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# Zinc-Catalyzed Alkylation of Aromatic Amines in Continuous Flow

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ABSTRACT: A practical approach to the synthesis of antioxidant 4,4'-dicumyldiphenylamine (DCDPA) and its derivatives by Friedel-Crafts alkylation of aromatic amines was developed under continuous-flow conditions. Because of the enhanced mass- and heat-transfer features of the microreactor, the reaction time was significantly reduced in contrast to a batch mode. The reaction was carried out by using co-solvent system (volume ratio of ethanol to Cl(CH<sub>2</sub>)<sub>2</sub>Cl is 1:6) with ZnCl<sub>2</sub> as the catalyst to achieve satisfied yields. It is an effective method for the synthesis of antioxidant DCDPA and its derivatives in excellent *para*-selectivity bearing the merits of saving reaction time, easily operation and straightforward scale-up.

KEYWORDS: 4,4'-dicumyldiphenylamine; alkylation; styrene; continuous flow

#### INTRODUCTION

Aromatic amines have been found widespread application in fine chemicals, pharmaceuticals, and organic functional materials.<sup>1</sup> The dialkylated diphenylamines are industrially important compounds as antioxidants and heat stabilizers, with high efficiency, non-toxic, colorless, odorless and other characteristics. Due to its high antioxidant activity and reduced tendency to discolor during heat aging, 4,4'-dicumyldiphenylamine was reported to be an ideal antioxidant for neoprene, acrylate material, synthetic lubricants, polyether polyols.<sup>2,3</sup> It is especially suitable for protecting natural rubber and synthetic rubber such as styrene butadiene, isoprene, chloroprene and butyl from aging caused by heat, light and ozone. Moreover, it has a good synergistic effect with sulfur-containing antioxidants and were easily dispersed in natural rubber, butadiene styrene rubber, neoprene and polyurethane.<sup>4,5</sup>

Recently, tremendous efforts have been devoted to synthesize aromatic amine derivatives. Catalytic Friedel-Crafts reaction of aromatic amines with alkenes is one of the most efficient and atom economic strategies to modify aromatic amine skeletons.<sup>6-15</sup> Regarding the synthesis of 4,4'-dicumyldiphenylamine, a number of available catalytic systems have been reported by using various catalysts.<sup>16-19</sup> Lately, Zhu and co-workers<sup>1</sup> reported using borate  $[Ph_3C][B(C_6F_5)_4]$  as a metal-free catalyst for hydroarylation of alkenes with primary, secondary, and tertiary aromatic amines (Table 1, entry 1). This method is applicable to a wide range of substrates, and affords mono-alkylated products with high *ortho*-regioselectivity. Chitnis<sup>2</sup> and Liu<sup>16</sup> developed new approaches to prepare 4,4'-dicumyldiphenylamine by using acid-treated clay and mesostructured aluminosilicate as the catalyst respectively (Table 1, entries 2 and 3). Moderate to excellent yields of 4.4'-dicumyldiphenylamine were obtained by using diphenylamine and  $\alpha$ methylstyrene as starting materials under different reaction conditions. Kostrab and co-workers<sup>17</sup> reported tert-butylation of diphenylamine with tert-butanol over H-BEA zeolite catalyst, which could be an alternative catalyst in industrial preparation of *tert*-butylated diphenylamines (Table 1, entry 4). Recently, Hu and co-workers<sup>18</sup> developed a new method for the hydroarylation reaction of  $\alpha$ -methylstyrene with N.N-diethylaniline with high para-selectivity in benzene by using Au(I)/pyrNHC as the catalyst (Table 1, entry 5). Although high conversions and good yields can be achieved in these previous methods, the dialkylated diphenylamines with high *para*-regioselectivity were still remain highly desired. Moreover, all of these synthetic methodologies were carried out in a batch reactor, and alkenes need to be fed slowly to prevent self-polymerization, which lead to much time consumption.

Table 1. Various methods for the functionalization of phenylamines in batch reactor

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-	En	Author	Catalyst	Solvent	Conditions	mole ratio of	Product	Yield	Ref
	try					amine/alkene		(%)	
_	1	Zhu	[Ph <sub>3</sub> C][B	PhCl	12 h, 60°C	1:2	H H H H H H H H H H H H H H H H H H H	38	1
	1		$(C_6F_5)_4]$						
		Chitnis	acid-	xylene	1.5 h, 90°C	1:2	Ph C N C	65	2
	2		treated						
			clay						
	2	Liu	aluminos	neat	24 h, 90°C	1:3	Ph C N C X	>90	16
	3		ilicate						
							→ <sup>H</sup> N		
	4	Kostrab	zeolite	<i>n</i> -	8 h, 180°C	1:4	$\times$	82	17
				neptane					
		Hu	Au(I)/pv	y benzen e	24 h, 135°C	1:4			
	5		rNHC				Ç	88	18
							≁ <sub>Ph</sub>		

Since the 21st century, the technology of chemical process intensification has been developed towards more efficient, fast, controllable, safe and environmentally friendly. Microreactor technology is becoming more popular among chemists for its large surface-to-volume ratio and excellent process intensification.<sup>20-21</sup> Due to the enhanced heat- and mass- transfer efficiency in microreactor, it brings many advantages such as improving safety of the process, accessing the extreme reaction conditions, excellent reproducibility, straightforward scale-up and automated operation.<sup>22-28</sup> As a result, microreactors are widely used in the academic, pharmaceutical and fine chemical production. Therefore, it is important to develop novel catalytic systems with low cost, high yield and selectivity in continuous flow.<sup>29-31</sup> Hence, we described a new approach for preparing 4,4'-dicumyldiphenylamine and its derivatives under continuous flow conditions.

**RESULTS AND DISCUSSION** 

First, the operation conditions were optimized in the batch reactor by exploring the effects of catalyst and solvent. 4,4'-dicumyldiphenylamine was chosen as the model product for optimization of the reaction parameters because of its wide use as an antioxidant in rubbers. We started our investigation by reacting diphenylamine 1a with  $\alpha$ -methylstyrene 2a in mole ratio of 1:2.4. The reaction was performed in the presence of 15.0 mol% catalyst at 160°C for 6 h in a sealed tube. Various commonly used acid catalysts were investigated, and the results were listed in Table 2. It was found that there was no or only trace of the desired product in the reaction mixture when  $SnCl_4$ ,  $H_2SO_4$ ,  $H_3PO_4$  and *p*-toluenesulfonic acid (TsOH) were selected as the catalyst (Table 2, entries 1-4). Self-polymerization of  $\alpha$ -methylstyrene was easily occurred when using SnCl<sub>4</sub> as the catalyst, which gave trace of the desired product. There was almost no conversion of diphenylamine in the presence of protonic acids (Table 2, entries 2-4). To our delight, good yields of 4,4'-dicumyldiphenylamine were obtained when using AlCl<sub>3</sub> and ZnCl<sub>2</sub> as the catalyst respectively (Table 2, entries 5 and 6). Meanwhile, the solvent effect was researched by screening toluene, chlorobenzene, fluorobenzene, xylenes, 1,4-dioxane, isopropyl ether, CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> and Cl(CH<sub>2</sub>)<sub>2</sub>Cl (Table 2, entries 6-14). Moderate to good yields ranging from 67% to 83% were given when using benzene compounds as the reaction solvent (Table 2, entries 6-9). Similarly, good yields were obtained when using chlorinated alkanes as the solvent (Table 2, entries 12-14). Unsatisfied yields were furnished when ether compounds were used as solvents (Table 2, entries 10 and 11).

**Table 2.** Optimization of reaction conditions in batch reactor<sup>a</sup>



Entry	Catalyst	Solvent	Yield $(\%)^b$
1	SnCl <sub>4</sub>	toluene	trace
2	$H_2SO_4$	toluene	-
3	$H_3PO_4$	toluene	-
4	TsOH	toluene	-
5	AlCl <sub>3</sub>	toluene	79
6	$ZnCl_2$	toluene	82
7	$ZnCl_2$	chlorobenzene	67
8	$ZnCl_2$	fluorobenzene	69
9	$ZnCl_2$	xylenes	83
10	$ZnCl_2$	1,4-dioxane	44
11	$ZnCl_2$	isopropyl ether	61
12	$ZnCl_2$	CHCl <sub>3</sub>	71
13	$ZnCl_2$	$CH_2Cl_2$	80
14	ZnCl <sub>2</sub>	Cl(CH <sub>2</sub> ) <sub>2</sub> Cl	84

<sup>a</sup> Reaction conditions: diphenylamine (1.0 mmol, 1.0 equiv), α-methylstyrene (2.4 mmol, 2.4 equiv), catalyst (15.0 mol%) and solvent (2.0 mL), stirred under air at 160°C for 6 h in a sealed tube. <sup>b</sup> Isolated yield.

To avoid self-polymerization of  $\alpha$ -methylstyrene and reduce the reaction time, we decided to perform this reaction in continuous flow. However, the optimal catalysts of AlCl<sub>3</sub> and ZnCl<sub>2</sub> exhibited poor solubility in benzene compounds and chlorinated alkanes. To overcome this problem, ethanol was chosen as auxiliary solvent because of its good solubility for AlCl<sub>3</sub> and

ZnCl<sub>2</sub>. As shown in Figure 1, co-solvent effect of ethanol in different solvent was investigated in the model reaction. The reaction between diphenylamine **1a** and  $\alpha$ -methylstyrene **2a** in mole ratio of 1:2.4 was performed in the presence of 15.0 mol% catalyst in 2.0 mL co-solvent at 160 °C for 6 h in a sealed tube. It should be noted that the desired product was not observed when using ethanol as the solvent. This result indicated that ethanol was detrimental to the alkylation of diphenylamine. Several solvents such as toluene, CH<sub>2</sub>Cl<sub>2</sub>, Cl(CH<sub>2</sub>)<sub>2</sub>Cl and xylenes were tested with ethanol in the volume ratio of 1:6. The highest yield of 4,4'-dicumyldiphenylamine was given when using Cl(CH<sub>2</sub>)<sub>2</sub>Cl and ethanol as the co-solvent. The second highest yield was obtained in the presence of xylenes with ethanol. In both of these two results, ZnCl<sub>2</sub> was used as the catalyst and provided the satisfactory yields. Because the co-solvent of DCE/EtOH exhibited better solubility for the catalyst, DCE/EtOH was utilized as the solvent to avoid any agglomeration in continuous flow. Therefore, it was decided to use ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl as the optimal co-solvent and ZnCl<sub>2</sub> as the catalyst in further studies.



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Figure 1. Optimization of co-solvent effect in batch reactor

Next, we examined the effect of the volume ratio of ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl on the product yield under the same reaction conditions. As the results listed in Figure 2, increasing the volume ratio of ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl from 1:2 to 1:8 resulted in the increasing yield of 4,4'dicumyldiphenylamine from 26% to 78%. Same yields were given when the volume ratios were 1:8 and 1:10. It is noteworthy that the solution containing catalyst and starting materials was a little clouding when the volume ratio of ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl was up to 1:8. Due to the poor solubility of ZnCl<sub>2</sub> in Cl(CH<sub>2</sub>)<sub>2</sub>Cl, increasing the percentage of Cl(CH<sub>2</sub>)<sub>2</sub>Cl in the co-solvent led to the catalyst dissolved incompletely. Obviously, the yield of the corresponding product in cosolvent (up to 78%) was lower than the reaction performed in the single solvent of Cl(CH<sub>2</sub>)<sub>2</sub>Cl (84%) because of the detrimental effect of ethanol.



Volume ratio of ethanol to Cl(CH2)2Cl

#### Figure 2. The effect of volume ratio for the reaction

With the optimal batch conditions in hand, we set out to explore the synthesis of 4,4<sup>2</sup>dicumyldiphenylamine in continuous flow. As shown in Figure 3, a continuous flow microreactor setup was assembled to study the reactivity of this catalytic system. The reactants were introduced into the microreactor (inner volume 25.0 mL) by using a plunger pump. A safety valve between the pump and the microreactor was used to release the extra pressure when the clog occurred in the microreactor. Another coiled stainless steel tube (inner volume 5.0 mL) was submerged into oil bath which maintained at 60 °C to cool the reaction mixture. And one 18.0 bar back pressure regulator (BPR) was attached at the end of flow system to avoid any gasification during the reaction process.



Figure 3. (a) General schematic for continuous flow setup; (b) Photograph of continuous flow setup.

Initially, the volume ratio of ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl was rescreened in the model reaction under continuous flow conditions. The starting materials of diphenylamine 1a and  $\alpha$ -methylstyrene 2a in mole ratio of 1:2.4 were dissolved in Cl(CH<sub>2</sub>)<sub>2</sub>Cl. 15.0 mol% ZnCl<sub>2</sub> was used as the catalyst and dissolved in ethanol. These two solutions were mixed in one round bottom flask for entering the flow system by the plunger pump. The residence time was 25 min when the flow rate was set as 1.0 mL/min. And the reaction temperature was set at 160 °C. Similarly, the highest yield was obtained when the volume ratio of ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl was 1:6 (Figure 4a). The yield of the corresponding product was decreased to 60% when the volume ratio was 1:8. The reason was the catalyst ZnCl<sub>2</sub> was not dissolved completely in co-solvent system. Thus, the amount of catalyst in the microreactor was less than 15.0 mol%. In addition, the yields of the desired product dropped significantly when the volume ratios were 1:10 and 1:12. Next, the effect of the reaction temperature was investigated by using ethanol/Cl(CH<sub>2</sub>)<sub>2</sub>Cl (1:6) as the solvent while keeping the residence time at 25 min. The yield of 4,4'-dicumyldiphenylamine was achieved up to 85% by increasing the reaction temperature to 185 °C (Figure 4b). However, the yield was reduced slightly when the reaction temperature was higher than 185 °C. Because the vapor pressure of cosolvent exceeded the threshold of BPR, leading to the gasification in the microreactor along with decreasing residence time. Meanwhile, self-polymerization of  $\alpha$ -methylstyrene raised in high reaction temperature also resulted in the lower yield of 4,4'-dicumyldiphenylamine. Therefore, 185 °C was chosen as the optimal reaction temperature. Furthermore, the residence time was investigated in the range of 10 to 35 min when the reaction temperature was 185 °C. The best result (87% yield) was obtained when increasing the residence time to 30 min (Figure 4c). Moreover, different catalyst loadings were screened to optimize the reaction conditions when the residence time was 30 min. 89% of the corresponding product was produced in the presence of

11.0 mol% and 13.0 mol%  $ZnCl_2$  (Figure 4d). Due to the long reaction time and high catalyst loading caused the self-polymerization of  $\alpha$ -methylstyrene, it was decided to choose 30 min and 11.0 mol%  $ZnCl_2$  as the optimal conditions in further studies.



Figure 4. Optimization of reaction conditions in continuous flow

After completion of the optimization study, we set out to explore the compatibility of alkylated aromatic amines and styrenes in this continuous flow system. Tertiary aromatic amine of *N*-methyl-*N*-phenylaniline **1b** was reacted with  $\alpha$ -methylstyrene **2a** in mole ratio of 1:2.4 in

continuous flow. And satisfied yield of the desired product was given in 30 min (Table 3, entry 2). Meanwhile, dialkyl substituted anilines were examined under the optimal flow conditions. The yield of the corresponding product was up to 80% when the substrate was N, N-dimethylaniline (Table 3, entry 3). Only 65% yield was obtained by ustilizeing N, N-diethylaniline as the substrate (Table 3, entry 4). It is worth noting that highly *para*-regioselectivity alkylation of the corresponding dialkyl substituted anilines was achieved in this continuous flow system. In addition, 1*H*-indene was utilized as styrene to explore the reactivity in this method. The desired product was obtained in 63% with excellent *para*-selectivity (Table 3, entry 5).







<sup>a</sup> Reaction conditions: aromatic amines (80.0 mmol, 1.0 equiv), styrenes (192.0 mmol, 2.4 equiv), ZnCl<sub>2</sub> (11.0 mol%) and co-solvent (20.0 mL ethanol and 120.0 mL 1,2-dichloroethane),
25.0 mL microreactor, at 185 °C for 30 min. <sup>b</sup> Isolated yield.

#### CONCLUSIONS

In summary, we have developed an efficient method for the preparation of 4,4'dicumyldiphenylamine (DCDPA) and its derivatives by Friedel-Crafts alkylation in continuous flow. The reaction was carried out by using co-solvent system (volume ratio of ethanol to Cl(CH<sub>2</sub>)<sub>2</sub>Cl is 1:6) in the presence of 11.0 mol% ZnCl<sub>2</sub> as the catalyst. Satisfied yields were achieved in 30 min at 185 °C. Compared with batch conditions, the reaction time was reduced significantly from 6 h to 30 min, the catalyst loading was reduced from 15.0 mol% to 11.0 mol%, the yield of DCDPA was up to 89%. Notably, excellent *para*-selectivities of the desired products were exhibited in this continuous flow system.

#### EXPERIMENTAL

All reagents and solvents were commercially available and used without any further purification. Unless otherwise noted, all reactions were run under air and the indicated reaction temperature was that of the oil bath. Purification of the reaction products was carried out by flash chromatography by using 100-200 mesh silica gel. The type of plunger pump was Sanotec MPF0102C. The maximum pressure of the pump was 20 bars. The connecters and back pressure regulator used in the system were purchased from X-Tec Fluid Technology Co., Ltd. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Bruker Ascend instrument at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in  $\delta$  (ppm) referenced to an internal TMS standard for <sup>1</sup>H NMR spectroscopy, CDCl<sub>3</sub> ( $\delta$  = 77.00) for <sup>13</sup>C NMR spectroscopy. The following abbreviations are used to explain multiplicities: s = singlet, d=doublet, t = triplet, q = quartet, hept = heptaplet, m = multiplet, and br = broad. High-resolution mass spectra (HRMS) were obtained with an Agilent mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Melting points were determined with a WRS-2 apparatus and were uncorrected.

2.1 Optimization studies for the synthesis of 4,4'-dicumyldiphenylamine in batch reactor

Diphenylamine (1.0 mmol, 1.0 equiv),  $\alpha$ -methylstyrene (2.4 mmol, 2.4 equiv), catalyst (15.0 mol%), and solvent (2.0 mL) were sequentially added to a 38.0 mL sealed tube (with a Teflon cap) equipped with a magnetic stir bar. The tube was capped and submerged into a pre-heated oil bath at the desired temperature. The reaction mixture was stirred for 6 h under air. Then, it was cooled to room temperature after the reaction was completed. The reaction mixture was diluted with EtOAc (10.0 mL) and washed with water 20.0 mL. The organic phase was separated and concentrated in vacuum. The resulting residue was purified by flash column chromatography by using EtOAc/*n*-hexane as the eluent to afford the product.

2.2 General procedure for the *para*-alkylation of aromatic amines with styrenes in continuous flow

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The reactants were introduced into a coiled stainless steel tube (ID = 1.0 mm) with an inner volume of 25.0 mL by using a plunger pump. This reaction tube was submerged into oil bath at the desired temperature. A safety valve was connected after the pump to release the extra pressure when the clog occurred in the microreactor. Another coiled stainless steel tube (ID = 1.0mm) with an inner volume of 5.0 mL was connected after the 25.0 mL microreactor to cool the reaction mixture. This tube was submerged into oil bath which maintained at 60 °C. And one 18.0 bar back pressure regulator (BPR) was attached at the end of flow system to avoid any gasification during the reaction process. The aromatic amines (80.0 mmol, 1.0 equiv) and styrenes (192.0 mmol, 2.4 equiv) were dissolved in 1.2-dichloroethane (120.0 mL). The catalyst (11.0 mol%) was dissolved in ethanol (20.0 mL). Then two solutions were mixed in one round bottom flask before entering the microreactor. The liquid flow rate of plunger pump was 0.83 mL/min, so the residence time in the microreactor was 30 min. The exiting reaction mixture in the first reaction period was discarded to ensure steady state data collection. Then, 25 mL reaction mixture was gathered in a round bottom flask. The reaction mixture was diluted with EtOAc (30.0 mL) and washed with water 50.0 mL. The organic phase was separated and concentrated in vacuum. The resulting residue was purified by flash column chromatography by using EtOAc/*n*-hexane as the eluent to afford the product.

#### ASSOCIATED CONTENT

#### Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

<sup>1</sup>H and <sup>13</sup>C NMR spectra for the products (PDF).

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#### Notes

The authors declare no competing finacial interest.

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