when coordinated to palladium.

With our suite of chiral titanium ligands in hand, we next investigated their reactivity in the intramolecular allylic amination with hindered *N*-alkyl electrophiles (**12**) via *in situ* catalyst assembly (Fig. 4). Hindered substrates of this class have been shown previously to react very slowly under palladium catalysis [38], but we previously demonstrated that catalysis with Pd–Ti complex **5** happens to form product **13** in under 10 min at room temperature [23]. With our *in situ* generated catalyst using ligand **6**, similar reactivity is observed (Fig. 4, ligand **6**). Encouragingly, each of our new titanium complexes synthesized in this work enable rapid allylic amination with this hindered substrate, generally reaching 100% consumption of starting material (as determined by ^{1}H NMR analysis) in less than 10 min (ligands **8**–**11**). If the titanium atom is omitted from the structure of the ligand, as with **14**, no reactivity is observed in the same time. We also investigated the reactivity of other common chiral ligands for palladium catalysis such as BINAP **15**, Trost ligand **16**, and PHOX ligand **17**. Each of these ligands displayed very modest reaction rates and struggled to achieve complete conversion even after extended reaction times (*vide infra*). Having established the high reactivity of our titanium-containing ligands, we next set out to investigate and optimize the enantioselectivity of the allylic amination reaction (Table 1). Disappointingly, with ligand **8** (and each of the other ligands as well) we initially saw very low enantioselectivity when the reaction was stopped at 10 min upon full conversion to product (entry 1). However, we observed very early on in our optimizations that allowing the reaction to continue, even after full conversion to the product, led to a gradual increase in the enantioselectivity (entry 2). Thus, when each of our ligands were screened at longer reaction times, we began to observe encouraging levels of enantioselectivity (entries 2–5). We also looked at the enantioselectivity of chiral ligands that lacked the titanium and found that these ligands led to only modest yields of the allylic amination product and similarly resulted in only modest enantioselectivity (entries 6–9). In order to further enhance the enantioselectivity of our titanium-containing ligand frameworks, we introduced ortho-tolyl substituents on the aryl phosphine moieties of several of the ligands to give complexes **18** and **19** (Fig. 5). With these ligands, we observed a slight enhancement of the selectivity (entries 10–11). As observed previously, when the reaction with binaphthyl ligand **17** was allowed to stir for extended reaction times, the enantioselectivity gradually increased to a maximum of 38% ee at 14 h. Unfortunately, lowering the temperature of the reaction did not lead to an enhancement in the overall % ee of the reaction upon full consumption of starting

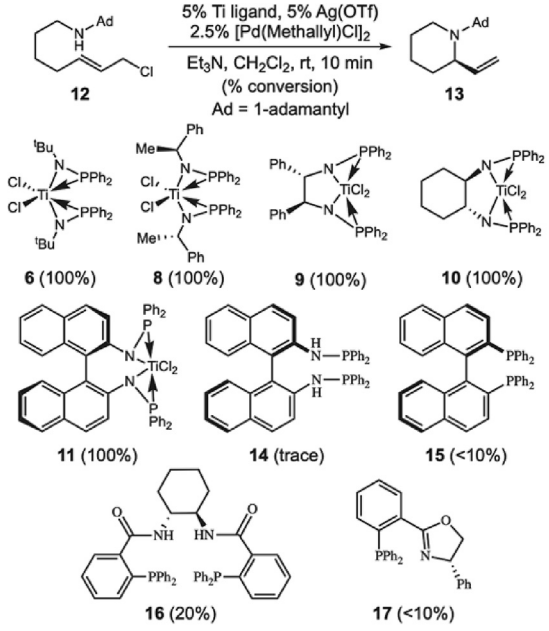
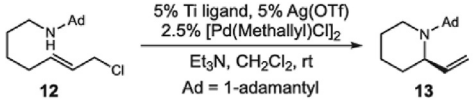


Fig. 4. Ligand reactivity study. Numbers in parentheses represent reaction conversions by comparing the ratio of product to remaining starting material.

Table 1
Optimization of enantioselectivity with chiral phosphine ligands.



Entry[a]	Ligand	Time	Yield (%)[b]	ee (%)[c]
1	**8**	10 min	99	2
2	**8**	5 h	93	15
3	**9**	5 h	99	6
4	**10**	4 h	95	12
5	**11**	5 h	82	4
6	**14**	4 h	40	15
7	**15**	4 h	40	8
8	**16**	4 h	75	28
9	**17**	4 h	40	4
10	**18**	10 h	79	17
11	**19**	1 h	89	12
12	**19**	10 h	81	18
13	**19**	14 h	83	38
14[d]	**19**	11 h	99[e]	24

[a] Reactions run with 0.05 mmol substrate, 2 equiv triethylamine in CH_2Cl_2 (0.11 M) for the time indicated.
[b] Isolated yields.
[c] Determined by analytical chiral HPLC separation.
[d] Run at 0 °C.
[e] Conversion determined by ^{1}H NMR of the crude reaction.

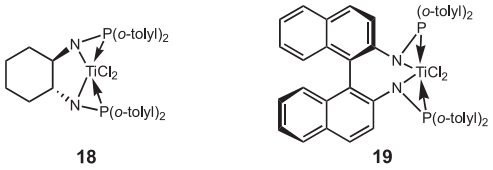


Fig. 5. *o*-Tolyl-substituted titanium ligands.

material (Table 1, entry 14).

We believe that the gradual increase in the enantioselectivity of the reaction, even after complete consumption of the starting material, can be explained by the reversibility of the C–N bond forming amination event. This equilibration would result from one of the diastereomeric complexes between the catalyst and the racemic product reacting faster in the reverse direction to regenerate the palladium allyl intermediate. This kinetic resolution type process would eventually result in an enhancement of the observed enantioselectivity of the reaction by selectively decomposing one of the enantiomers of product, even if the subsequent reformation of the amination product proceeded in very low % ee [39,40]. The palladium-catalyzed kinetic resolution of racemic allylic amines via formation of pi-allyl intermediates has been demonstrated, but we are unaware of examples where reformation of the allylic amine product leads to an enhancement in the % ee of the allyl amine product [41–43].

Alternatively, the rise in the enantioselectivity could be explained by a more traditional kinetic resolution, where reformation of the achiral allyl intermediate could slowly build up one enantiomer of product via selective formation of the amination product [42]. We cannot completely rule out the possibility that the increase in the enantiomeric excess over time is due to selective decomposition of one of the enantiomers of the product by the catalyst, but this seems unlikely because a consecutive drop in the yield of the reaction is not observed (see Table 1, entries 1–2 and 11–13). We also do not believe that the increase in ee can be explained by a photoinduced deracemization process because reactions performed in the dark proceed with the same % ee and yield as those conducted under ambient light (16% ee vs 15% ee respectively with ligand **8** after 10 h).

In order to gain more insight into the dynamics of this bimetallic catalysis systems, we performed a series of catalyst formation and ligand concentration studies. For example, the increase in the % ee of the reaction over time could be due to slow kinetics of formation of the heterobimetallic catalyst. Thus, the slow rise in % ee could be due to slow formation of a more selective catalyst species. To test this, we pre-stirred ligand **8** with the palladium precatalyst and Ag(OTf) for 1, 5, and 12 h and then allowed each separate reaction to proceed for 10 min. The product was then isolated in 99% yield and 10% ee for the reaction stirred 1 h, and in 83% yield (5% ee) and 80% yield (7% ee) for the reactions pre-stirred for 5 and 12 h respectively. As observed, allowing additional time for the catalyst to pre-stir does not lead to an increase in the enantioselectivity. We also constructed a Job plot as a function of ee of the reaction (Fig. S1, supporting information). In this study, the ratio of ligand **8** to catalyst was varied from 0.33:1 to 9:1 without any significant change in the enantioselectivity of the reaction. Thus, we believe that the addition of the Ti-containing ligand to the metal forms a highly active Ti–Pd complex that is responsible for the conversion to product and that non-ligated palladium species are inactive in the reaction. This is evident from entries 6–9 in Table 1, where ligands that do not contain titanium react much more slowly (partial consumption at 4 h) than ligands containing titanium (full consumption in >10 min).

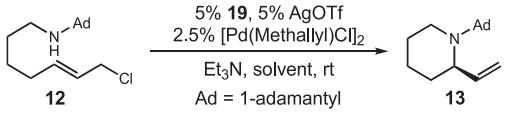
Our next optimization studies focused on the impact of solvent on enantioselectivity with titanium ligand **19**, especially over extended reaction times (Table 2). We found that with each solvent screened, longer reaction times led to greater levels of enantioselectivity up to the maximum % ee shown. In chloroform (entries 1–3), the reaction was finished in 1 h, but the product only exhibited 5% ee. The enantioselectivity was, however, increased to 23% in 23 h. The reaction is much slower in toluene and reached completion after 5 h (7% ee). However, after 52 h the enantioselectivity reached a maximum of 53% (entries 4–7). The reaction proceeds the slowest in THF, reaching completion in 7 h (5% ee). The enantioselectivity increases to 31% in 13 h but then decreases to 22% after 35 h.

Finally, we explored the impact of substrate structure on enantioselectivity by synthesizing the amine substrate (**20**) that would lead to the 5-membered pyrrolidine product **21** (Fig. 6). With this substrate, we again observed an increase in the enantioselectivity of the transformation as the reaction was allowed to proceed. Unfortunately, the pyrrolidine product was generated in lower enantioselectivity than the corresponding piperidine heterocycle under the same reaction conditions (Table 1, entry 13).

3. Conclusion

In conclusion, we have synthesized six new chiral titanium-containing phosphinoamide ligands and applied these ligands to enantioselective allylic aminations under palladium catalysis. These ligands were shown to assemble heterobimetallic Pd–Ti complexes under the reaction conditions and enable highly efficient intramolecular allylic aminations with hindered amine nucleophiles. Optimization studies demonstrated that the enantioselectivity of the process increased even after complete consumption of the starting material, suggesting a reversible enantio-determining step, which enables equilibration of the

Table 2
Solvent and time optimization with **19**.



Entry[a]	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	$CDCl_3$	1	93	5
2	$CDCl_3$	11	89	17
3	$CDCl_3$	23	98	23
4	Toluene	5	100[d]	7
5	Toluene	12	100[d]	12
6	Toluene	36	100[d]	36
7	Toluene	52	100[d]	53
8	THF	7	85	5
9	THF	13	98	31
10	THF	35	100[d]	22

[a] Reactions run with 0.1 mmol substrate, 2 equiv triethylamine in the indicated solvent (0.11 M) for the time indicated.
[b] Isolated yields.
[c] Determined by analytical chiral HPLC separation.
[d] Conversion determined by ^{1}H NMR of the crude reaction.

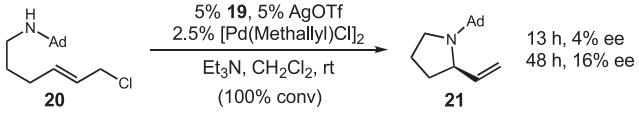


Fig. 6. Formation of pyrrolidine product via enantioselective amination.

product enantioselectivity via a kinetic resolution type process. Under optimized reaction conditions, piperidine and pyrrolidine heterocycles can be obtained in near quantitative yields and with enantioselectivity up to 53% ee.

4. Experimental section

4.1. General information

All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. Solvents were dried by J. C. Meyer's Solvent Purification System. Reactions requiring a moisture and oxygen-free environment were done in a nitrogen atmosphere glove box (Innovative Technology, PreLab HE system, double glove box). Triethylamine and chlorodiphenylphosphine were distilled and stored with 4 Å molecular sieves. Titanium tetrachloride was freshly distilled before use. Flash chromatography was performed with Sorbtech silica gel (0.040–0.063 μm grade) and Sigma-Aldrich activated, neutral, Brockmann I aluminum oxide (58 Å pore size). Analytical thin-layer chromatography was done with 0.25 mm coated commercial silica gel plates (Merck KGaA, DC silicagel 60 F_{254}). Proton nuclear magnetic resonance (^{1}H NMR) data were acquired on an Inova 300 (300 MHz) or on an Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in delta (δ) units relative to the ^{2}H signal of the $CDCl_3$ solvent. Carbon-13 nuclear magnetic resonance (^{13}C NMR) data were acquired on an Inova 500 at 125 MHz. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), qd (quartet of doublets), brs (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). Chemical shifts are reported in ppm relative to the center line of a triplet at 77.23 ppm for chloroform-d. Infrared (IR) data were recorded as films on sodium chloride plates on a Thermo Scientific Nicolet IR 100 FT-IR spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). Chiral HPLC analyses were performed on a Thermo Separation Products Spectra Series P-100 or 200 and UV100 using Chiralcel® columns. Optical rotations were measured on a Jasco P-2000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated. Mass spectral data were obtained using ESI techniques (Agilent, 6210 TOF). Ligands **13**–**15** and other reagents were used as obtained unless otherwise noted.

4.2. Ligand synthesis

Titanium-containing ligands, including **6**, were synthesized via a modified procedure as originally reported by Nagashima and coworkers [37].

4.2.1. ((1R,2R)-N,N′-bis(diphenylphosphino)-1,2-diphenylethan-1,2-diamido)titanium(IV)dichloride (**9**)

General Procedure for Titanium Ligand Synthesis: (1*R*,2*R*)-(+)-1,2-Diphenylethylenediamine (1 g, 4.7 mmol) was dissolved in 25 mL toluene. Triethylamine (1.4 mL, 10.34 mmol, 2.2 eq.), chlorodiphenylphosphine (1.9 mL, 10.34 mmol, 2.2 eq.) and 1 crystal 4-(dimethylamino)pyridine were added and reaction stirred overnight. Reaction was filtered and concentrated to yield (*1R,2R*)-*N,N′*-bis(diphenylphosphino)-1,2-diphenylethylene-diamine. Spectral data were in accordance to previously reported values [44]. The crude solids were dissolved in ether (30 mL) and cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 3.76 mL, 9.4 mmol, 2 eq.) was added dropwise. The reaction was allowed to warm to room temperature and stirred 3 h. Titanium tetrachloride (0.516 mL, 9.4 mmol, 2 eq.) was added dropwise at −78 °C. The reaction then was allowed to stir 1 h at room temperature, sonicated briefly, and allowed to stir overnight. The reaction was next moved to glove box and the ether was removed in vacuo. The resulting solids were dissolved in toluene, the mixture was filtered, and the solvent removed to give a dark solid (1.75 g, 50%). X-ray quality single crystals were grown via slow vapor deposition with CH_2Cl_2/pentane. ^{1}H NMR (500 MHz, $CDCl_3$, TMS as internal standard): δ (ppm) = 5.71 (s, 2H), 6.85 (d, 4H), 6.98 (t, 4H), 7.08 (t, 6H), 7.28 (t, 2H), 7.32–7.47 (m, 14H); ^{31}P NMR (500 MHz, $CDCl_3$): δ (ppm) = −12.62; ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 88.4, 126.8, 127.7, 127.9, 128.4, 128.6, 130.0, 130.6, 131.1, 132.5, 135.0, 140.9.

4.2.2. bis((S)-(−)-N-(diphenylphosphino)-α-methylbenzylamido)-titanium(IV)dichloride (**8**)

(S)-(−)-*N*-diphenylphosphino-α-methylbenzylamine was prepared according to the general procedure from 1.3 g (11 mmol) of(S)-(−)-α-Methylbenzylamine, triethylamine (1.2 g, 12.1 mmol, 1.1 eq.), chlorodiphenylphosphine, (2.42 g, 11 mmol, 1 eq.) and 1 crystal 4-(dimethylamino)pyridine. For spectra information see work by Nethaji and coworkers [45]. Ligand **8** was prepared according to the general procedure from 11 mmol (S)-(−)-*N*-diphenylphosphino-α-methylbenzylamine, *n*-BuLi (1.6 M in hexanes, 6.9 mL, 11 mmol, 1 eq.) and titanium tetrachloride (0.606 mL, 5.5 mmol, 0.5 eq.) to give a dark solid (2.1 g, 27%). X-ray quality single crystals were grown via slow vapor deposition with CH_2Cl_2/pentane. ^{1}H NMR (500 MHz, $CDCl_3$, TMS as internal standard): δ (ppm) = 1.68 (d, 6H), 5.23 (q, 2H), 7.02–7.34 (m, 30H); ^{31}P NMR (500 MHz, $CDCl_3$, TMS as internal standard): δ (ppm) = −16.46 (s, 2P); ^{13}C NMR (500 MHz, $CDCl_3$, TMS as internal standard)): (ppm) = 25.1, 66.0, 127.0, 127.9, 128.0, 128.1, 128.3, 130.2, 144.9.

4.2.3. ((1R,2R)-(−)-N,N′-bis(diphenylphosphino)-1,2-diamidocyclohexane)titanium(IV) dichloride (**10**)

(*1R,2R*)-(−)-*N,N′*-bis(diphenylphosphino)diaminocyclohexane was synthesized via the general procedure from (*1R,2R*)-(−)-1,2-diaminocyclohexane (45.7 mg, 0.4 mmol) triethylamine (81 mg, 0.8 mmol, 2 eq.), chlorodiphenylphosphine, (176.5 mg, 0.8 mmol, 2 eq.) and 1 crystal 4-(dimethylamino)pyridine. Spectral data matched previously reported values [46]. Ligand 10 was prepared according to the general procedure from 0.4 mmol (*1R,2R*)-(−)-*N,N′*-bis(diphenylphosphino)diaminocyclohexane, *n*-BuLi (2.5 M in hexanes, 0.32 mL, 0.8 mmol, 2 eq.) and titanium tetrachloride (0.044 mL, 0.4 mmol, 1 eq.) to give 70 mg of the desired product 29% yield. Solids were further purified by dissolving in CH_2Cl_2 and equal amounts of hexane were added to crash out the product. X-ray quality single crystals were grown via slow vapor deposition with CH_2Cl_2/pentane. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.24 (d, 2H), 1.54 (d, 2H), 1.72 (d, 2H), 2.04 (d, 2H), 4.05 (d, 2H), 7.28 (s, 2H), 7.36–7.53 (m, 10H), 7.61 (q, 4H), 7.77 (q, 4H); ^{31}P NMR (500 MHz, $CDCl_3$): δ (ppm) = −12.18; ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 24.9, 33.1, 79.2, 128.5, 128.7, 130.1, 130.8, 132.5, 134.2.

4.2.4. bis(((R)-(+)-1,1′-Bi(napthylamine)diphenylphosphanyl) amino)titanium(IV)dichloride (**11**)

(R)-(+)-1,1′-Binaphthyl-2,2′-diamine (2.3 g, 8.2 mmol) was dissolved in toluene (30 mL) and triethylamine (1.9 g, 18 mmol), chlorodiphenylphosphine (4 g, 18 mmol), and 1 crystal 4-(dimethylamino)pyridine (DMAP) were added and the reaction was stirred overnight. Reaction was then filtered and the solvent removed in vacuo. A short column in 100% toluene was run on product (R_f = 0.95, 3.67 g, 68%) and solvent removed to yield pure (R)-(+)-2,2′-bis(diphenylphosphinoamino)-1,1′-binapthyl. Spectral

values matched reported values [47]. Ligand **11** was synthesized according to the general procedure from (*R*)-(+)-2,2′-bis(diphenylphosphinoamino)-1,1′-binapthyl (1 g, 1.5 mmol) *n*-BuLi (2.5 M in hexanes, 1.2 mL, 3 mmol, 2 eq.) and titanium tetrachloride (0.164 mL, 1.5 mmol, 1 eq) to give a dark solid (0.97 g, 84%). Product was isolated as a 10:1 mixture of starting material and product. X-ray quality single crystals were grown via slow vapor deposition with benzene/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.42 (d, 2H), 6.55 (t, 4H), 6.83 (q, 4H), 6.97 (t, 4H), 7.18–7.28 (m, 2H), 7.31 (d, 2H), 7.42 (t, 2H), 7.54 (d, 4H), 7.63 (t, 2H), 7.82 (d, 2H), 8.07 (q, 4H); ^{31}P NMR (500 MHz, $CDCl_3$): δ (ppm) = −12.53 (s, 2P); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 119.3, 125.0, 125.5, 126.4, 127.8, 128.0, 128.1, 128.3, 128.5, 128.7, 128.9, 129.6, 131.1, 131.2, 132.1, 133.5, 136.2.

4.2.5. *bis((1R,2R)-(−)-1,2-Diaminocyclohexane(di(o-tolyl) phenylphsophanyl)amino)titanium (IV)dichloride (**18**)*

(*1R,2R*)-(−)-1,2-Diaminocyclohexane (80 mg, 0.7 mmol) was dissolved in 6 mL dry toluene. Chlorodi(*o*-tolyl)phosphine (348 mg, 1.4 mmol, 2 eq.), distilled triethylamine (141.4 mg, 1.4 mmol, 2 eq.), and one crystal of DMAP were added. The reaction was stirred overnight. The mixture was then filtered and concentrated. 20 mL dry diethyl ether was added and the reaction was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 0.56 mL, 1.4 mmol, 2 eq.) was added dropwise, the reaction was stirred for 3 h at room temperature, and then distilled $TiCl_4$ (0.072 mL, 0.7 mmol, 1 eq.) was added dropwise at −78 °C. The reaction was allowed to warm to room temperature and then moved to a glovebox where it was stirred overnight. The ether was evaporated and then toluene added and the solids were filtered off. The filtrate was concentrated to give a dark solid (70 mg, 29% yield), which was used directly in the enantioselective allylic amination. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.32 (d, 2H), 1.52 (d, 2H), 1.77 (d, 2H), 2.22 (d, 2H), 2.52 (s, 3H), 2.57 (s, 3H), 4.40 (d, 2H), 7.12 (t, 4H), 7.21 (m, 4H), 7.32 (m, 4H), 7.47 (m, 4H); ^{31}P NMR (500 MHz, $CDCl_3$): δ (ppm) = −18.2; ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 24.9, 29.7, 33.0, 125.6, 125.7, 130.2, 130.7, 131.0, 132.4, 134.0.

4.2.6. *bis(((R)-(+)-1,1′-Bi(napthylamine)di(o-tolyl)-phenylphosphanyl)amino)titanium(IV)dichloride (**19**)*

(R)-(+)-1,1′-Binaphthyl-2,2′-diamine (199 mg, 0.7 mmol) was dissolved in 6 mL dry toluene. Chlorodi(*o*-tolyl)phosphine (348 mg, 1.4 mmol, 2 eq.), distilled triethylamine (141.4 mg, 1.4 mmol, 2 eq.), and one crystal of DMAP were added. The reaction was stirred at 40 °C overnight. The reaction was filtered and concentrated and a short column was run in 100% toluene (R_f = 0.95). Product was concentrated and 20 mL dry diethyl ether was added. The reaction was cooled to −78 °C and *n*-BuLi (2.5 M in hexanes, 0.56 mL, 1.4 mmol, 2 eq.) was added dropwise. The reaction was stirred for 3 h at room temperature and then distilled $TiCl_4$ (0.072 mL, 0.7 mmol, 1 eq.) was added dropwise at −78 °C. The mixture was allowed to warm to room temperature and then moved to glovebox where it was stirred overnight. The ether was evaporated and then toluene added and the solids filtered off. The filtrate was concentrated to give a dark solid, which was used in the enantioselective allylic amination without further purification. Product was isolated as a 4:1 mixture with starting material. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.57 (12H, s), 6.44 (2H, d), 6.51 (2H, m), 6.61 (2H, m), 6.80 (2H, m), 7.06 (2H, m), 7.44 (8H, m), 7.50 (4H, m), 7.56 (d, 4H); ^{31}P NMR (500 MHz, $CDCl_3$): δ (ppm) = −23.9.

4.9. Substrate synthesis

4.9.1. *N-((E)-7-chlorohept-5-en-1-yl)adamantan-1-amine (**12**)*

(*E*)-7-((adamantan-1-yl)amino)hex-2-en-1-ol (0.37 g, 1.4 mmol) was placed in dry flask and dissolved in 10 mL dry CH_2Cl_2. *N,N*-Diisopropylethylenediamine (0.366 mL, 2.1 mmol, 1.5 eq.) was added and the reaction was cooled to 0 °C. Methanesulfonyl chloride was added (0.326 mL, 4.2 mmol, 3 eq.) and reaction was stirred overnight. Reaction was then diluted with 10 mL CH_2Cl_2 and washed with 5 mL aqueous, saturated sodium bicarbonate. The organic layer was dried over sodium sulfate and concentrated. Purification on silica gel with 90% DCM, 9% MeOH, and 1% water afforded the desired chloride product. R_f = 0.39. The product was then dissolved in CH_2Cl_2 and washed with sodium bicarbonate to obtain the free base and then the organic layer was dried over sodium sulfate and the solvent removed. The product was azeotroped with benzene three times to remove residual water and collected as a yellow solid (0.187 g, 48%). IR (film): ν = 3305, 3029, 2908, 2848, 2773, 2436, 1451, 1356, 968; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.44 (m, 1H), 1.68 (m, 9H), 1.77 (m, 6H), 2.1 (m, 6H), 2.67 (m, 2H), 4.04 (d, 2H), 5.64 (m, 1H), 5.76 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 26.7, 29.5, 29.7, 31.9, 36.5, 40.1, 41.8, 45.4, 69.9, 126.2, 135.7. HRMS (ESI): $C_{17}H_{28}ClN$ (M + H) calculated 282.1983, found 282.1982.

4.9.2. *N-((E)-6-chlorohex-4-en-1-yl)adamantan-1-amine (**20**)*

N-((*E*)-6-chlorohex-4-en-1-yl)adamantan-1-amine was prepared with the same procedure as substrate 12 with 6-((adamantan-2-yl)amino)hex-2-en-1-ol (1.24 g, 5 mmol), *N,N*-Diisopropylethylenediamine (1.3 mL, 7.5 mmol, 1.5 eq.), methanesulfonyl chloride (1.17 mL, 15 mmol, 3 eq.) in 13 mL DCM. A silica gel column was run with 9% MeOH and 1% water in DCM (R_f = 0.33). Product was washed with sodium bicarbonate to give free base and then dried over sodium sulfate to give a yellow solid (1.02 g, 76%) IR (film): ν = 966, 1024, 1227, 1363, 1653, 1700, 2480, 2907, 3744; ^{1}H NMR (500 MHz, $CDCl_3$, TMS as internal standard): δ (ppm) = 1.56 (m, 3H), 1.72 (m, 6H), 2.08 (m, 4H), 2.18 (m, 6H), 2,89 (m, 2H), 4.02 (d, 2H), 5.71 (m, 2H), 8.96 (s, 2H); ^{13}C NMR (500 MHz, $CDCl_3$, TMS as internal standard): δ (ppm) = 20.9, 28.7, 29.5, 30.2, 36.4, 39.7, 41.4, 65.1, 124.7, 170.9. HRMS (ESI): $C_{17}H_{28}ClN$ (M + H) calculated 268.1827, found 268.1827.

5. Enantioselective catalysis

General Procedure: In glove box, (2-methylallyl)palladium(II) chloride dimer (0.4 mg, 0.0011 mmol, 0.025 eq.) and silver triflate (0.6 mg, 0.00225 mmol, 0.05 eq.) were diluted with 0.1 mL CH_2Cl_2 and then stirred for 10 min. In a separate vial, the respective chiral titanium phosphonamide ligand or other chiral ligand (0.00225 mmol, 0.05 eq.) was dissolved in 0.1 mL CH_2Cl_2 and then added slowly to the palladium solution and stirred 20 min. Chloride **12** or **20** (12.5 mg, 0.045 mmol, 1 eq.) was then added and triethylamine (0.006 mL, 0.045 mmol, 1 eq.), diluted in 0.1 mL CH_2Cl_2, was added. The reaction was stirred until completion (10–15 min) and then taken out of box. Product was purified on a short column of neutralized aluminum oxide using 9% MeOH and 1% water in CH_2Cl_2 as eluent. R_f = 0.9. Fractions containing product were collected and washed with sodium bicarbonate to obtain free base. Product was dried using sodium sulfate and then solvent was removed to obtain the pure product. Yields obtained are shown in Table 1, Table 2, and Fig. 6.

5.1. *1-(1-adamantyl)-2-vinylpiperidine (**13**)*

Product matched previously reported spectra [23]. IR (film): ν = 3060, 2931, 2907, 2845, 2680, 1441, 1220, 1113; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.59 (m, 9H), 1.71 (m, 3H), 1.79 (m, 4H), 2.03, (m, 2H), 2.66 (t, 1H), 2.88 (d, 1H), 3.85 (m, 1H), 5.05 (m, 1H), 6.5 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 20.5, 27.3,

29.9, 34.8, 36.9, 39.1, 40.2, 54.8, 55.7, 113.3, 140.1. HRMS (ESI): $C_{17}H_{27}N$ (M + H) calculated 246.2216, found 246.2217. Enantioselectivity was then determined on a chiral HPLC using a Chiralcel IG-3 column with 0.1% diethylamine in MeOH as eluent with 0.12 mL/min flow rate ($t_1 = 50.2$ min, $t_2 = 56.6$ min).

5.2. 1-(1-adamantyl)-2-vinylpyrrolidine (**21**)

Product matched previously reported spectra [23]. IR (film): $\nu = 1050$, 1128, 1490, 1652, 1670, 2359, 2903, 3744; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 1.67 (m, 9H), 1.79 (m, 7H), 2.07 (m, 3H), 2.79 (m, 1H), 2.95 (m, 1H), 3.61 (m, 1H), 4.90 (d, 1H), 5.09 (d, 1H), 5.91 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) = 23.3, 29.2, 33.2, 35.6, 37.8, 47.8, 53.5, 64.3, 118.5, 135.6. HRMS (ESI): $C_{17}H_{27}N$ (M + H) calculated 232.2065, found 232.2066. Enantioselectivity was then determined on a chiral HPLC using a Chiralcel IG-3 column with 0.1% diethylamine in MeOH as eluent with 0.12 mL/min flow rate ($t_1 = 53.1$ min, $t_2 = 57.0$ min).

Acknowledgment

Acknowledgment is made to the donors of the American Chemical Society Petroleum Research Fund for support of this research (PRF No. 56371-DNI1). Financial support was also provided by the National Science Foundation (CHE-1665015). We also thank Daniel H. Ess of Brigham Young University for helpful discussions and feedback.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.04.063.

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