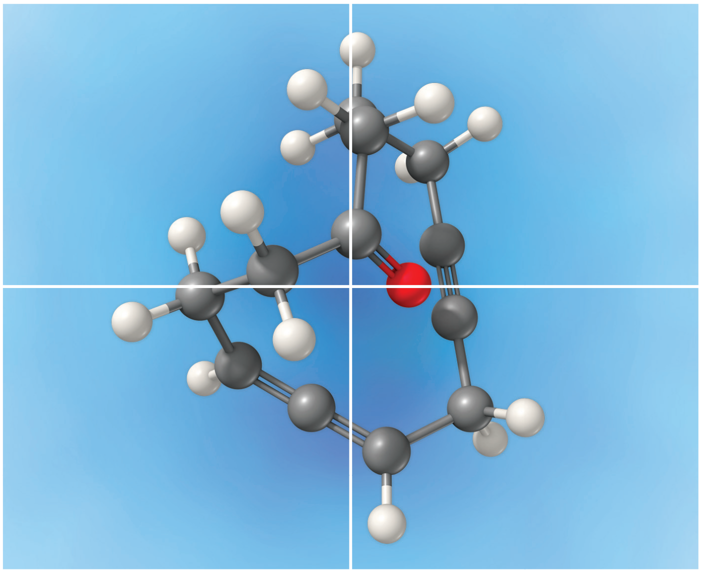
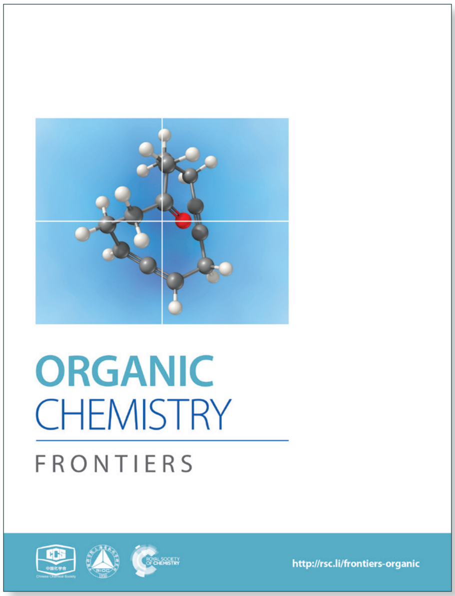
ORGANIC
CHEMISTRY

FRONTIERS





http://rsc.li/frontiers-organic

Palladium-Catalyzed Amination of Allylic Carbonates with Ammonia: Access to Primary Amines

Peng Yin,[a,b] **Mun Yee Wong,**[b] **Jieying Tham**[b] **and Teck-Peng Loh***[b,c]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/x000000x

Allylic amination of allylic carbonates with ammonia gas or aqueous ammonia was successfully carried out using (SIPr)Pd(allyl)Cl as catalyst and Ph_3P, which is essential for the reaction. The aqueous ammonia reactions proceeded smoothly at room temperature, using a low catalyst load. But a higher temperature and catalyst loading were needed for the corresponding ammonia gas reactions. Moderate to good yields were achieved for both reactions. This study demonstrates the feasibility of using ammonia as an aminating reagent, and it opens the field for further development of metal-catalyzed allylic amination in the future.

Introduction

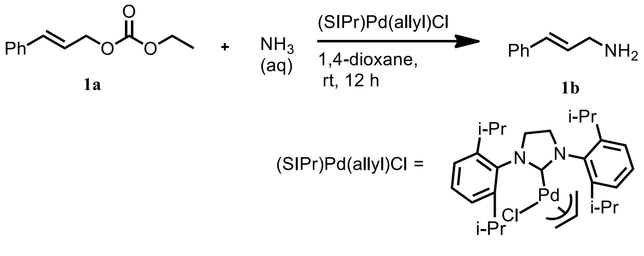
Primary amines are important building blocks and are featured prominently in a wide variety of functional compounds, such as pharmaceuticals, agrochemicals, and advanced materials.[1] Therefore, the synthesis of primary amines has attracted significant attention. Among the methods reported, the transition metal-catalyzed allylic amination provides one of the most powerful methods for the synthesis of allylic amines.[1d, 2] However, conventional metal-catalyzed allylic amination methods to access primary amines require the use of protecting groups for the amine functionality thereby reducing the transformation efficiency.[3] The direct use of low-cost and easily available ammonia as the nitrogen source is thus an attractive solution to this major synthetic challenge. Unfortunately, the direct use of ammonia in metal-catalyzed amination that leads to unprotected primary amines remains poorly explored.[4] This is probably because ammonia rapidly displaces ligands on the metal center of many metal complexes to give stable non-chiral amine complexes. Furthermore, the resulting primary amine product is more reactive than ammonia, which can cause undesired reaction on the product.[5] Consequently, it is not surprising that the direct use of ammonia in metal-catalyzed reactions remains a synthetic challenge to chemists.[6, 2b] In 2009, Kobayashi made a major breakthrough in this area by describing a $Pd(PPh_3)_4$ catalyzed allylic amination reaction using aqueous ammonia as the nitrogen source, providing the primary amine products in high yields.[4a] Despite this breakthrough, the direct use of ammonia gas in allylic amination reactions catalyzed by palladium catalysts is still unavailable. Therefore, an intense effort is underway to discover a palladium-catalyzed allylic amination using ammonia solution or ammonia gas, and adapt the methodology to wide range substrates.

We envisage that palladium carbene complexes may be applicable to the allylic amination using ammonia gas or aqueous ammonia.[5b, 7] This hypothesis was made according to the following premises: It is well established that N-heterocyclic carbenes (NHC) palladium complexes are easy accessible, thermally stable, tunable (both electronically and sterically), and they are inert towards air and moisture. In contrast to palladium phosphine complexes, carbene dissociation from NHC palladium complexes is not a favorable process. This special property should suppress the potential displacement of the ligands by ammonia. Accordingly, in this paper, we report the results on amination of allylic carbonates with ammonia gas or aqueous ammonia using (SIPr)Pd(allyl)Cl as a catalyst, and in the presence of Ph_3P.

Results and discussion

Ethyl cinnamyl carbonate was selected as a model substrate

Table 1. Optimization of the reaction conditions [a]

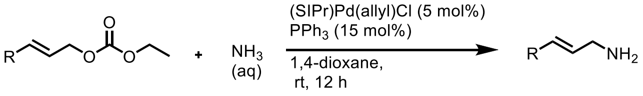


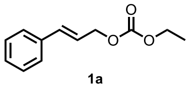
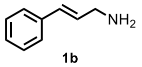
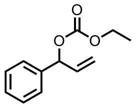
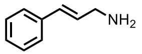
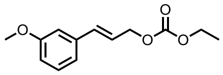
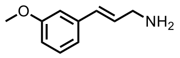
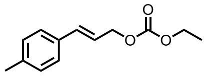
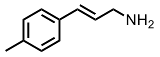
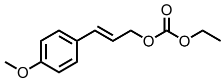
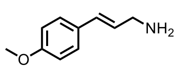
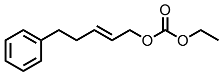
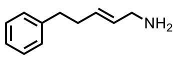
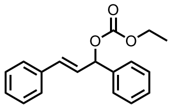
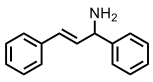
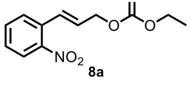
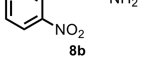
Entry	NH_3/1,4-dioxane	Conc. (M)	Cat. (mol%)	PPh_3 (mol%)	Yield[b] (%)
1	1 : 2	0.03	10	10	43
2	1 : 2	0.03	10	20	50
3	1 : 2	0.03	10	30	63
4	1 : 2	0.03	10	40	62
5	1 : 2	0.04	10	30	57
6	1 : 1	0.03	10	30	55
7	2 : 1	0.02	10	30	43
8	1 : 2	0.03	5	15	62
9	1 : 2	0.03	1	3	-[d]
10	1 : 2	0.03	10	-[c]	-[d]

[a] Conditions: (SIPr)Pd(allyl)Cl and PPh_3 were added to 1,4-dioxane and stirred for 30 min. Next, ethyl cinnamyl carbonate (0.3 mmol) and aqueous ammonia (25%) were added to the solution successively. The solution was stirred under an atmosphere of Ar at room temperature for 12 h. [b] Isolated yields containing 4% of the branched primary amines. [c] No PPh_3 was added. [d] No desired product was obtained.

for screening of the reaction conditions with aqueous ammonia. As shown in Table 1, when the concentration of the carbonate was kept at 0.03 M, the yield increased with the amount of PPh_3 (entries 1–4, Table 1). Increasing the concentration of carbonate to 0.04 M, the yield dropped to 57% (entry 5, Table 1). Changing the ratio of aqueous NH_3 to 1,4-dioxane from 1 : 2 to 1 : 1 led to a further drop in yield (compare entries 6 to 3, Table 1). Increasing the amount of aqueous ammonia did not increase the yield either (entry 6, Table 1); however, in this reaction the concentration of carbonate was also reduced to 0.02 M. Next, we reduced the catalyst loading from 10 mol% to 5 mol%, and the yield was not affected (entry 8, Table 1). But no reaction occurred when the catalyst loading was further decreased to 1 mol% (entry 9, Table 1). As a control reaction, no reaction took place without the addition of Ph_3P (entry 10, Table 1). Furthermore, 4% of the branched primary amine was observed, and no dialkylamine or trialkylamine was obtained (entries 1–8, Table 1).

Table 2. Scope of allylic amination with aqueous ammonia.[a]



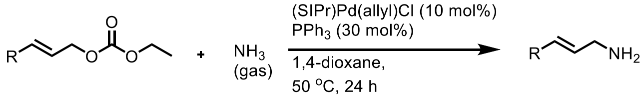
Entry	Substrate	Product	Yield(%)[b]
1	 1a	 1b	62
2	 2a	 2b	68
3	 3a	 3b	61
4	 4a	 4b	60
5	 5a	 5b	57[c] (84 : 16)[d]
6	 6a	 6b	50[c] (55 : 45)[d]
7	 7a	 7b	35
8	 8a	 8b	52[e]

[a] Conditions: (SIPr)Pd(allyl)Cl (5 mol%) and PPh_3 (15 mol%) were added to 1,4-dioxane (6.8 mL) and stirred for 30 min. Then substrates (0.3 mmol) and aqueous ammonia (25%, 3.4 mL) were added to the solution successively. The solution was stirred at room temperature for 12 h. [b] Isolated yields containing 4% of the branched primary amines. [c] Combined yield. [d] Ratio of the linear primary amine to the branched primary amine. [e] The reaction time was 40 h. Only linear primary amine was obtained.

Using the optimized reaction conditions, the substrate scope was investigated. Good yields were achieved for four different substrates (entries 1–4, Table 2). No secondary amines were obtained, but judging from the ^{1}H NMR, 4% of the branched primary amines were formed. For substrates 5a and 6a, the ratio of branched primary amines increased to 15% and 45% respectively (entries 5 and 6, Table 2). In the case of substrate 7a, only 35% yield was obtained, which may be due to significant steric hindrance on the allylic carbon (entry 7, Table 2). For the less reactive substrate 8a, longer reaction time was needed for completion, and a moderate yield of 52% was obtained (entry 8, Table 2).

Next, the amination of allylic carbonates using ammonia gas was investigated. No reaction was observed when the reaction conditions used for aqueous ammonia were tried. After optimization, almost quantitative yield was achieved when the reaction was carried out using 30 mol% of PPh_3 and 10 mol% of (SIPr)Pd-(allyl)Cl at 50 ℃ for 24 h (entry 1, Table 3). The scope of the reaction with ammonia gas was further investigated. When the reaction time was reduced to 12 h, the yield decreased dramatically (entry 2, Table 3). In contrast to the reaction with aqueous ammonia, the catalyst loading was critical for this reaction. No reaction took place

Table 3. Substrate scope of allylic amination with ammonia gas.[a]

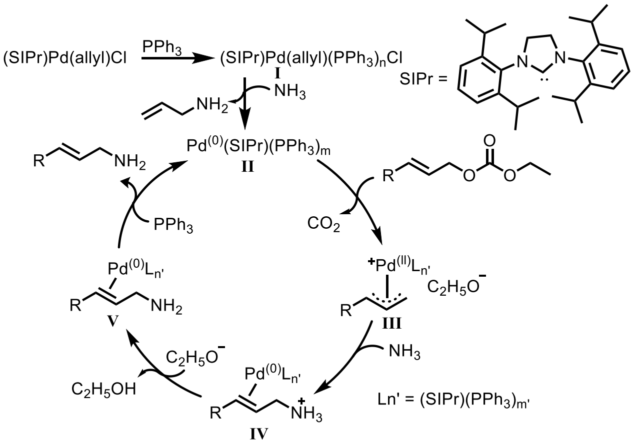


Entry	Substrate	Product	Yield(%)[b]
1	1a	1b	99
2	1a	1b	30[c]
3	1a	1b	-[d]
4	2a	2b	75
5	3a	3b	69
6	4a	4b	82
7	5a	5b	51[e] (81 : 19)[f]
8	6a	6b	63[e] (51 : 49)[f]
9	7a	7b	10
10	8a	8b	trace[g]

[a] Conditions: (SIPr)Pd(allyl)Cl (10 mol%) and PPh_3 (30 mol%) were added to 1,4-dioxane (10 mL) and stirred for 30 min. Next the substrates (0.3 mmol) and liquid ammonia (4.4 mL, 500 equiv) were added to the solution successively. The solution was stirred at 50 ℃ for 24 h. [b] Isolated yields containing 4% of the branched primary amines. [c] The reaction time was 12 h. [d] (SIPr)Pd(allyl)Cl (5 mol%) and PPh_3 (15 mol%) were used. [e] Combined yield. [f] Ratio of the linear primary amine to the branched primary amine. [g] The reaction time was 40 h.

when only 5 mol% of (SIPr)Pd(ally)Cl was used (entry 3, Table 3). Moderate to good yields were achieved for other substrates (entries 4–6, Table 3). For substrates 5a and 6a, a higher proportion of branched primary amines was obtained (entries 7 and 8, Table 3). In the case of substrate 7a, only 10% yield was obtained, which may be again due to steric hindrance around the allylic carbon (entry 9, Table 3). For the less reactive substrate 8a, no desired product was obtained even upon prolonged reaction time (entry 10, Table 3).

Recently, a number of reports pertaining to mechanistic studies of the Tsuji-Trost allylation reactions have been published.[2,8] A plausible catalytic cycle is proposed (Scheme 1). It is suggested that the chloride ion in (SIPr)Pd(allyl)Cl is firstly replaced by PPh_3 to generate complex I, which is subsequently reduced to complex II Then, the complex II reacts with the carbonates with release of CO_2. The resulting complex III reacts with ammonia to give the complex IV. After deprotonation by the base and dissociation from the palladium catalyst, the desired primary amine is obtained. Further detailed mechanistic studies are in progress.



Scheme 1 Proposed mechanism

Conclusions

The amination of allylic carbonates with aqueous and gaseous ammonia was successfully developed using a combination of (SIPr)Pd(allyl)Cl as catalyst and PPh_3. To our best knowledge, this is the first report of a Pd-catalyzed allylic amination with ammonia gas. It is important to note that PPh_3 is crucial for this reaction. Further studies on the selectivity between linear and branched primary amines are in progress. In the future, it is anticipated that this new methodology will inspire others to develop a broad range of transition metal catalyzed reactions that utilize ammonia gas as the nitrogen source.

Acknowledgments

We gratefully acknowledge Nanyang Technological University and Singapore Ministry of Education Academic Research Fund Tier 2 (MOE2010-T2-2-067 and MOE2011-T2-1-013) for financial support.

Notes and references

[a] *Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research(Ministry of Education), College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081 (PR China).*

[b] *Division of Chemistry and Biological Chemistry, Nanyang Technological University, Singapore 637371 (Singapore); Fax: +65 6515 8229;Tel: +65 6513 8203; E-mail: teckpeng@ntu.edu.sg*

[c] *Hefei National Laboratory for Physical Science at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026 (P.R. China).*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 (a) G. Petranyi, N. S. Ryder, A. Stutz, *Science* 1984, **224**, 1239; (b) A. Stutz, *Angew. Chem. Int. Ed.* 1987, **26**, 320; (c) S. M. Nanavati, R. B. Silverman, *J. Am. Chem. Soc.* 1991, **113**, 9341; (d) B. M. Trost, M. L. Crawley, *Chem. Rev.* 2003, **103**, 2921; (e) S. Hayashi, H. Yorimitsu, K. Oshima, *Angew. Chem. Int. Ed.* 2009, **48**, 7224.

2 For a general overview of allylic amination, see: (a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* 1996, **96**, 395; (b) M. Johannsen, K. A. Jorgensen, *Chem. Rev.* 1998, **98**, 1689; (c) J. Tsuji, *New J. Chem.* 2000, **24**, 127; (d) Z. Lu, S. Ma, *Angew. Chem., Int. Ed.* 2008, **47**, 258; (e) M. L. Crawley, *Sci. Synth., Stereosel. Synth.* 2011, **3**, 403; (f) B. Sundararaju, M. Achard, C. Bruneau, *Chem. Soc. Rev.* 2012, **41**, 4467.

3 For some examples, see: (a) S. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, *J. Org. Chem.* 1989, **54**, 3292; (b) R. Weihofen, O. Tverskoy, G. Helmchen, *Angew. Chem., Int. Ed.* 2006, **45**, 5546; (c) C. Defieber, M. A. Ariger, P. Moriel, E. M. Carreira, *Angew. Chem., Int. Ed.* 2007, **46**, 3139.

4 (a) T. Nagano, S. Kobayashi, *J. Am. Chem. Soc.* 2009, **131**, 4200; (b) M. J. Pouy, L. M. Stanley, J. F. Hartwig, *J. Am. Chem. Soc.* 2009, **131**, 11312; (c) K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima, *Angew. Chem., Int. Ed.* 2012, **51**, 150；（d）R. Grigg, S. Akkarasamiyo, N. Chuanopparat, E. E. Elboray, M. F. Aly, H. H. Abbas-Temirek, B. Kongkathip and N. Kongkathip, *Chem. Commun*. 2013, 49, 2007.

5 (a) J. I. Van Der Vlugt, *Chem. Soc. Rev* 2010, **39**, 2302 and the corresponding citing references; b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem., Int. Ed.* 2007, **46**, 2768; c) J. L. Klinkenberg, J. F. Hartwig, *Angew. Chem., Int. Ed.* 2011, **50**, 86; d) T. Ohshima, K. Mashima, *Yuki Gosei Kagaku Kyokaishi* 2012, **70**, 1145.

6 B. M. Trost, E. Keinan, *J. Org. Chem.* 1979, **44**, 3451.

7 (a) S. P. Nolan, Ed.; *N-Heterocyclic Carbenes in Synthesis;* Wiley-VCH: Weinheim, 2006; b) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem., Int. Ed.* 2007, **46**, 2768; c) S. Diez-Gonzalez, N. Marion, S. P. Nolan, *Chem. Rev.* 2009, **109**, 3612; d) J. A. Mata, M. Poyatos, *Curr. Org. Chem.* 2011, **15**, 3309; e) A. Correa, S. P. Nolan, L. Cavallo, *Top. Curr. Chem.* 2011, **302**, 131; f) G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* 2011, **40**, 5151; g) C. Valente, S. Calimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem., Int. Ed.* 2012, **51**, 3314; h) S. Gaillard, J.-L. Renaud, *Dalton Trans.* 2013, **42**, 7255.

8 (a) H. Kurosawa, *J. Organomet. Chem.* 1987, **334**, 243; b) N. Nomura, K. Tsurugi, M. Okada, *Angew. Chem., Int. Ed.* 2001, **40**, 1932.