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A Water Promoted-PBM Protocol for Synthesize Tertiary Amines with Arylboronic Acids, Paraformaldehyde and Secondary Amines

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Abstract: A practical and efficient synthetic method for synthesis of benzylic tertiary amines by using arylboronic acids, paraformaldehyde and secondary amines was established in the absence of catalyst. This reaction is very simple and can be efficiently performed under mild conditions, which establishes a practical approach toward a wide range of benzylic tertiary amines.

Key words: arylboronic acids; aminals; paraformaldehyde; tertiary amines; PBM reaction

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Tertiary amines represent one of the most important and abundant compounds in chemistry and can be found in bulk chemicals, fine chemicals, natural products as well as drugs[1-4]. Therefore, the development of an efficient method for the synthesis of these compounds continues to attract interest from both academia and industry in the past several decades. The earliest methods used for construction of tertiary amines often involved *N*-alkylation of ammonia or amines as well as degradation of quaternary ammonium salts[5-10]. However, these reactions often produce large amounts of unwanted by-products which made these reactions environmentally unfavorable. Petasis Borono-Mannich (PBM) reaction provided another rapid and straightforward access to tertiary amines, which has been extensively used for synthesis of a wide range of functional materials[11-17]. In comparison to other methods of generating tertiary amines, the PBM reaction could tolerate a multifunctional scaffold. Additionally, the reaction does not require anhydrous or inert conditions. As a mild selective synthetic method, the PBM reaction has been utilized in combinatorial chemistry and drug discovery. However, the classical PBM reaction is often restricted to activated aldehydes, such as glyoxalate and salicylaldehyde, especially when arylboronic acids are utilized as coupling partners. to the best of our knowledge, the simple formaldehyde had never been used as starting material to react with arylboronic acids to synthesis of benzyl tertiary amines.

Recently, we have identified that aminals can serve as useful electrophiles for undergoing the oxidative addition with Pd(0) to form the unique electrophilic cationic cyclometalated Pd-alkyl species, which have been successfully reacted with alkenes to form allylic amines and amino aldehydes[18-21]. Inspired by these results, we envisioned that aminals would be used as a kind of coupling partner to react with aryboronic acids to form benzylic tertiary amines via the Pd-catalyzed C-N activation. Conceivably, this strategy offers a versatile platform for transferring the simple formaldehyde into some valuable compounds since aminals can be readily prepared from formaldehyde under mild conditions. The reaction indeed took place in the

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presence of Pd-catalyst, and to our surprise, a three-component reaction of arylboronic acid, paraformaldehyde, and secondary amine could readily occurred to give the corresponding tertiary amines under mild reaction condition. Herein, we describe this practical and efficient PBM reaction, which can be carried out with a broad range of arylboronic acids, secondary amines and paraformaldehyde to furnish tertiary amines.

1 Experimental

1.1 General experiment

Arylboronic acids were obtained from commercial sources and used without further purification. Aminals were known compounds and synthesized according to the reported methods[22].

All of the solvents were dried according to the standard methods and stored under argon. All of the reactions were monitored by TLC with silica gel-coated plates. NMR spectra were recorded on a Bruker DRX 400 spectrometer (City, Country). chemical shifts were reported in parts per million (ppm) down field from tetramethylsilane (TMS) as an internal standard. Coupling constants (J) were reported in Hz and refer to apparent peak multiplications. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-QII mass instrument using electrospray ionization (ESI).

1.2 General procedure for the reaction

The aminal(0.4 mmol), phenylboronic acid (0.8 mmol), catalyst (0.02 mmol) and solvent (2 mL) were added to a 25 mL Young-type tube under air atmosphere and the resulting mixture was stirred for 12 h at 110 ℃, then cooled to the room temperature. The solvent was removed under reduced pressure, which was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (100∶1) as eluent to afford the desired products.

Three-component reaction: Secondary amine (0.4 mmol), boronic acid (0.8 mmol), paraformaldehyde (0.5 mmol) and solvent (2 mL) were added to a 25 mL Young-type tube under air atmosphere and the resulting mixture was stirred for 5 ~ 9.5 h at 110 ℃, then cooled to the room temperature. The solvent was removed under reduced pressure, which was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether (100∶1 ~ 3∶1) as the eluent to afford the desired products.

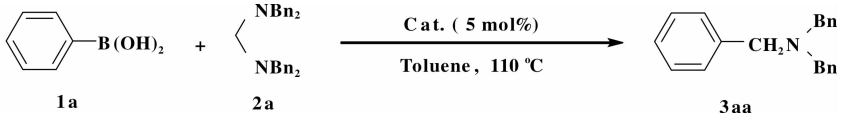
2 Results and discussion

2.1 Optimization of reaction conditions

Initially, a model reaction of phenylboronic acid (**1a**) and *N*,*N*,*N*',*N*'-tetrabenzylmethanediamine (**2a**) was used to optimize the reaction conditions (Table 1). Treatment the reaction with 5% Pd(Xantphos)$(CH_3CN)_2(OTf)_2$, which has been shown to be highly effective for the generation of cyclometalated Pd-alkyl species, in toluene at 110 ℃ for 12 h produced the desired tribenzylamine **3aa** in 26% yield. Several other palladium sources were also tested, including Pd(Xantphos)Cl_2, Pd$(PPh_3)_2Cl_2$, $PdCl_2$, and Pd$(OAc)_2$, these results indicated that $PdCl_2$ was the best choice. The effects of different solvents were also examined and toluene was identified as the best solvent for the reaction. After several unsuccessful trials, some additives containing hydroxyl group were subjected to the reaction system. The results demonstrated that water could increase the yield efficiently. Furthermore, when adding 0.5 mL of water, the yield of product could increase to 89%. To our delight, the tribenzylamine was still obtained in 90% yield even in the absence of the palladium catalyst, this result illustrated that water played an important role in the reaction[23] and the water may act as a kind of catalyst to activate the aryboronic acids via coordination to boron atom.

Encouraged by the above promising results, we next performed this reaction in one pot manner starting from phenylboronic acid, dibenzylamine and paraformaldehyde without separation of the aminal. The yield of the resulted tribenzylamine achieved to 90%, which increased the practicality of the reaction process dramatically. To the best our knowledge, this is the first report that arylboronic acids could react with paraformaldehyde and secondary amines in the absence of catalyst.

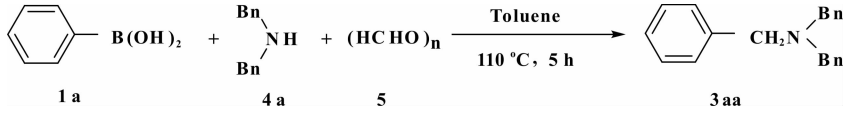
Table 1 Screening of reaction conditions[a]



1a　　2a　　3aa

Entry	Catalyst	Solvent	Additive	Yield/%[b]
1	$Pd(Xantphos)(CH_3CN)_2(OTf)_2$	toluene	–	26
2	$Pd(Xantphos)Cl_2$	toluene	–	34
3	$Pd(PPh_3)_2Cl_2$	toluene	–	29
4	$PdCl_2$	toluene	–	39
5	$Pd(OAc)_2$	toluene	–	32
6	$PdCl_2$	THF	–	28
7	$PdCl_2$	CH_3CN	–	27
8	$PdCl_2$	Dioxane	–	30
9	$PdCl_2$	CH_2Cl_2	–	26
10	$PdCl_2$	xylene	–	34
11	$PdCl_2$	benzene	–	37
12	$PdCl_2$	toluene	HCOOH	45
14	$PdCl_2$	toluene	CH_3COOH	35
15	$PdCl_2$	toluene	$TsOH\cdot H_2O$	35
16	$PdCl_2$	toluene	H_2O (2eq)	69[c]
17	$PdCl_2$	toluene	H_2O (0.5 mL)	89[c]
18	–	toluene	H_2O (0.5 mL)	90[c]

a. Reaction conditions: **1a** (0.8 mmol), **2a** (0.4 mmol), catalyst (0.02 mmol), additive (0.02 mmol) in solvent (2.0 mL), 12 h; b. Yields were determined by GC analysis relative to the aminal, with *n*-dodecane as internal standard; c. Isolated yields.



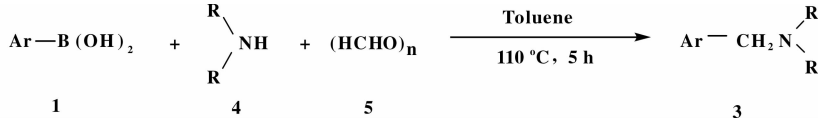
1a　　4a　　5　　3aa

Scheme 1 One pot three-component reaction

2.2 Substrate scope of phenylboronic acids and secondary amines

With this protocol in hand, we subsequently explored the substrates scope of the arylboronic acids and amines. As summarized in Table 2, in general, good to high yields are obtained with various arylboronic acids **1** (76% ~93% yields, entries 1-11). A series of arylboronic acids containing electron-donating or electron-withdrawing groups at the *orth*, *meta* or *para* position of the benzene ring could afford the desired products in good to excellent yields in five hours. In addition to substituted phenylboronic acid, the naphthyl-substituted boronic acids and heteroaryl-substituted boronic acid, such as 1-naphthylboronic acid, 2-naphthylboronic acid and 2-thiophenylboronic acid, are also compatible with this reaction, affording the corresponding tertiary amines in good yields. Next, the scope of the secondary amines was also explored (entries 12-15). For the electron-rich and electron-poor substituted dibenzylamines are converted the desired product smoothly, although longer reaction time is needed. Typical dialkyl amine such as di- butylamine was also successfully transformed into the corresponding product **3ad** in moderate yield. Moreover, the cyclic secondary amine was compatible with this reaction condition. For example, morpholine smoothly furnished the desired tertiary amine **3ae** in 60% yield.

Table 2 Substrates scope of the three-component reaction[a]



1 4 5 3

Entry	Ar	R	Product **3**	Yield/%[c]
1	C_6H_5	Bn	**3aa**	90
2	2-$CH_3C_6H_5$	Bn	**3ba**	77
3	3-$CH_3C_6H_5$	Bn	**3ca**	81
4	4-$CH_3C_6H_5$	Bn	**3da**	88
5	2-$CH_3OC_6H_5$	Bn	**3ea**	91
6	3-$CH_3OC_6H_5$	Bn	**3fa**	77
7	4-$CH_3OC_6H_5$	Bn	**3ga**	90
8	4-FC_6H_5	Bn	**3ha**	76
9	1-Naphthyl	Bn	**3ia**	81
10	2-Naphthyl	Bn	**3ja**	93
11	2-Thiophenyl	Bn	**3ka**	78
12	C_6H_5	2-MeBn	**3ab**	64[b]
13	C_6H_5	4-BrBn	**3ac**	75[b]
14	C_6H_5	^{n}Bu	**3ad**	63[b]
15	C_6H_5	Morpholine	**3ae**	60[b]

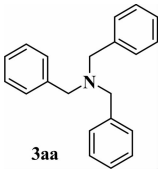
a. Reaction conditions: **1** (0.8 mmol), **4** (0.4 mmol) and **5** (0.5 mmol) in toluene (2 mL), 5 h;

b. Reaction conditions: **1** (0.8 mmol), **4** (0.4 mmol) and **5** (0.5 mmol) in toluene (2 mL), 9.5 h; c. Isolated yield

So far, the mechanism for this reaction has not been completely clear, but we believe the success of this three-component reaction might be resulted from water which generated by the condensation reaction between aldehyde and the secondary amines. Water could coordinate to the boron atom of the arylboronic acid and activate the arylboronic acid to facilitate the C-B bond cleavage.

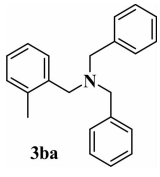
2.3 Experimental characterization data for products

The structures and purities of all of the products were confirmed by NMR and HRMS analyses. The data for the products have been listed below.



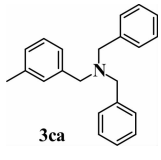
3aa

Tribenzylamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 6H), 7.20–7.24 (m, 3H), 7.30–7.33 (m, 6H), 7.40–7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.9, 126.9, 128.2, 128.7, 139.7.



3ba

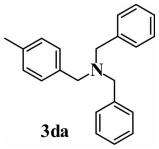
N, *N*-dibenzyl-1-*o*-tolylmethanamine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), .3.52 (s, 2H), 3.53 (s, 4H), 7.09–7.18 (m, 3H), 7.20–7.23 (m, 2H), 7.28–7.32 (m, 4H), 7.36–7.38 (m, 4H), 7.36–7.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 56.3, 58.4, 125.7, 126.8, 126.9, 128.2, 129.0, 129.6, 130.2, 137.2, 137.5, 139.6; HRMS (ESI) calcd for $C_{12}H_{24}N$ [M+H]: 302.1903, found: 302.1904.



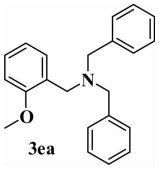
3ca

***N*, *N*-dibenzyl-1-*m*-tolylmethanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), .3.53 (s, 2H), 3.55 (s, 4H), 7.03–7.04 (m,1H), 7.21–

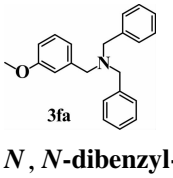
7.24 (m,5H), 7.30-7.33 (m,4H), 7.41-7.42 (m,4H); ^{13}C NMR (100 MHz,$CDCl_3$)δ21.6, 57.8, 125.9, 126.9,127.6,128.2,128.3,128.8,130.0, 137.8, 139.6, 139.8; HRMS (ESI) calcd for $C_{12}H_{24}N$[M+H]: 302.1903, found: 302.1909.



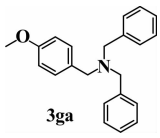
***N*,*N*-dibenzyl-1-*p*-tolylmethanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), .3.51 (s, 2H), 3.54 (s, 4H), 7.11-7.13 (m, 2H), 7.20-7.24 (m, 2H), 7.28-7.32 (m, 6H), 7.39-7.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 57.6, 57.8, 126.8, 128.2, 128.7, 128.8, 128.9, 136.4, 136.5, 139.7; HRMS (ESI) calcd for $C_{12}H_{24}N$[M+H]: 302.1903, found: 302.1917.



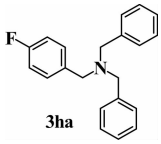
***N*,*N*-dibenzyl-1-(2-methoxyphenyl) methanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 4H), 3.61 (s, 2H), 3.75 (s, 3H), 6.79-6.80 (m, 1H), 6.81-6.97 (m, 1H), 7.15-7.20 (m, 3H); 7.26-7.31 (m, 4H), 7.41-7.42 (m, 4H), 7.60-7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ51.3, 55.3, 58.3, 110.3, 120.6, 126.8, 127.7, 127.8, 128.2, 128.7, 129.7, 140.1, 157.8; HRMS (ESI) calcd for $C_{12}H_{24}NO$[M+H]: 312.1852, found: 312.1850.



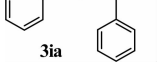
***N*,*N*-dibenzyl-1-(3-methoxyphenyl) methanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 2H), 3.54 (s, 4H), 3.78 (s, 3H), 6.74-6.76 (m, 1H), 6.99-7.00 (m, 2H) 7.20-7.21 (m, 3H), 7.27-7.31 (m, 4H), 7.38-7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 58.0, 58.1, 112.2, 114.4, 121.2 127.0, 128.3, 128.8, 129.3, 139.7, 141.5, 159.7; HRMS (ESI) calcd for $C_{12}H_{24}NO$[M+H]: 312.1852, found: 312.1856.



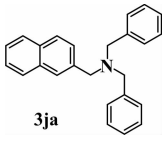
***N*,*N*-dibenzyl-1-(4-methoxyphenyl) methanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 2H), 3.53 (s, 4H), 3.77 (s, 3H), 6.83-6.86 (m, 2H), 7.19-7.23 (m, 2H) 7.28-7.32 (m, 6H), 7.38-7.40(m,4H); ^{13}C NMR(100 MHz,$CDCl_3$) δ 55.3, 57.2, 57.8, 113.7, 126.8, 128.3, 128.8, 130.0, 131.6, 139.8, 158.6; HRMS (ESI) calcd for $C_{12}H_{24}NO$[M+H]: 312.1852, found: 312.1843.



***N*,*N*-dibenzyl-1-(4-fluorophenyl) methanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (s, 2H), 3.55 (s, 4H), 7.14-7.16 (m, 2H), 7.21-7.25 (m, 2H), 7.30-7.34 (m, 4H), 7.38-7.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.1, 58.0, 120.8, 127.0, 128.3, 128.7, 129.9, 138.5, 139.3, ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.8; HRMS (ESI) calcd for $C_{21}H_{21}FN$ [M+H]: 306.1653, found: 306.1658.

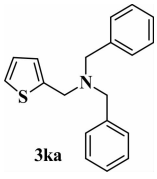


***N*, *N*-dibenzyl-1-(naphthalen-1-yl) methanamine**. ^{1}H NMR(400 MHz, $CDCl_3$) δ 3.49 (s, 4H), 3.88 (s, 2H), 7.11-7.15 (m, 2H), 7.19-7.23 (m, 4H), 7.27-7.32 (m, 4H), 7.33-7.36 (m, 3H), 7.49-7.50 (m, 1H), 7.62-7.64 (m, 1H), 7.70-7.72 (m, 1H), 8.00-8.02 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.8, 58.5, 124.9, 125.2, 125.5, 125.6, 127.0, 127.4, 127.8, 128.2, 128.4, 129.2, 132.5, 133.9 135.1 139.6; HRMS (ESI) calcd for $C_{25}H_{24}N$ [M+H]: 338.1903, found: 338.1889.



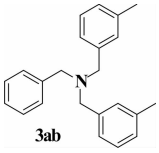
***N*, *N*-dibenzyl-1-(naphthalen-2-yl) methanamine.** ^{1}H NMR(400 MHz, $CDCl_3$) δ 3.59 (s, 4H), 3.70

(s, 2H), 7.20-7.25 (m, 2H), 7.30−7.34 (m, 4H), 7.42−7.47 (m, 6H), 7.58−7.60 (m, 1H), 7.80−7.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.0, 58.1, 125.4, 125.9, 126.9, 127.2, 127.3, 127.7, 127.9, 128.3, 128.8, 132.8, 133.4, 137.3, 139.6; HRMS (ESI) calcd for $C_{25}H_{24}N$ [M+H]: 338.1903, found: 338.1901.



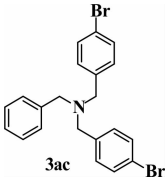
3ka

***N*, *N*-dibenzyl-1-(thiophen-2-yl) methanamine** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 4H), 3.77 (s, 2H), 6.90−6.94 (m, 2H), 7.22−7.25 (m, 3H), 7.30−7.34 (m, 4H), 7.43−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 57.6, 124.7, 125.5, 126.4, 127.0, 128.3, 128.7, 139.3, 143.3; HRMS (ESI) calcd for $C_{19}H_{20}NS$ [M + H]: 294.1311, found: 294.1306.



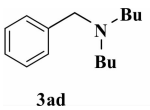
3ab

***N*-benzyl-*N*-(3-methylbenzyl)-1-m-tolylmethanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s,6H), 3.50 (s,4H), 3.53 (s,2H), 7.01 (s,2H), 7.17−7.20 (m, 7H), 7.27−7.29 (m, 2H), 7.37−7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 58.1, 125.9, 126.9, 127.7, 128.2, 128.3, 128.9, 129.6, 137.8, 139.7, 139.9; HRMS (ESI) calcd for $C_{23}H_{26}N$ [M+H]: 316.2060, found:316.2046.



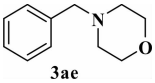
3ac

***N*-benzyl-*N*-(4-bromobenzyl)-1-(4-bromophenyl) methanamine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (s, 4H), 3.43 (s, 2H), 6.89 (m, 4H), 7.13−7.17(m, 1H),7.21−7.29(m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.1, 57.8, 115.0, 115.2, 127.1, 128.3, 128.7, 130.1, 130.2, 135.1, 139.3, 160.8, 163.2.



3ad

***N*-benzyl-*N*-butylbutan-1-amine**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, *J* = 14.6 Hz, 6H), 1.19 (q, *J* = 22.4 Hz, 4H), 1.33 (q, *J* = 22.8 Hz, 4H), 2.30 (t, *J* = 14.8 Hz, 4H), 3.46 (s, 2H), 7.18−7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 19.6, 28.2, 52.5, 57.6, 125.5, 127.0, 127.8, 139.3; HRMS (ESI) calcd for $C_{15}H_{26}N$[M+H]: 220.2060, found: 220.2056.



3ae

4-benzylmorpholine. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43−2.46 (m, 4H), 3.50 (s, 2H), 3.70 (t, *J* = 9.3 Hz, 4H), 7.23−7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9, 53.6, 63.5, 67.0, 127.2, 128.3, 129.2; HRMS (ESI) calcd for $C_{11}H_{16}NO$[M+H]: 178.1226, found: 178.1221.

3 Conclusions

In summary, we disclose an efficient PBM reaction conducted with arylboronic acids, paraformaldehyde and secondary amines, which establishes a practical and operational simple protocol to synthesize functional tertiary amines. This method is very simple and can be efficiently performed without catalyst, which displays a broad substrate scope and good functional group tolerance. This efficient method gives a supplement to the traditional PBM reaction to generate tertiary amines.

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水促进的三组分 PBM 反应合成三级胺

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摘要: 首次报道了甲醛衍生的胺缩醛和芳基硼酸在水的促进下, 可以在没有催化剂的条件下高效的合成三级胺. 在此基础上建立了一种利用多聚甲醛, 二级胺和芳基或杂环硼酸合成三级胺的高效合成方法. 此反应条件温和, 操作简单, 具有很好的底物适应性, 目标产物的收率最高可达 93%.

关键词: 芳基硼酸; 胺缩醛; 多聚甲醛; 取代三级胺; PBM 反应