Organic LETTERS

Letter

pubs.acs.org/OrgLett

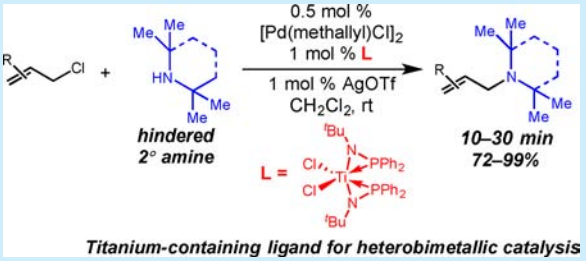
Allylic Aminations with Hindered Secondary Amine Nucleophiles Catalyzed by Heterobimetallic Pd−Ti Complexes

Whitney K. Walker, Diana L. Anderson, Ryjul W. Stokes, Stacey J. Smith, and David J. Michaelis*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, United States

Supporting Information

ABSTRACT: Phosphinoamide-scaffolded heterobimetallic palladium−titanium complexes are highly effective catalysts for allylic aminations of allylic chlorides with hindered secondary amine nucleophiles. Three titanium-containing ligands are shown to assemble active catalysts *in situ* and enable catalysis at room temperature. A variety of sterically bulky secondary amines are efficiently allylated in high yields with as little as 1 mol % palladium catalyst. Piperidine and pyrrolidine products are also efficiently generated via intramolecular aminations with hindered amine nucleophiles.



Heterobimetallic complexes represent a promising class of catalysts for organic synthesis due to the potential of the second metal "ligand" to tune the properties of the reactive metal center in ways difficult to achieve with organic supporting ligands alone.[1] Early/late transition metal binuclear complexes are of particular interest in this area because of the ability of electronically dissimilar metals to form strong dative interactions that facilitate enhanced electronic communication. Despite a recent resurgence in the design and synthesis of heterobimetallic complexes that form dative metal−metal bonds,[2] relatively few catalytic processes have been developed that capitalize on this type of interaction.[1a] Our laboratory is interested in the potential of metal−metal interactions in heterobimetallic complexes to provide uniquely active catalysts and thus address current and significant limitations in transition-metal-catalyzed transformations.

Basic, *N*-alkyl substituted amines are important pharmacophores in bioactive molecules, and many naturally occurring alkaloids contain sterically hindered amine functional groups. Hindered amines in this class are notoriously challenging to incorporate and manipulate in organic synthesis due to their high basicity and low nucleophilicity, as well as their potential to bind to and deactivate transition metal catalysts. Thus, a vast majority of synthetic methods that generate C−N bonds, including those that involve palladium catalysts, utilize electron-withdrawing amine protecting groups that mitigate these undesired side effects.[3]

The transition-metal-catalyzed allylic amination is a powerful method for generating C−N bonds under mild conditions from readily available allylic electrophiles.[4] While various transition metal catalysts have been developed that efficiently catalyze this transformation, many of these aminations are limited to acidic amines (e.g., phthalimides, urethanes, sulfonamides) or electronically deactivated, weakly basic amines (e.g., benzyl, aryl, propargylic amines).[5] Few studies have focused on basic alkylamines,[6] and aminations with sterically hindered secondary amines have not been reported.

Nagashima and co-workers recently reported that heterobimetallic Pd−Ti complex **1** undergoes rapid addition of diethylamine to the palladium-bound allyl ligand (Figure 1).[7]

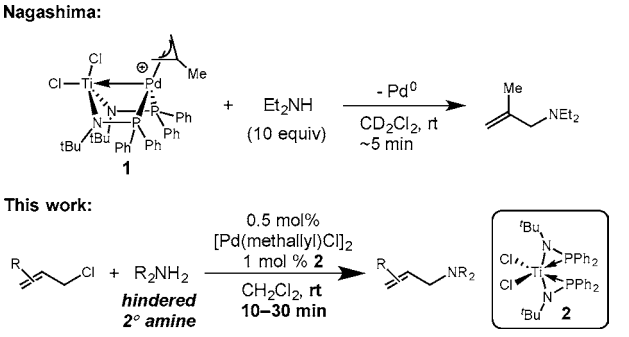


Figure 1. Allylic aminations with heterobimetallic complexes.

They postulated that formation of an electron-withdrawing dative interaction between titanium and palladium in **1** accelerates the amine addition by making palladium more electrophilic. We hypothesized that this electron-withdrawing Pd−Ti interaction could be employed to generate exceptionally active catalysts for allylic aminations that address a significant limitation in current methods by enabling efficient catalysis with hindered secondary amine nucleophiles. Herein we report that Pd−Ti catalysts generated *in situ* from titanium-containing ligand **2** are highly active in allylic amination reactions and enable efficient aminations of allylic chlorides with hindered secondary amine nucleophiles (Figure 1). To the best of our

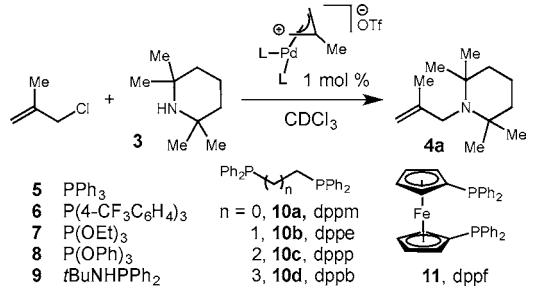
Received: January 8, 2015
Published: January 22, 2015

DOI: 10.1021/acs.orglett.5b00058
Org. Lett. 2015, 17, 752−755

knowledge, transition-metal-catalyzed allylations of hindered amine nucleophiles of this type have not been reported.

Our initial investigations into the potential of heterobimetallic complex **1** to enable allylic aminations with secondary amines were performed using 2,2,6,6-tetramethylpiperidine (**3**) and methallyl chloride (Table 1). To our delight, we found that

Table 1. Optimization Studies on Allylic Aminations with 3

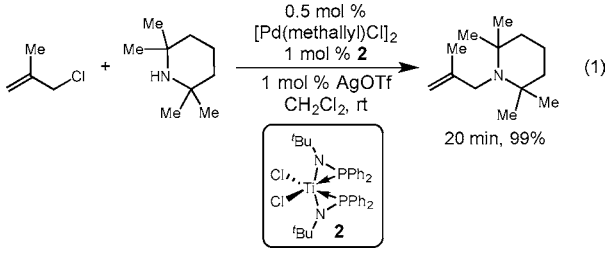


entry[a]	ligand	temp	time	% conv[b]
1[c]	**1**	rt	35 min	100
2	**5**	rt	24 h	N.R.
3	**5**	90 °C	24 h	7
4	**6**	90 °C	24 h	6
5	**7**	90 °C	24 h	14
6	**8**	90 °C	10 h	67
7	**9**	90 °C	24 h	<5
8	**10a**	90 °C	24 h	11
9	**10b**	90 °C	24 h	<5
10	**10c**	90 °C	24 h	<5
11	**10d**	90 °C	24 h	<5
12	**11**	90 °C	24 h	<5

[a]Reactions performed using 1 mmol of methallyl chloride, 2.2 equiv of **3**, and 0.05 mmol of the indicated allyl complex formed *in situ* (0.025 mmol $[Pd(methallyl]Cl]_2$, 0.05 mmol of AgOTf, and either 0.05 mmol of bisphosphine or 0.10 mmol of monophosphine) in $CDCl_3$ (1 M) for the indicated time. [b]Determined by ^1H NMR. [c]Run with 1 mol % of preformed complex **1**.

complex **1** enabled rapid formation of the desired amination product **4a** at room temperature in just 35 min (entry 1). To demonstrate that the Pd–Ti heterobimetallic complex had superior reactivity to traditional palladium catalysts, we next performed the amination with a series of palladium complexes lacking the titanium center. No allylation product was observed with the bis(triphenylphosphine) complex at room temperature (entry 2).[8] Only when this reaction was heated for 24 h (90 °C) in a sealed tube was any of the desired product observed (entry 3). Although electron-deficient aryl phosphine **6** did not improve conversion (entry 4), we found that modest conversions could be obtained with phosphite ligands (entries 5 and 6). While full conversion to the allylation product could be obtained in 24 h at 90 °C with the triphenylphosphite complex, no reaction occurred at room temperature (data not shown). Phosphinoamine palladium complexes lacking the titanium atom (**9**) provided no conversion to product (entry 7). Other bis(phosphine) ligands also failed to provide efficient conversion in this system (entries 8–12).

Having established the exceptional reactivity of complex **1** with hindered amine nucleophiles, we next explored the potential to assemble the active bimetallic catalyst *in situ*, precluding the need to presynthesize and purify the heterobimetallic complex. We found that addition of 0.5 mol % $[Pd(methallyl)Cl]_2$ as a precatalyst and 1 mol % each of silver triflate[9] and titanium-containing ligand **2** provided the desired amination product in 20 min at room temperature (eq 1). The equivalent rate of amination observed via this *in situ*



(1)

preparation method suggests that the active bimetallic catalyst is assembled under the reaction conditions. In addition, ^{31}P NMR studies confirmed the presence of bimetallic complex **1** in the reaction mixture prior to allylic amination.[10]

Ligand **2** is easily synthesized using standard air-free Schlenk techniques as previously reported,[2f] and we found **2** to be rather stable in the solid state. Thus, aminations can be set up on the benchtop without the use of a glovebox, as long as **2** is stored under argon and the reaction solvents and reagents are thoroughly dried. In control studies, we found that addition of $TiCl_4$ to the room temperature Pd-catalyzed reaction of methallyl chloride and **3** with either phosphite ligand **8** or phosphinoamine ligand **9** resulted in very low (~20%, 24 h) or no product formation, respectively (data not shown). In addition, $[Pd(methallyl)Cl]_2$ by itself, or with added AgOTf, also failed to provide any of the amination product. These results suggest that the titanium–phosphinoamide structure is critical for generating an active catalyst and facilitating catalysis.

With the result that ligand **2** can assemble an active palladium catalyst *in situ*, we next investigated the impact of the titanium ligand structure on catalysis. To accomplish this, we synthesized phosphinoamide–titanium complexes **12** and **13** (Figure 2). This is the first reported synthesis of monophosphinoamide and tris(phosphinoamide) titanium complexes,[11] and we confirmed their identity and structure via single crystal X-ray analysis. Titanium phosphinoamide ligands of this type have been shown to contain a dynamic Ti–P bond capable of capturing a late transition metal and assembling a dative Ti–M interaction.[11] When $[Pd(methallyl)Cl]_2$ and silver triflate were added to ligand **12**, the disappearance of the starting material phosphorus peak (−11.0 ppm) and appearance of phosphorus

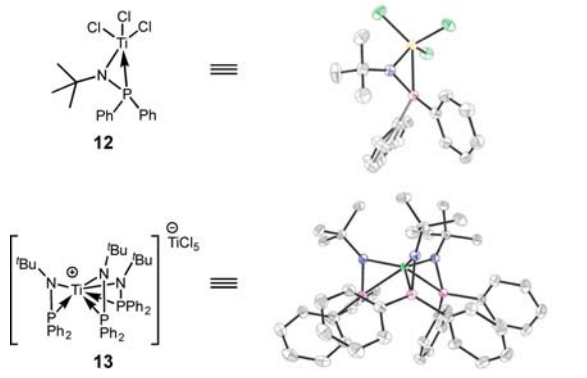


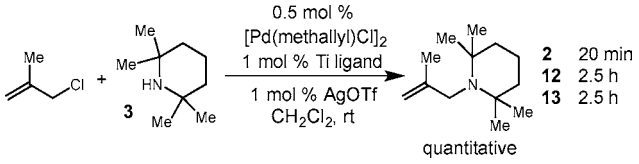
Figure 2. Novel titanium-containing ligands. Hydrogen atoms omitted for clarity.

DOI: 10.1021/acs.orglett.5b00058
Org. Lett. 2015, 17, 752–755

peaks characteristic of a Pd−P interaction (−2.6 ppm) were observed. Although our efforts to characterize heterobimetallic complexes with ligands **12** and **13** have not been successful to date, these preliminary studies suggest the potential of these titanium-containing ligands to assemble Pd−Ti catalysts *in situ* and facilitate efficient catalysis.

In the catalytic amination reaction between hindered amine **3** and methallyl chloride, we found that both ligands **12** and **13** enabled room temperature amine allylation (Scheme 1). This

Scheme 1. Aminations with Titanium-Containing Ligands

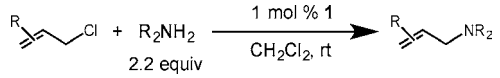


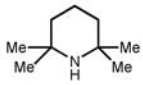
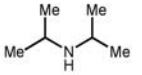
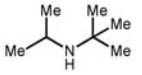
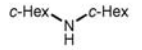
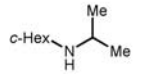
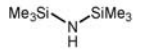
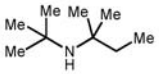
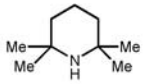
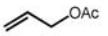
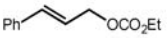
result is particularly important because no monometallic catalysts tested to date have enabled room temperature catalysis in this system, confirming the unique potential of metal-containing ligands to enable catalysis with hindered amines. We believe, as was proposed by Nagashima,[7] that formation of a dative Pd−Ti interaction generates a more electrophilic palladium center, thus accelerating the rate of turnover-limiting reductive amine addition to the Pd-bound allyl. Both **12** and **13** provided slightly less reactive catalysts than **2**, and we are currently seeking to characterize discrete bimetallic complexes with these ligands to understand further how the strength of the Ti−Pd interaction and the dynamics of heterobimetallic catalyst formation effect catalysis in this reaction.

A general method to employ sterically hindered amine nucleophiles in allylic amination reactions would be a valuable tool for organic synthesis. Therefore, we next explored the scope of our bimetallic catalytic system with respect to the amine and allylic chloride reaction partners (Table 2). A variety of sterically hindered secondary amines readily undergo allylic substitution in less than 10 min in most cases (entries 1−6). Even bis(trimethylsilyl)amine undergoes allylation, but at slightly longer reaction times (4.5 h, entry 6). Only highly hindered *tert*-amyl-*tert*-butylamine failed to react in our system (entry 7). A variety of allylic electrophiles were also tolerated in the reaction, including crotyl, cinnamyl, and allyl chlorides (entries 8−10). Allyl acetates and carbonates, on the other hand (entries 11 and 12), provided only modest conversions, presumably due to decomposition of the Pd−Ti catalyst due to formation of Lewis basic acetate or alkoxide ions. In addition, only the linear product is observed when nonsymmetrical allyl chlorides are employed (entries 8 and 9), even when an internal chloride is used (entry 13). In all cases tested, similar rates and yields were obtained using either preformed bimetallic complex **1** or our *in situ* catalyst preparation protocol.

Due to the importance of piperidine and pyrrolidine structures in natural products and pharmaceuticals, we next investigated the ability of hindered amine nucleophiles to undergo intramolecular cyclization to generate cyclic products (Figure 3). Hindered substrates of this type have previously been shown to require forcing conditions and in certain cases (R = *t*Bu) to fail altogether.[12] Under our standard optimized conditions with 3 mol % catalyst, we found that intramolecular amination occurred rapidly at room temperature to generate the desired heterocycles in high yield over two steps from the

Table 2. Substrate Scope with Hindered Amines



entry[a]	amine	chloride	4	yield[b]
1[c]			**4a**	99%
2			**4b**	72%
3			**4c**	98%
4			**4d**	99%
5			**4e**	82%
6[d]			**4f**	99%[e]
7			**4g**	<5%
8[c]			**4h**	97%[f,g]
9[c]			**4i**	87%[f]
10[c]			**4j**	85%
11[d]			**4j**	5%[e]
12[d]			**4i**	33%[e]
13[c]			**4h**	78%[f,h]

[a]Reactions run with 1 mmol of allyl chloride, 2.2 mmol of amine, and 0.01 mmol of **1** (or 0.005 mmol of $[Pd(methallyl)Cl]_2$, 0.01 mmol of **2**, and 0.01 mmol of AgOTf) in $CDCl_3$ or CH_2Cl_2 (1 M) for 10 min at room temperature. [b]Isolated yields. [c]Run for 20 min. [d]Run for 4.5 h. [e]Internal standard yield. [f]Linear product only. [g]5:1 *trans*/*cis*. [h]1.3:1 *trans*/*cis*. *c*-hex = cyclohexyl.

corresponding alcohols (Figure 3). Both 5-membered (**14**) and 6-membered (**15**) heterocycles can be efficiently formed with this method. In addition, morpholine heterocycles (**16**) are also readily generated via our protocol. As with the intermolecular amination reactions, similar rates and yields were observed with catalyst **1** or the *in situ* generated catalyst.

In conclusion, we have established that Pd−Ti heterobimetallic complexes are efficient catalysts for allylic aminations and for the first time enable catalysis with hindered secondary amine nucleophiles at room temperature. In addition, a variety of titanium-containing ligand structures were shown to enable room temperature catalysis with hindered amines, presumably via *in situ* formation of an electron-withdrawing M−M dative

DOI: 10.1021/acs.orglett.5b00058
Org. Lett. 2015, 17, 752−755

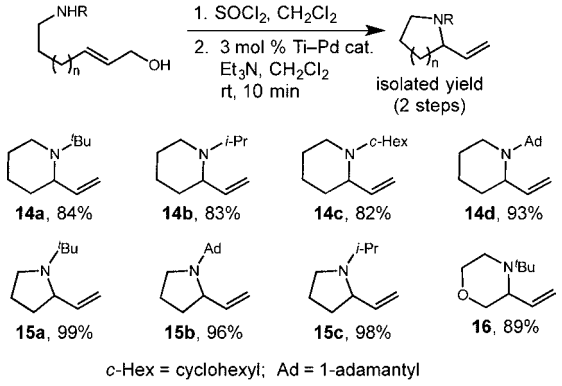


Figure 3. Intramolecular aminations for heterocycle synthesis.

interaction. These catalysts are efficient for a range of hindered amine nucleophiles, including for the formation of pyrrolidines and piperidines via intramolecular aminations. These results confirm the potential of bimetallic complexes to enable catalysis that is currently unachievable with monometallic catalysts and suggest that heterobimetallic complexes could find application more broadly in organic synthesis. Continuing efforts in our laboratory are aimed at understanding and quantifying the catalytic potential of the M−M interaction in these complexes and the ability of this interaction to expand reactivity in a variety of transition-metal-catalyzed processes.

■ ASSOCIATED CONTENT

Supporting Information

General reaction procedures and characterization data for all new compounds, including crystallographic data for **12** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dmichaelis@chem.byu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank Brigham Young University for their generous support of our research program.

■ REFERENCES

(1) For reviews, see: (a) Cooper, B. G.; Napoline, J. W.; Thomas, C. W. *Catal. Rev.* **2012**, *54*, 1. (b) Oelkers, B.; Butovskii, M. V.; Kempe, R. *Chem.—Eur. J.* **2012**, *18*, 13566. (c) Mandal, S. K.; Roesky, H. W. *Acc. Chem. Res.* **2010**, *43*, 248. (d) Ritleng, V.; Chetcuti, M. J. *Chem. Rev.* **2007**, *107*, 797. (e) Collman, J. P.; Boulatav, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3948. (f) Gade, L. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2658. (g) Wheatley, N.; Kalck, P. *Chem. Rev.* **1999**, *99*, 3379.

(2) For selected recent examples, see: (a) Tereniak, S. J.; Carlson, R. K.; Clouston, L. J.; Young, V. G., Jr.; Bill, E.; Maurice, R.; Chen, Y.-S.; Kim, H. J.; Gagliardi, L.; Lu, C. C. *J. Am. Chem. Soc.* **2014**, *136*, 1842. (b) Clouston, L. J.; Siedschlag, R. B.; Rudd, P. A.; Planas, N.; Hu, S.; Miller, A. D.; Gagliardi, L.; Lu, C. C. *J. Am. Chem. Soc.* **2013**, *135*, 13142. (c) Cooper, B. G.; Fafard, C. M.; Foxman, B. M.; Thomas, C. M. *Organometallics* **2010**, *29*, 5179. (d) Greenwood, B. P.; Forman, S. I.; Rowe, G. T.; Chen, C.-H.; Foxman, B. M.; Thomas, C. M. *Inorg. Chem.* **2009**, *48*, 6251. (e) Nippe, M.; Berry, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 12684. (f) Nagashima, H.; Sue, T.; Oda, T.; Kanemitsu, A.; Matsumoto, T.; Motoyama, Y.; Sunada, Y. *Organometallics* **2006**, *25*, 1987.

(3) (a) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283. (b) *Science of Synthesis, Cross Coupling and Heck-Type Reactions, Vol. 2*; Molander, G. A., Wolfe, J. P., Larhed, M., Eds.; Thieme: Stuttgart, 2013. (c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (d) Wolfe, J. P. *Top. Heterocycl. Chem.* **2013**, *32*, 1. (e) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351.

(4) (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2010; pp 593−649. (b) Diéguez, M.; Pàmies, O. *Acc. Chem. Res.* **2010**, *43*, 312. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (d) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (e) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659. (f) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (g) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(5) (a) Tosatti, P.; Nelson, A.; Marsden, S. P. *Org. Biomol. Chem.* **2012**, *10*, 3147. (b) Milhau, L.; Guiry, P. J. *Top. Organomet. Chem.* **2011**, *38*, 95. (c) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461. (d) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. (e) Helmchen, G. In *Asymmetric Synthesis*; Christman, M., Brase, S., Eds.; Wiley-VHC: Weinheim, 2007; pp 95−99. (f) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, *11*, 1641.

(6) For recent selected examples, see: (a) Kawatsura, M.; Terasaki, S.; Minakawa, M.; Hirakawa, T.; Ikeda, K.; Itoh, T. *Org. Lett.* **2014**, *16*, 2442. (b) Kawatsura, M.; Uchida, K.; Terasaki, S.; Tsuji, H.; Minakawa, M.; Itoh, T. *Org. Lett.* **2014**, *16*, 1470. (c) Boualy, B.; Harrad, M.; El Houssame, S.; El Firdoussi, L.; Ait Ali, M.; Karim, A. *Catal. Commun.* **2012**, *19*, 46. (d) Touchet, S.; Carreaux, F.; Molander, G. A.; Carboni, B.; Bouillon, A. *Adv. Synth. Catal.* **2011**, *353*, 3391. (e) Tosatti, P.; Horn, J.; Campbell, A. J.; House, D.; Nelson, A.; Marsden, S. P. *Adv. Synth. Catal.* **2010**, *352*, 3153. (f) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (g) Roggen, M.; Carreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11917. (h) Pouy, M. J.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11312. (i) Adak, L.; Chattopadhyay, K.; Ranu, B. C. *J. Org. Chem.* **2009**, *74*, 3982. (i) Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200. (k) Kawatsura, M.; Ata, F.; Hirakawa, T.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2008**, *49*, 4873. (l) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172. (m) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525.

(7) Tsutsumi, H.; Sunada, Y.; Shiota, Y.; Yoshizawa, K.; Nagashima, H. *Organometallics* **2009**, *28*, 1988.

(8) Cationic bis(triphenylphosphine)(η^3-allyl)palladium complexes are among the most active catalysts for allylic aminations. See: Canovese, L.; Visentin, F.; Levi, C.; Dolmella, A. *Dalton Trans.* **2011**, *40*, 966.

(9) Silver triflate led to faster reaction kinetics in the *in situ* formation protocol, but its omission still provided full conversion in 1 h.

(10) ^{31}P NMR of the *in situ* formed catalyst solution shows a characteristic shift from −17.2 ppm for ligand **2** to +9.08 ppm for complex **1**.

(11) (a) Sue, T.; Sunada, Y.; Nagashima, H. *Eur. J. Inorg. Chem.* **2007**, 2897. (b) Kühl, O.; Koch, T.; Somoza, F. B., Jr.; Junk, P. C.; Hey-Hawkins, E.; Plat, D.; Eisen, M. S. *J. Organomet. Chem.* **2000**, *604*, 116.

(12) Olszewska, B.; Kryczka, B.; Zawisza, A. *Tetrahedron* **2013**, *69*, 9551.

DOI: 10.1021/acs.orglett.5b00058
Org. Lett. 2015, 17, 752−755