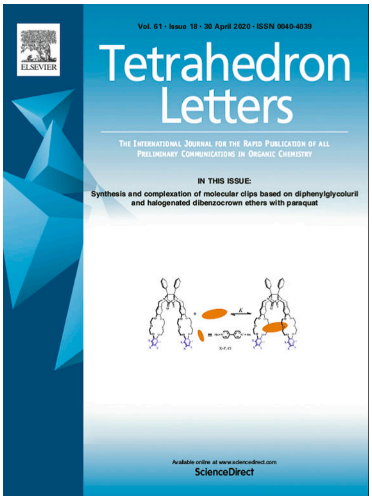

Direct benzylation of amines with benzylic alcohols catalyzed by palladium/phosphine-borane catalyst system

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Direct Benzylation of Amines with Benzylic Alcohols Catalyzed by Palladium/Phosphine-Borane Catalyst System

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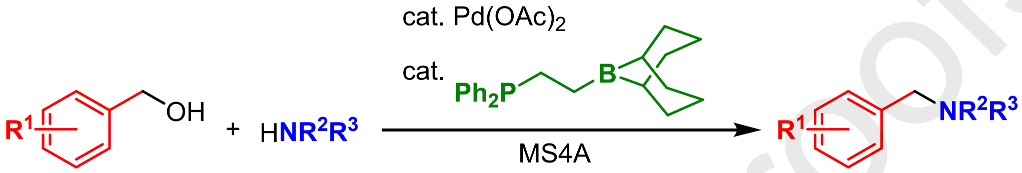

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Direct benzylation of amines with benzylic alcohols catalyzed by palladium/phosphine-borane catalyst system

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ABSTRACT

Direct catalytic benzylation of amines with benzylic alcohols to give benzylamines has been newly developed by using palladium/phosphine-borane catalyst system. In this catalytic reaction, the linking between both phosphine and borane moieties in the ligand is very important. Hydroxy group of benzylic alcohols is activated by Lewis acidic borane to form a benzylpalladium intermediate which is attacked by amines to give benzylamine products.

Introduction

Benzyl alcohol derivatives such as benzylic carbonates and acetates are useful starting materials as benzylation reagents in the presence of a suitable palladium-catalyst. Oxidative addition of benzyl alcohol derivatives to a palladium complex gives a σ- and/or π-benzylpalladium complex, which is a very useful intermediate to form a variety of carbon–carbon and carbon–heteroatom bonds [1]. In the early stage, α- and β-naphthylmethyl and 1-(α- and β-naphthyl)ethyl esters were used for obtaining benzylpalladium intermediates as electrophiles [2]. Kuwano and his co-workers reported that benzylic carbonates could also be used as a benzylation reagent [3]. Nucleophilic substitutions of benzylic esters were also catalyzed by some palladium complexes [4]. Although benzylic esters and carbonates derived from benzylic alcohols have so far been mainly used as starting materials, less examples have been reported about the direct transformation of benzylic alcohols. One of the methods for activation of benzylic alcohols to form a benzylpalladium intermediate is an addition of acid to protonate the hydroxy group [5]. Hikawa and his co-workers have developed the palladium-catalyzed benzylation by using benzylic alcohols in neutral water, where water plays a crucial role to activate the hydroxy group [6]. On the other hand, less examples of reactions of benzylic alcohols in organic solvents in the presence of a palladium catalyst have been reported [7]. Thus, the direct benzylic substitution reaction is still an attractive method for the organic synthesis.

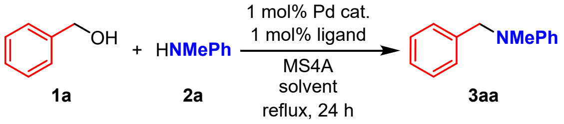
In the course of our study on a transition-metal-catalyzed organic synthesis, we were interested in using phosphine-borane compounds as ligands. Some phosphine-borane complexes have been known to be useful for the transition-metal-catalyzed organic reactions [8,9]. Palladium-catalyzed Suzuki-Miyaura coupling [10] and rhodium-catalyzed hydroformylation [11] using phosphine-borane ligands were reported by Bourissou and his co-workers. In our group, we found that a phosphine-borane palladium complex is efficient for the direct allylation of amines and active methylene compounds using allylic alcohols [12]. In these reactions, Lewis acidic borane moiety of a phosphine-borane ligand activates the hydroxy group of allylic alcohols and the oxidative addition of allylic alcohols to palladium proceeds smoothly to form an electrophilic π-allylpalladium intermediate. We envisaged that this methodology might be applicable to the formation of a π-benzylpalladium species via an oxidative addition of benzylic alcohols. In this manuscript, we report the palladium-catalyzed direct benzylation of amines with benzylic alcohols in the presence of a phosphine-borane ligand.

Results and discussion

Palladium-catalyzed benzylation of *N*-methylaniline (**2a**) with benzyl alcohol (**1a**) was investigated under a variety of reaction conditions (Table 1). At first, the reaction was investigated in toluene by using 2.5 mol% of $Pd(OAc)_2$ and 2.5 mol% of **L1**, the latter of which was revealed to be the best ligand for the so-far disclosed allylation of amines. As a result, benzylamine **3aa** was obtained in 73% isolated yield (entry 1). The addition of MS4A as a dehydrating agent was effective for this reaction to improve the yield to 99% probably by removing water formed in situ (entry 2). The catalyst loading can be reduced to 1 mol% without decreasing the yield (entry 3). In the place of $Pd(OAc)_2$, the other Pd(II) species such as $PdCl_2$ and $Pd(acac)_2$ could not be used as a catalyst precursor in this reaction (entries 4 and 5). On the

corresponding product in good yield (entry 6) [13]. We found that toluene was the best solvent for this reaction among some other organic solvents (entries 7-10). Then, the effect of a variety of phosphine-borane ligands was investigated. The ligand having dicyclohexylboryl group **L2** was also revealed to be the good ligand to give **3aa** in quantitative yield (entry 11). Propylene-, butylene-, and *o*-phenylene-linked phosphine-borane ligands (**L3**, **L4**, and **L5**) were less effective than **L1** (entries 12-14). No benzylamine **3aa** was obtained by use of either ligand **L6** or ligand **L7** (entries 15 and 16). The reaction in the co-presence of both $EtPPh_2$ and *B*-*n*-hexyl-9-BBN did not produce any products (entry 17). These results show that the linkage between phosphine and borane moieties is necessary and that the length between phosphorus and boron atoms and its flexibility are important for this reaction, the ligand **L1** and **L2** being well matched.

Table 1. Reactions of *N*-methylaniline (**2a**) with benzyl alcohol (**1a**).[a]



Entry	Pd catalyst	Ligand	Solvent	Yield (%)[b]
1[c,d]	$Pd(OAc)_2$	**L1**	toluene	73
2[c]	$Pd(OAc)_2$	**L1**	toluene	99
3	$Pd(OAc)_2$	**L1**	toluene	99
4	$PdCl_2$	**L1**	toluene	0
5	$Pd(acac)_2$	**L1**	toluene	0
6[e]	$Pd_2(dba)_3$	**L1**	toluene	75
7	$Pd(OAc)_2$	**L1**	p-xylene	94
8	$Pd(OAc)_2$	**L1**	benzene	43
9	$Pd(OAc)_2$	**L1**	THF	9
10	$Pd(OAc)_2$	**L1**	1,4-dioxane	19
11	$Pd(OAc)_2$	**L2**	toluene	99
12	$Pd(OAc)_2$	**L3**	toluene	91
13[f]	$Pd(OAc)_2$	**L4**	toluene	72
14	$Pd(OAc)_2$	**L5**	toluene	76
15	$Pd(OAc)_2$	**L6**	toluene	0
16	$Pd(OAc)_2$	**L7**	toluene	0
17[f,g]	$Pd(OAc)_2$	$EtPPh_2$	toluene	0

[a] A mixture of **1a** (2.0 mmol), **2a** (1.0 mmol), Pd catalyst, ligand, MS4A (20 mg) and solvent (1 mL) was stirred under N_2.

[b] Isolated yield.

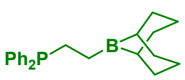
[c] 2.5 mol% of $Pd(OAc)_2$ and 2.5 mol% of **L1** were used.

[d] In the absence of MS4A.

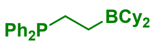
[e] 0.5 mol% of $Pd_2(dba)_3\cdot CHCl_3$ was used.

[f] 2 mol% of $Pd(OAc)_2$ and 2 mol% of ligand were used.

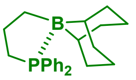
[g] 2 mol% of *B*-*n*-C_6H_{13}-9-BBN was added.



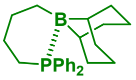
L1



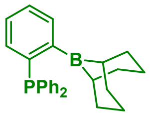
L2



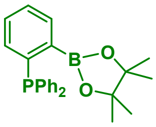
L3



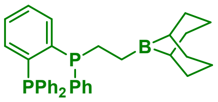
L4



L5



L6

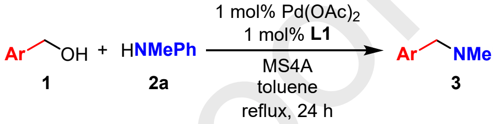


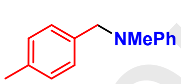
L7

d be

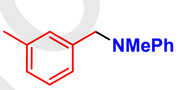
used in this benzylation reaction. Results of the reactions with *N*-methylaniline (**2a**) are summarized in Table 2. The reactions of **2a** with *p*- and *m*-tolylmethanol (**1b** and **1c**) afforded the corresponding amines **3ba** and **3ca** in high yields, while *o*-tolylmethanol (**1d**) gave no benzylated product **3da**. A slightly larger amount of catalyst and a higher reaction temperature were needed to obtain the amine **3ea** in quantitative yield from 4-methoxyphenylmethanol (**1e**). When [4-(dimethylamino)phenyl]methanol (**1f**) was used, the moderate yield of amine **3fa** was obtained, while 4-chlorophenylmethanol (**1g**) did not react at all even if 2 mol% of catalyst was used in refluxing *p*-xylene. 2-Naphthylmethanol (**1h**) gave the corresponding amine **3ha** in 43% yield, however, 1-naphthylmethanol (**1i**) gave no desired product.

Table 2. Reactions of *N*-methylaniline (**2a**) with a variety of arylmethanols **1**.[a,b]

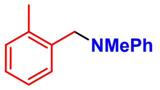




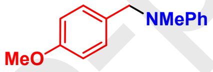
3ba, 82%



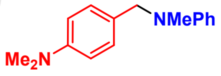
3ca, 99%



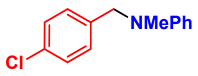
3da, 0%



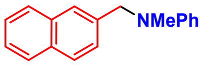
3ea, 99%[c]



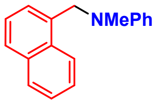
3fa, 51%[c]



3ga, 0%[c]



3ha, 43%[c]



3ia, 0%[c]

[a] A mixture of **1** (2.0 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.01 mmol), **L1** (0.01 mmol), and MS4A (20 mg) was stirred in refluxing toluene (1 mL) under N_2.

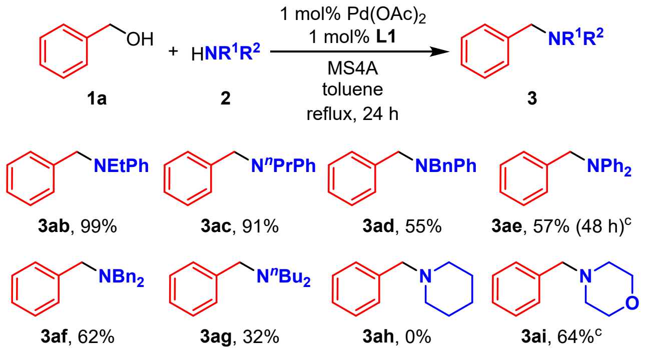
[b] Isolated yield.

[c] 2 mol% of $Pd(OAc)_2$ and 2 mol% of **L1** were used in refluxing *p*-xylene instead of toluene.

Different from primary arylmethanols **1**, the reactions of **2a** with 1-phenylethanol and diphenylmethanol (secondary alcohols) did not proceed at all, suggesting that this reaction does not proceed via a carbocation intermediate.

Results of *N*-benzylation reactions of a variety of secondary amines **2b-i** with benzyl alcohol (**1a**) under the optimized reaction conditions (Table 1, entry 3) are summarized in Table 3. *N*-Ethylaniline (**2b**) and *N*-*n*-propylaniline (**2c**) gave the products **3ab** and **3ac** in high yields, respectively. The product yield of **3ad** was lower from *N*-benzylaniline (**2d**). Because of the steric hindrance, the reactivity of diphenylamine (**2e**) was low, and a longer reaction time and a larger catalyst loading were needed to achieve the moderate yield of **3ae**. Dibenzylamine (**2f**) and di-*n*-butylamine (**2g**) gave the products **3af** and **3ag** in 62% and 32% yields, respectively. While piperidine (**2h**) gave no corresponding amine **3ah**, morpholine (**2i**) reacted with **1a** to afford the corresponding amine **3ai** in 64% yield.

Tab
benzyl alcohol (**1a**).[a,b]

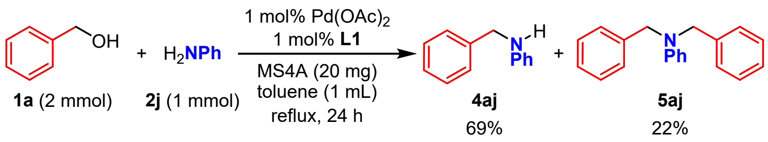


(0.01 mmol), and MS4A (20 mg) was stirred in refluxing toluene (1 mL) under N_2.

[b] Isolated yield.

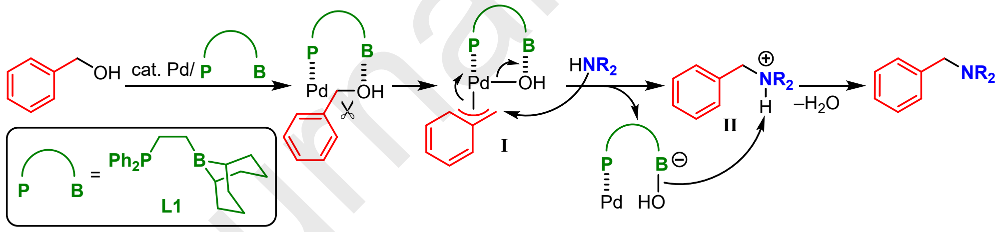
[c] 2 mol% of Pd(OAc)$_2$ and 2 mol% of **L1** were used.

The reaction of aniline (**2j**) (primary amine) with benzyl alcohol (**1a**) proceeded to give *N*-benzylaniline (**4aj**) in 69% yield along with a less amount of *N*,*N*-dibenzylaniline (**5aj**) by use of 2 equivalents of **1a** (Scheme 2).



Scheme 2. Reaction of aniline (**2j**) with benzyl alcohol (**1a**).

In this benzylation reaction, three deferent reaction pathways can be conceivable. First, the reaction proceeds via a benzyl cation intermediate. However, as shown above, secondary benzylic alcohols which can give more stable carbocation did not react at all, omitting this possibility. The second pathway is a hydrogen transfer strategy, including oxidation and reduction process [14]. In this type of reaction, a starting alcohol is oxidized to the carbonyl compound, which reacts with amine to form an imine or iminium ion intermediate. A successive reduction gives the corresponding amine. In a palladium-catalyzed reaction system, the use of a base is necessary to form a palladium-alkoxide intermediate giving the carbonyl compound via a β-hydride elimination. In our reaction system, however no base is needed to produce the benzylamine in high yield. We tentatively propose the reaction pathway for our catalytic reaction as shown in Scheme 3. At first, benzyl alcohol reduces Pd(OAc)$_2$ to Pd(0). Then, boryl group of the phosphine-borane ligand acts as a Lewis acid to activate the hydroxy group of benzyl alcohol. The ethylene linker in **L1** is competent to bring Pd nearby to C–O bond. Successive oxidative addition proceeds intramolecularly to give a π-benzylpalladium intermediate **I** which can be attacked by a nucleophilic amine. The produced ammonium salt **II** is deprotonated by the hydroxy group to give the product amine and 1 equivalent of water as a sole byproduct. The intramolecular oxidative addition may proceed smoothly by using ethylene-linked phosphine-borane ligand **L1**.



Scheme 3. Plausible reaction pathway.

Conclusion

In summary, we have now found that the benzylation of amines using benzylic alcohols can be catalyzed by palladium/phosphine-borane catalyst system. The linking between phosphine and borane moieties in the ligand is very important for this catalytic reaction.

Declaration of Competing Interest

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

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.xxxxxx.

References

[1] For reviews, see: (a) Liégault, B.; Renaud, J.-L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290; (b) Kuwano, R. *Synthesis* **2009**, 1049; (c) Weaver, J. D.; Recio, A. III; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846; (d) Trost, B. M.; Czabaniuk, L. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 2826; (e) Le Bras, J.; Muzart, J. *Eur. J. Org. Chem.* **2016**, 2565.

[2] (a) Baird, J. M.; Kern, J. R.; Lee, G. R.; Morgans, D. J., Jr.; Sparacino, M. L. *J. Org. Chem.* **1991**, *56*, 1928; (b) Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2509; (c) Legros, J.-Y.; Toffano, M.;

M.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **1995**, *6*, 1899; (e) Toffano, M.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett.* **1997**, *38*, 77; (f) Legros, J.-Y.; Boutros, A.; Fiaud, J.-C.; Toffano, M. *J. Mol. Catal. A: Chem.* **2003**, *196*, 21; (g) Assié, M.; Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 1183; (h) Assié, M.; Meddour, A.; Fiaud, J.-C.; Legros, J.-Y. *Tetrahedron: Asymmetry* **2010**, *21*, 1701.

[3] (a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12104; (b) Kuwano, R.; Kondo, Y. *Org. Lett.* **2004**, *6*, 3545; (c) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973; (d) Kuwano, R.; Kusano, H. *Chem. Lett.* **2007**, *36*, 528; (e) Yokogi, M.; Kuwano, R. *Tetrahedron Lett.* **2007**, *48*, 6109; (f) Kuwano, R.; Kusano, H. *Org. Lett.* **2008**, *10*, 1979; (g) Ueno, S.; Komiya, S.; Tanaka, T.; Kuwano, R. *Org. Lett.* **2012**, *14*, 338; (h) Makida, Y.; Usui, K.; Ueno, S.; Kuwano, R. *Chem. Lett.* **2017**, *46*, 1814.

[4] (a) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534; (b) Yuan, F.-Q.; Gao, L.-X.; Han, F.-S. *Chem. Commun.* **2011**, *47*, 5289; (c) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111; (d) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2012**, *134*, 5778; (e) Trost, B. M.; Czabaniuk, L. C. *Chem. Eur. J.* **2013**, *19*, 15210; (f) Franzoni, I.; Guénée, L.; Mazet, C. *Org. Biomol. Chem.* **2015**, *13*, 6338; (g) Tabuchi, S.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6973; (h) Punna, N.; Das, P.; Gouverneur, V.; Shibata, N. *Org. Lett.* **2018**, *20*, 1526.

[5] (a) Papadogianakis, G.; Maat, L.; Sheldon, R. A. *J. Chem. Tech. Biotechnol.* **1997**, *70*, 83; (b) Verspui, G.; Papadogianakis, G.; Sheldon, R. A. *Catal. Today* **1998**, *42*, 449; (c) Lin, Y.-S.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 723.

[6] (a) Hikawa, H.; Yokoyama, Y. *Org. Lett.* **2011**, *13*, 6512; (b) Hikawa, H.; Yokoyama, Y. *Org. Biomol. Chem.* **2012**, *10*, 2942; (c) Hikawa, H.; Ino, Y.; Suzuki, H.; Yokoyama, Y. *J. Org. Chem.* **2012**, *77*, 7046; (d) Hikawa, H.; Yokoyama, Y. *RSC Adv.* **2013**, *3*, 1061; (e) Hikawa, H.; Suzuki, H.; Yokoyama, Y.; Azumaya, I. *Catalysts* **2013**, *3*, 486; (f) Hikawa, H.; Matsuda, N.; Suzuki, H.; Yokoyama, Y.; Azumaya, I. *Adv. Synth. Catal.* **2013**, *355*, 2308; (g) Hikawa, H.; Azumaya, I. *Org. Biomol. Chem.* **2014**, *12*, 5964; (h) Hikawa, H.; Izumi, K.; Ino, Y.; Kikkawa, S.; Yokoyama, Y.; Azumaya, I. *Adv. Synth. Catal.* **2015**, *357*, 1037.

[7] (a) Toyoshima, T.; Mikano, Y.; Miura, T.; Murakami, M. *Org. Lett.* **2010**, *12*, 4584; (b) Grünberg, M. F.; Gooßen, L. J. *Chem. Eur. J.* **2013**, *19*, 7334; (c) Maji, T.; Ramakumar, K.; Tunge, J. A. *Chem. Commun.* **2014**, *50*, 14045; (d) Cao, Z.-C.; Yu, D.-G.; Zhu, R.-Y.; Wei, J.-B.; Shi, Z.-J. *Chem. Commun.* **2015**, *51*, 2683.

[8] For a recent review, see: Bouhadir, G.; Bourissou, D. *Chem. Soc. Rev.* **2015**, *45*, 1065.

[9] Liu reported the palladium-catalyzed hydroboration using 1,4-azaborine-based phosphine as a ligand, see: Xu, S.; Haeffner, F.; Li, B.; Zakharov, L. N.; Liu, S. Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 6795.

[10] (a) Malacea, R.; Saffon, N.; Gómez, M.; Bourissou, D. *Chem. Commun.* **2011**, *47*, 8163; (b) Malacea, R.; Chahdoura, F.; Devillard, M.; Saffon, N.; Gómez, M.; Bourissou, D. *Adv. Synth. Catal.* **2013**, *355*, 2274.

[11] Bebbington, M. W. P.; Bontemps, S.; Bouhadir, G.; Hanton, M. J.; Tooze, R. P.; van Rensburg, H.; Bourissou, D. *New J. Chem.* **2010**, *34*, 1556.

[12] (a) Hirata, G.; Satomura, H.; Kumagae, H.; Shimizu, A.; Onodera, G.; Kimura, M. *Org. Lett.* **2017**, 19, 6148; (b) Shimizu, A.; Hirata, G.; Onodera, G.; Kimura, M. *Adv. Synth. Catal.* **2018**, *360*, 1954.

[13] Fairlamb, I. J. S. *Org. Biomol. Chem.* **2008**, *6*, 3645.

[14] Palladium catalyst for this type of alkylation of amines has been reported, see: (a) Martínez-Asencio, A.; Yus, M.; Ramón, D. J. *Synthesis* **2011**, 3730; (b) Dang, T. T.; Ramalingam, B.; Shan, S. P.; Seayad, A. M. *ACS Catal.* **2013**, *3*, 2536; (c) Liu, X.; Hermange, P.; Ruiz, J.; Astruc, D. *ChemCatChem* **2016**, *8*, 1043.

Declaration of interests

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

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

[15]

Highlights

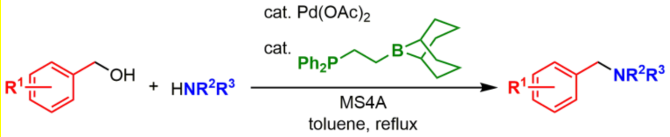
Direct benzylation of amines with benzylic alcohols has been developed.

Palladium/phosphine-borane catalyst system was effective.

The linking between phosphine and borane moieties in the ligand was important.

A variety of benzylic alcohols and amines could be used.

[16]



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