

Article

Polymer Supported Triphenylphosphine-Palladium Acetate Complex PS-TPP-Pd(OAc)₂ as a Heterogeneous and Reusable Catalyst for Indirect Reductive Amination of Aldehydes

Sunil S. Ekbote, Sandip T. Gadge and Bhalchandra M. Bhanage *

Department of Chemistry, Institute of Chemical Technology, N. P. Marg, Matunga, Mumbai 400019, India; E-Mails: sunil.ekbote@gmail.com (S.S.E.); st.gadge4@gmail.com (S.T.G.)

* Author to whom correspondence should be addressed; E-Mail: bm.bhanage@ictmumbai.edu.in or bm.bhange@gmail.com; Tel.: +91-22-33612601.

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Abstract: Indirect reductive amination of aldehydes, catalyzed by polymer supported triphenylphosphine-palladium acetate complex PS-TPP-Pd(OAc)₂ catalyst have been developed. The imine is prepared with molecular sieves in the first stage, followed by reduction with potassium formate catalyzed by PS-TPP-Pd(OAc)₂. The recovered catalyst could be reused for four consecutive cycles without loss in activity and provided an excellent yield of the desired products.

Keywords: heterogeneous catalyst; amination; reduction; aldehydes; polymer

1. Introduction

Amines are very important industrial organic compounds that have found widespread applications as solvents, intermediates for pharmaceuticals, textile additives, disinfectants, rubber stabilizers, corrosion inhibitors, and in manufacturing of detergents and plastics. Two of the common methods to prepare amines are the reductive amination of the carbonyl compounds and hydrogenation of nitrile [1]. The direct and indirect reductive amination of aldehydes is also a useful transformation for the synthesis of secondary and tertiary amines. The reductive amination proceeds in several consecutive steps. Condensation of the carbonyl compound and amine form a carbinol-amine, which eliminates water from imines. Subsequently, the imine intermediate is reduced to amine. The term,

direct reductive amination, also describes a reaction in which a reaction mixture of carbonyl compound and amine is treated with a suitable reducing agent in a one-pot [2].

The Borch reduction is a process in which sodium cyanoborohydride is used as reducing agent and there is formation of toxic cyanide as the by-product, which limits its wide applications [3]. The indirect reductive amination of aldehydes involves the formation of the intermediate imine, followed by reduction to amines. Such a system uses various catalytic systems, along with the hydride donor, such as trichlorosilanes [4], piperazine-2-carboxylic acid derived *N*-formamide, hydrosilylation of imine with trichlorosilane [5], picolinic acid derived formamides for mild reduction with trichlorosilanes [6], hydrosilylation with PhMe_2SiH catalyzed by $\text{B}(\text{C}_6\text{F}_5)_3$ [7], phosphoric acid as catalyst along with Hantzsch ester as hydride donor [8], rhodium complex and heterolytically active hydrogen [9], sodium borohydride as a reducing agent and activators like boric acid, *p*-toluenesulfonic acid monohydrate or benzoic acid [10], a powerful reducing agent with a combination of HMPA and SmBr_2 in THF [11], organic reductant like 1-acetyl-2,3-dimethylimidazolidine [12], reduction with tributyltinhydrides [13], *etc.*

In 2003, Basu *et al.* reported indirect reductive amination, in which imines are formed with molecular sieves/silica gel in the first stage of reaction, followed by the reduction of imine with potassium formate, catalyzed with palladium acetate [14]. However, the loss of palladium acetate in the effluent, even at the ppm level is not desirable due to its cost and environmental effects. The method for overcoming these drawbacks would involve the use of a heterogeneous palladium catalyst, which is investigated in a variety of organic chemical fields, from sustainable and industrial standpoints, due to its recoverability, reusability, and avoidance of residual metals in the desired products.

In an effort to develop a convenient system we, hereby, propose our observation, which constitutes a reductive amination protocol, forming imine in the first stage by reacting amines with aldehydes, followed by reduction of imine in the second stage with sodium formate as a biodegradable reducing agent in presence of polymer, supported triphenylphosphine-palladium acetate complex $\text{PS-TPP-Pd}(\text{OAc})_2$ catalyst. The polymer supported triphenylphosphine ligand along with the palladium metal precursor is well explored for the various reactions [15–19]. However, to best of our knowledge, such a type of catalyst has not yet been explored for its reduction of imines.

2. Results and Discussion

In the present work, reductive amination is carried out in two stages. In the first stage, aldehydes and amines are reacted with molecular sieves in DMF forming imines. In the second stage, reduction of imines is carried out with sodium formate, catalyzed by $\text{PS-TPP-Pd}(\text{OAc})_2$. The influence of various reaction parameters, such as catalyst loading, effect of solvents, catalyst to ligand ratio, temperature, time, *etc.*, were studied.

2.1. Effect of Catalyst Loading

Various catalyst loading ranging from 2.5 mol-% to 15 mol-% were studied. Initially, reaction, carried out with 2.5 mol-% of catalyst, provided desired product of *N*-(4-methoxybenzyl) aniline in a 19% yield. An increase in the catalyst concentration to 10 mol-% resulted in a 74% yield (Table 1, entry 3). Further increase in the amount of catalyst had no profound effect on the yield of product (Table 1, entry 4).

Table 1. Effect of catalyst loading. ^a

Entry	Catalyst conc. mol-%	(%) Yield by G.C.
1	2.5	19
2	5	65
3	10	74
4	15	74

^a Reaction conditions: imine (1 mmol), sodium formate (3 mmol), temp (85 °C), time (6 h) and DMF (5 mL).

2.2. Effect of Various Solvents on the Reaction

Various polar and non-polar solvents were studied for their effectiveness in the reduction of imine (Table 2, entries 1–5). The effect of nonpolar solvent toluene showed practically no reaction. The polar solvents, such as DMF, ethanol, dioxane, and acetonitrile showed reduction of imine ranging from 12% to 74%, (Table 2, entries 2 to 5). Best yields were obtained by employing DMF as solvent, which provided a 74% yield. Hence, DMF was selected as suitable solvent for the reduction of imines.

Table 2. Effect of various solvents on the reaction. ^a

Entry	Solvent	(%) Yield by G.C.
1	Toluene	Traces
2	Ethanol	47
3	Dioxane	18
4	DMF	74
5	Acetonitrile	12

^a Reaction conditions: imine (1 mmol), PS-TPP-Pd(OAc)₂ (10 mol %), sodium formate (3 mmol), temp (85 °C), time (6 h) and DMF (5 mL).

2.3. Effect of Temperature on the Reaction

The reaction was carried out at different temperature ranging from 40 °C to 100 °C (Table 3, entries 1 to 6). It was observed that, at temperatures of 40 °C, 50 °C, and 60 °C yields are lower (Table 3, entries 1–3). Increasing the temperature to 70 °C and 85 °C, higher yields of product are obtained (Table 3, entries 4 to 5). However, further increasing the temperature to 95 °C showed the lowering of the yield to 69% (Table 3, entry 6).

Table 3. Effect of temperature on the reaction. ^a

Entry	Temp °C	(%) Yield by G.C.
1	40	58
2	50	64
3	60	71
4	70	72
5	85	74
6	95	69

^a Reaction conditions: imine (1 mmol), PS-TPP-Pd(OAc)₂ (10 mol-%), sodium formate (3 mmol), time (6 h) and DMF (5 mL).

2.4. Effect of Time on Reaction Yields

Influence of time in the reaction yields was also studied (Table 4, entries 1 to 6), reflecting 6 h to be sufficient under the present reaction conditions (Table 4, entry 5).

Table 4. Effect of time on reaction yields. ^a

Entry	Time (h)	(%) Yield by G.C.
1	2	56
2	3	64
3	4	70
4	5	73
5	6	74
6	7	72

^a Reaction conditions: imine (1 mmol), PS-TPP-Pd(OAc)₂ (10 mol-%), sodium formate (3 mmol), temp (85 °C) and DMF (5 mL).

2.5. Preparation and Evaluation of PS-TPP-Pd(OAc)₂ Complex Catalyst Varying Ratio of Pd(OAc)₂ to PS-TPP

The catalytic activity at different Pd/P ratio was studied for reduction of imine intermediate. By using Pd/P ratios of 1:1, 1:2, 1:3, 1:4, 1:5, studies were carried to evaluate the performance of catalyst. During the reaction with Pd/P ratios of 1:1, 1:2, and 1:3, the yields of the product were found to be 23%–65%, however, the color of catalyst was found to change from yellow to black (Table 5, entries 1–3). The best yields were obtained for a Pd/P ratio of 1:4, providing a 74% yield of the desired product. The catalyst was isolated quantitatively after reaction as yellowish solid. The further increase in the ratio of Pd/P to 1:5, almost similar results were obtained. Pd/P ratio of 1:4 was used and found to be optimum. We also studied the comparative study of homogeneous Pd/PPh₃ and heterogeneous Pd/PS-TPP complex catalyst for the present protocol. The product yields for reactions catalyzed by such resins were the same as those homogeneously catalyzed by PPh₃ plus Pd(OAc)₂ when compared at equal P:Pd ratios (Table 5, entry 6).

Table 5. Preparation and evaluation of PS-TPP-Pd(OAc)₂ complex catalyst varying ratio of Pd(OAc)₂: PS-TPP. ^a

Entry	Pd/P Ratio	Pd(OAc) ₂ (mol-%)	PS-TPP (mol-%)	Color changes	(%) Yield by G.C.
1	1:1	10	10	Black	23
2	1:2	10	20	Black	45
3	1:3	10	30	Brown-black	65
4	1:4	10	40	Yellow	74
5	1:5	10	50	Yellow	74
6 ^b	1:4	10	---	Yellow	75

^a Reaction conditions: imine (1 mmol), sodium formate (3 mmol), temp (85 °C), time (6 h) and DMF (5 mL);

^b The PPh₃ (40 mol-%) was used as ligand.

2.6. Effect of Formic Acid Salts in Reduction of Amine

Formic acid salts, such as HCOONa, HCOOK, and COONH₄, were studied as hydrogen donors in the reduction of imine catalyzed by PS-TPP-Pd(OAc)₂. Sodium formate was found to be best reducing agent in comparison with potassium formate and ammonium formate (Table 6, entries 1–6). Reduction with potassium formate and ammonium formate provided lower yields of the desired product.

Table 6. Effect of formic acid salts in reduction of amine. ^a

Entry	Hydrogen donor	Hydrogen donor (mmol)	(%) Yield by G.C.
1	HCOONa	1.5	67
2	HCOONa	2	71
3	HCOONa	2.5	73
4	HCOONa	3	74
5	HCOOK	3	59
6	HCOONH ₄	3	21

^a Reaction conditions: imine (1 mmol), PS-TPP-Pd(OAc)₂ (10 mol-%), temp (85 °C), time (6 h) and DMF (5 mL).

2.7. Reductive Amination of Aldehydes Using Sodium Formate

With optimized reaction conditions in hand, we studied various aldehydes for the indirect reductive amination (Table 7). The various aldehydes containing the electron donating and electron withdrawing substituents were showed excellent reactivity and selectivity under the present reaction conditions. The ketones are also found the reactive substrates under optimized reaction condition, provided excellent yield of the desired product. The primary and secondary aliphatic and aromatic amines are found to be reactive, and provided an excellent yield of the desired product.

Table 7. Indirect Reductive amination of aldehydes using sodium formate, catalyzed by PS-TPP-Pd(OAc)₂ a heterogeneous catalyst. ^a

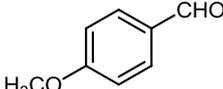
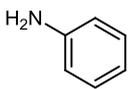
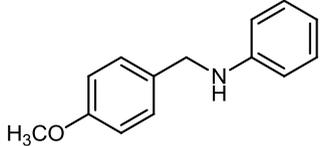
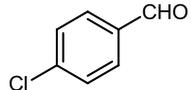
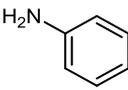
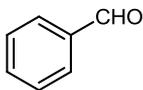
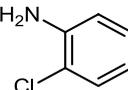
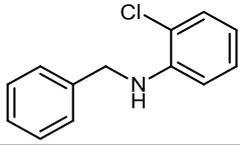
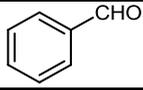
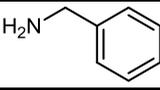
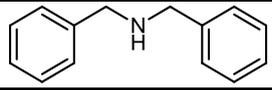
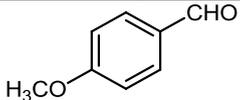
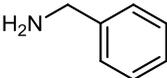
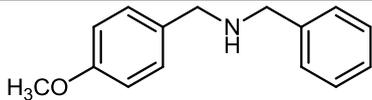
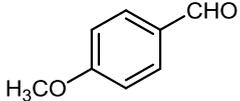
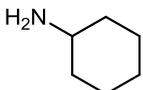
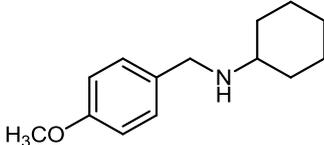
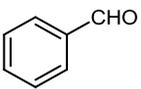
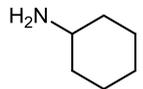
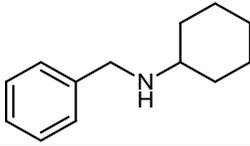
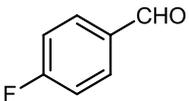
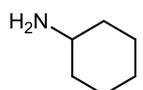
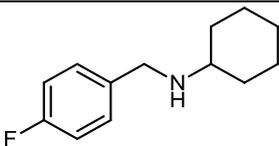
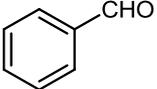
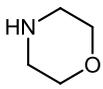
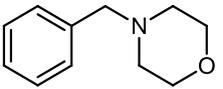
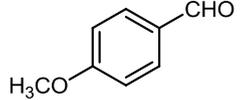
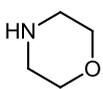
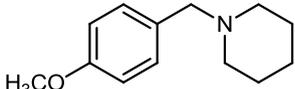
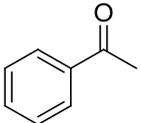
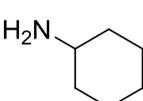
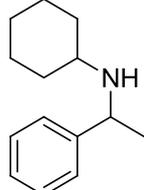
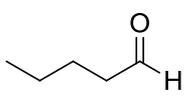
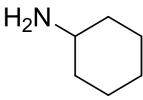
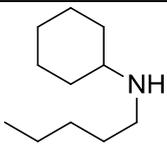
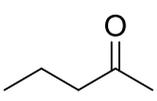
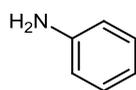
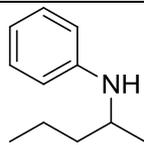
Entry	Aldehyde	Amine	Product	%Yield ^b
1				74
2				84
3				56
4				85

Table 7. Cont.

Entry	Aldehyde	Amine	Product	%Yield ^b
5				76
6				82
7				84
8				77
9				68
10				65
11				70
12				58
13				61

^a Reaction conditions: aldehyde or ketone (1 mmol), amine (1 mmol), molecular sieves 4A° (1 g), PS-TPP-Pd(OAc)₂ (10 mol %), sodium formate (3 mmol), Temp 85 °C, Time 6 h and solvent DMF (5mL);

^b Isolated yields.

2.8. Recycle Study of Catalyst

The reusability of PS-TPP-Pd(OAc)₂ is a great advantage in decreasing environmental pollution and cost reduction in process chemistry. We examined the reuse of PS-TPP-Pd(OAc)₂ in the indirect reductive amination (Table 8). The catalyst could be reused for four consecutive provided the excellent yield of the desired products. The lowering of the yield of the product after the fourth recycle was due to the handling loss of the catalyst in successive recycles and there is also possibility of exposure of the catalytic system to air during the recycle handling.

Table 8. Recycle study of catalyst. ^a

Entry	Catalyst recycle number	Yield (%) ^b
1	0	74
2	1	71
3	2	68
4	3	66
5	4	65

^a Reaction conditions: anisaldehyde (1 mmol), aniline (1 mmol), molecular sieves 4A° (1 g), catalyst PS-TPP-Pd(OAc)₂ (10 mol-%), sodium formate (3 mmol) and solvent DMF (5 mL); ^b Product yield is based on GC analysis.

3. Experimental Section

3.1. General

Palladium acetate, polymer-supported triphenylphosphine (loading 3 mmol/g), amines, aldehydes, reducing agents like formic acid salts, molecular sieve, *etc.*, were purchased from Sigma-Aldrich (Taufkirchen, Germany). Optimized yields were based on GC and GC-MS (Shimadzu QP 2010, Kyoto, Japan). All products are known, and representative products were characterized by ¹H NMR and GC-MS. Purity of the compounds were determined by GC-MS.

3.1.1. Preparation of Polymer Supported Triphenylphosphane Palladium Acetate PS-TPP-Pd(OAc)₂ Complex [15–19]

An amount of 134 mg of PS-TPP, 22.4 mg of Pd(OAc)₂, and 5 mL DMF (dried, nitrogen bubbled) were added to 20 mL glass vial with magnetic bar was closed with silicon septum and screw cap. The mass was stirred magnetically and heated to 45–50 °C for 4 h. The yellow product was precipitated. The product was recovered by filtration and washed with ethanol until the filtrate was colorless. The yellow solid was dried for 50 h under vacuum.

3.1.2. Stage No. 1, Preparation of Imine

Anisaldehyde (1 mmol) and aniline (1 mmol), Molecular Sieves 4A° activated (1 g) and DMF dry (2 mL) were added in to 20 mL flask with guard tube (CaCl₂). Reaction mass was stirred magnetically at room temperature for five hours, progress of the reaction was monitored by G.C. Imine mass dissolved in DMF was transferred to 25 mL flask by slow decantation. The content of the flask were kept well protected from moisture and was taken for next stage of reaction.

3.1.3. Stage No. 2, Reduction of Imine

The imine mass kept in 25 mL flask, sodium formate (210 mg 3 mmol), and DMF (3 mL) added. The reaction mass stirred for 10 min with nitrogen bubbling, followed by addition of PS-TPP-Pd(OAc)₂ (10 mol %). The nitrogen gas was bubbled through flask and the contents were protected with calcium chloride guard tube to condenser. The temperature was raised to 85 °C, and kept in kept in a nitrogen atmosphere for the period of six hours until the completion of the reaction.

The reaction mass was cooled to room temperature, 15 mL water was added and extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate and filtered, filtrate was evaporated in a vacuum to give the desired product. The crude product was analyzed and further purified by short silica gel column with a mixture of 5% ethyl acetate in petroleum ether. Aqueous filtrate and washings containing catalyst particle was taken for the recovery of catalyst.

3.1.4. Recovery and Recycle of PS-TPP-Pd(OAc)₂ Catalyst

The reaction mass was cooled to room temperature, water was added, and extracted with ethyl acetate. The aqueous layer containing suspended catalyst particles were filtered and catalyst was washed with distilled water, followed by methanol to remove trace impurities. Catalyst was dried under reduced pressure. Catalyst was further activated at 60–70 °C, for 4–5 h, prior to its use. The catalyst was then used for recyclability experiment. It was observed that the recovered catalyst could be reused for four consecutive cycles with good yields.

3.1.5. Characterization Data of Products

***N*-(4-methoxy benzyl) Aniline (Table 7 entry 1):** ¹H-NMR (400 MHz, CDCl₃): δ 3.76 (s, 3H), 4.20 (s, 2H), 6.60 (d, 2H), 6.69 (t, 1H), 6.85 (d, 2H), 7.15 (m, 2H), 7.25 (d, 2H); GC-MS (*m/z*): 213 (M⁺ 28), 121 (100), 91 (6), 77 (14).

Dibenzylamine (Table 7 entry 4): ¹H-NMR (400 MHz, CDCl₃): δ 7.33–7.28 (m, 8H), 7.26–7.21 (m, 2H), 3.55 (s, 4H); GC-MS (*m/z*): 197 (M⁺ 37), 106 (86), 91 (100).

***N*-benzyl morpholine (Table 7 entry 9):** ¹H-NMR (400 MHz, CDCl₃): δ 7.38–7.20 (m, 5H), 3.80 (s, 2H), 2.42 (m, 1H), 1.98–1.10 (m, 8H); GC-MS (*m/z*): 177 (M⁺ 35), 146 (26), 110 (10), 91 (100), 86 (38), 65 (14).

4. Conclusions

In conclusion, we have developed an efficient protocol for indirect reductive amination with polymer supported triphenylphosphine palladium acetate complex as a heterogeneous and recyclable catalyst. The reaction was optimized with respect to various parameters and enabled reductive amination reaction with various electron rich, electron deficient aldehydes, affording excellent yield of the desired product and, thus, illustrating a wide applicability of scheme. Further, PS-TPP-Pd(OAc)₂ complex was recycled for four consecutive cycle without significant loss in catalyst activity.

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Author Contributions

Sandip T. Gadge wrote the first draft of the manuscript that was then extensively improved by Bhalchandra M. Bhanage and as the result of comments from our reviewers. Experimental work was carried out by Sunil S. Ekbote. Each member sufficiently contributed in the work to take responsibility of the content.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Haddenham, D.; Pasumansky, L.; DeSoto, J.; Eagon, S.; Singaram, B. Reductions of aliphatic and aromatic nitriles to primary amines with diisopropylaminoborane. *J. Org. Chem.* **2009**, *74*, 1964–1970.
2. Abdel-Majid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. Reductive amination of aldehydes and ketones with Sodium Triacetoborohydride. *J. Org. Chem.* **1996**, *61*, 3849–3862.
3. Borch, R.F.; Bernstein, M.D.; Durst, H.D. Reductive amination reduction with use of Sodium Cyano-borohydride. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
4. Malkov, A.V.; Figlus, M.; Stoncius, S.; Kocovsky, P. Assymetric reduction of ketimines with trichlorosilanes catalyzed by *N*-methylvaline derived lewis-basic formamide with enantio selectivity at room temperature. *J. Org. Chem.* **2007**, *72*, 1315–1325;
5. Wang, Z.; Cheng, M.; Wu, P.; Wei, S.; Sun, J. L-Piperazine-2-carboxylic acid derived *N*-Formamide, highly enantioselective Lewis basic catalyst for hydrosilylation of imines with trichlorosilane. *Org. Lett.* **2006**, *8*, 3045–3048.
6. Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. L-Picolinic acid derived *N*-formamide, highly efficient and enantioselective Lewis basic organocatalyst for mild reduction of various *N*-aryl imines with trichlorosilane. *Org. Lett.* **2006**, *8*, 999–1001.
7. Blackwell, J.M.; Sonmer, E.R.; Scoccitti, T.; Piers, W.E. Various benzaldimines and ketimines hydrosilated effectively with PMe_2SiH employing $\text{B}(\text{C}_6\text{F}_5)_3$ as a catalyst. *Org. Lett.* **2000**, *2*, 3921–3923.
8. Li, G.; Liang, Y.; Antilla, J.C. α -imino esters derived from aryl and alkyl esters could be reduced to corresponding α -amino esters in excellent yields, using 5 mol% of chiral phosphoric acid. *J. Am. Chem. Soc.* **2007**, *129*, 5830–5831.
9. Misumi, Y.; Seino, H.; Mizobe, Y. A benzene dithiolate Ru(III) complex catalyzes hydrogenation of imines under ambient temperature and pressure. *J. Am. Chem. Soc.* **2009**, *131*, 14636–14637.
10. Cho, B.T.; Kang, S.K. A simple and convenient procedure for reductive amination of aldehydes and ketones using sodium borohydride as reducing agent and boric acid, PTSA H_2O , benzoic acid as activator under solvent free conditions. *Tetrahedron* **2005**, *61*, 5725–5734.
11. Knettle, B.W.; Flowers, R.A. The combination of HMPA and SmBr_2 in THF is powerful reductant in reducing ketamines and alkyl chlorides at room temperature. *Org. Lett.* **2001**, *3*, 2321–2324.

12. Li, D.; Zhang, Y.; Zhou, G.; Guo, W. The organic reductant 1-Acetyl-2,3-dimethylimidazolidine is able to reduce a series of aromatic, aliphatic and α,β -unsaturated aldehydes as well as imines in high yields. *Synlett* **2008**, 225–228.
13. Khedkar, V.; Tillak, A.; Beller, M. Aryl oxotitanium complex as catalyst in intramolecular hydroamination of terminal alkynes. Branched imines are obtained in good yields with various primary aromatic and aliphatic amines. *Org. Lett.* **2003**, *5*, 4767–4770.
14. Basu, B.; Jha, S.; Bhuiyan, M.M.H.; Das, P. Simple protocol for direct reductive amination of aldehydes and ketones using potassium formate and catalytic palladium acetate. *Synlett* **2003**, *4*, 555–557.
15. Pittman, C.U.; Wu, S.I.; Jacobson, S.E. 1,3-Butadiene oligomerization catalyzed by polymer-attached palladium complexes. Comparison with homogeneous catalysis. *J. Catal.* **1976**, *44*, 87–100.
16. Andersson, C.M.; Karabelas, K.; Hallberg, A.; Andersson, C. Palladium/phosphinated polystyrene as a catalyst in the Heck arylation. A comparative study. *J. Org. Chem.* **1985**, *50*, 3891–3895.
17. Terasawa, M.; Kaneda, K.; Imanaka, T.; Teranishi, S. Study of hydrogenation of olefins catalyzed by polymer-bound palladium (II) complexes. *J. Catal.* **1978**, *51*, 406–421.
18. Bergbreiter, D.E.; Chen, B.; Weatherford, D. New strategies in using macromolecular catalysts in organic synthesis. *J. Mol. Catal.* **1992**, *74*, 409–419.
19. Wagh, Y.S.; Tambade, P.J.; Sawant, D.N.; Bhanage, B.M. Allylic amination of internal alkynes with aromatic and aliphatic amines using polymer-supported triphenylphosphane-palladium complex as a heterogeneous and recyclable catalyst. *Eur. J. Org. Chem.* **2010**, 5071–5076.

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