

## A Practical Synthesis of Asymmetric Biphenyl Tetracarboxylic Acid Dianhydride (a-BPDA) for Isomeric Polyimides

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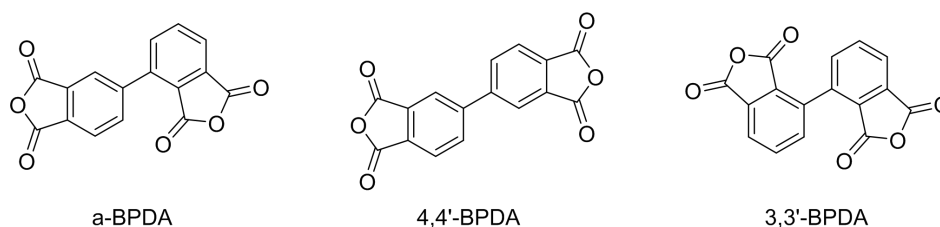
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**Abstract** Asymmetric biphenyl tetracarboxylic acid dianhydride (a-BPDA) is a monomer used in the production of isomeric polyimides. This paper presents a practical approach to synthesis of a-BPDA from halogenated xylenes. The synthesis is started with Ni-catalyzed cross coupling of 3/4-halo-1,2-xylene with Grignard reagent of 4/3-halo-1,2-xylene to give 2,3,3',4'-tetramethylbiphenyl, which is converted to biphenyl-2,3,3',4'-tetracarboxylic acid by Co/Mn-catalyzed oxidation in quantitative yield. Dehydration of the acid is completed in acetic acid anhydride to form a-BPDA. This route is easy to process in large scale with lower material cost and waste output in comparison with classic method involving reductive coupling of phthalate.

**Keywords:** biphenyl tetracarboxylic acid dianhydride, cross-coupling, tetramethyl biphenyl, catalytic oxidation, isomeric polyimide

### Introduction

Polyimides (PIs) have found a wide range of applications as advanced materials for their unique physical and mechanical properties. In the last half century, hundreds of PIs with different structure have been studied. However, one of most challenged to polymer community is the balance between higher service temperature and processability, the poor solubility of wholly aromatic PIs and costs. Recently, PIs based on isomeric dianhydrides or diamines, so-called isomeric PIs, have attracted much attention because of characteristic properties that are en route to solutions to the challenges.<sup>1</sup> For example, isomeric PIs from asymmetric biphenyl-2,3,3',4'-tetracarboxylic acid dianhydride (a-BPDA) usually exhibits higher solubility, lower  $\beta$ -transition, higher  $T_g$  and other difference in properties in comparison to PIs from most-common symmetric biphenyl-3,3',4,4'-tetracarboxylic acid dianhydride (4,4'-BPDA) (Scheme 1).<sup>2</sup> The mechanical properties (strength and modulus) of isomeric PIs from a-BPDA are comparable to or lower than those from 4,4'-BPDA, but isomeric PIs are of higher strength owing to higher conservation rate of mechanical properties.<sup>3</sup> What is most attractive property for isomeric PIs is lower melt viscosity that affords lower processing temperature and wide processing window.<sup>4</sup>



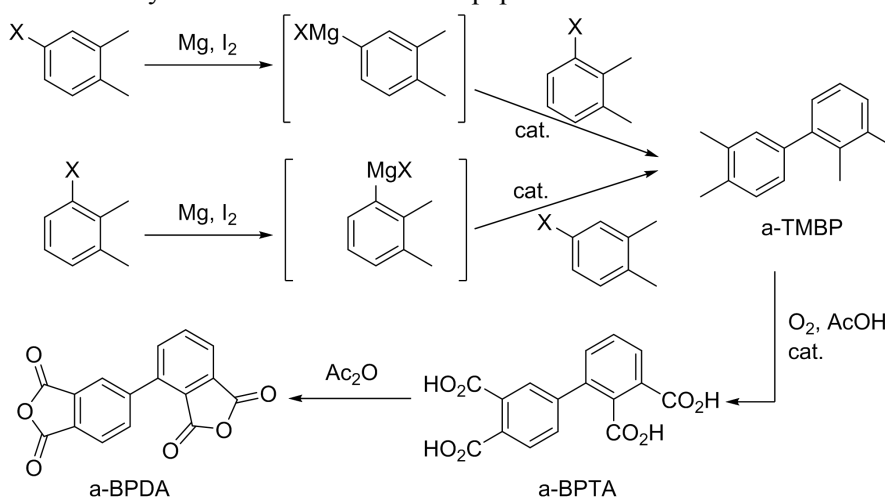
**Scheme 1**

Though isomeric PIs from a-BPDA are of promising high processability, lower cost-effectiveness in the synthesis of a-BPDA has been a barrier for large-scale production of PIs from the isomeric dianhydride. In oxidative coupling of dimethyl phthalate catalyzed by Pd salts, a mixture containing

tetramethyl esters of 4,4'-BPDA, biphenyl-2,2',3,3'-tetracarboxylic acid dianhydride (3,3'-BPDA) and a-BPDA was obtained, of which the ester of a-BPDA was a minor product as well as the ester of 3,3'-BPDA.<sup>5</sup> The esters can be converted to corresponding dianhydrides. A synthetic method via Ni-catalyzed reductive coupling started from a mixture of dimethyl 3-chlorophthalate and dimethyl 4-chlorophthalate also produce a mixture of three isomers of tetramethyl esters of BPDA, in which the content of a-BPDA ester is slightly more than any of two others.<sup>6</sup> The isolation of a-BPDA ester and conversion to a-BPDA is a tedious and energy-consuming (distillations) process.<sup>7</sup> Some recent developments on synthesis of BPDAs by our group and other group were started with Ni-catalyzed reductive coupling of one or a mixture of 4-chloro-1,2-xylene and 3-chloro-1,2-xylene to give one of symmetric isomers or three isomers of tetramethylbiphenyl, which were converted to biphenyl tetracarboxylic acids by oxidation under catalytic conditions or using quantitative oxidants.<sup>8</sup> With those considerations in hand, we have been focusing on development of synthesis of a-BPDA in higher efficiency, particularly practical, cost-effective and suitable for large-scale preparation. Here presents our primary results.

### Results and Discussions

We have designed a three-stage process started with catalytic coupling of halogenated xylenes and followed by catalytic oxidation and dehydration to dianhydride (Scheme 2). The first stage is based on Kumada cross-coupling of halogenated 1,2-xylenes to give 2,3,3',4'-tetramethylbiphenyl (a-TMBP).<sup>9</sup> Pd-catalyzed direct coupling of 1,2-xylene by C-H activation seems attractive, but the regioselectivity and yield of the reaction is too low to be applied.<sup>10</sup> Some reports have discussed homo-coupling of Grignard reagent of halogenated xylenes, in which equal quantitative amount of magnesium is used for the formation of Grignard reagents with 1,2-dihaloethane (DCE) or 1,3-dihalopropane as oxidant.<sup>11</sup> Two drawbacks for the homo-coupling are large reagent consuming and inapplicable for synthesis of asymmetric a-TMBP for poor regioselectivity. The second stage and the final stage are carried out in catalytic selective oxidation in liquid-phase and dehydration by acid-anhydride exchange.<sup>12</sup> Since the conditions of the last two stages are relative more mature than the first, we would like to make up more discussions on the synthesis of a-TMBP in this paper.

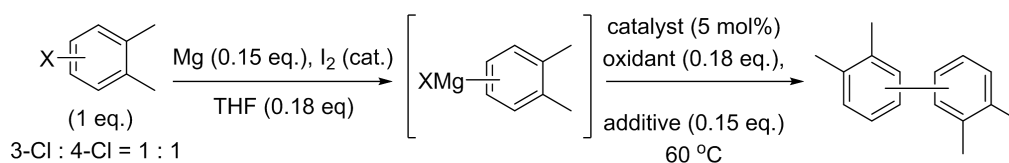


**Scheme 2**

Our initial attempts on Kumada cross-coupling are conducted under neat conditions in a mixture of 3-chloro-1,2-xylene and 4-chloro-1,2-xylene (50 : 50) to investigate regioselectivity controlled by catalysts, which produces a mixture of 3,3'-BPDA, 4,4'-BPDA and a-BPDA. The conversion of chlorinated 1,2-xylenes to Grignard reagent was carried out by addition of magnesium in 0.15

equivalent to chlorinated 1,2-xylenes in the presence of catalytic iodine and 0.18 equivalent of THF. The residual chlorinated 1,2-xylenes conserved initial molar ratio of two isomers, indicating no regioselectivity in the formation of magnesium reagents. Mn, Fe, and Ni salts were used as catalysts for promoting homo- or cross-coupling (Table 1). The reaction in the presence of 1,2-dichloroethane (DCE) is usually recognized as oxidative homo-coupling of Grignard reagents,<sup>11</sup> in which additives, particularly N,N,N',N'-tetramethylethyldiamine (TMEDA), are beneficial for higher proportion of a-TMBP (Table 1, entry 1-6). TMEDA significantly depressed the formation of 3,3'-TMBP, probably resulted from steric hindering on close of two molecules of 3-substituted Grignard reagent. The cross-coupling between Grignard reagents and chlorinated 1,2-xylenes is of higher efficiency for that one molecule of magnesium would produce one molecule of product in theory.<sup>9</sup> Ni-catalyzed reactions renders this advantage with yield up to 88% thanks to the introduction of TMEDA (Table 1, entry 7-10). The selectivity for the formation a-TMBP seems not tightly related to additives in current limited results from Ni-catalyzed coupling.

**Table 1.** Coupling of mixed chlorinated 1,2-xylenes under neat conditions



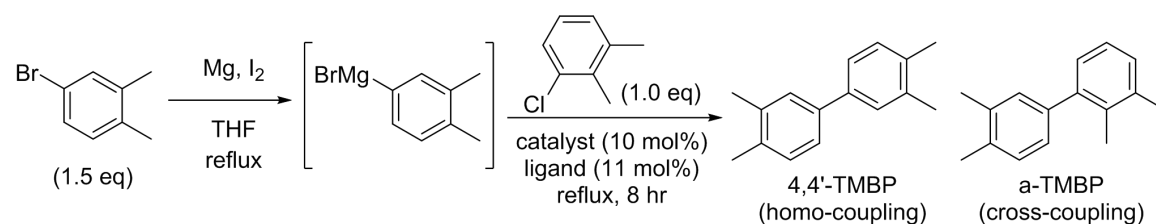
Entry	catalyst	oxidant	additive	Yield <sup>a</sup>	3,3'-TMBP : a-TMBP : 4,4'-TMBP <sup>b</sup>	selectivity <sup>c</sup>
1	MnCl <sub>2</sub>	DCE	-	71%	0.55 : 1 : 0.68	45%
2	MnCl <sub>2</sub>	DCE	DMG	50%	0.17 : 1 : 1.05	45%
3	MnCl <sub>2</sub>	DCE	TMEDA	42%	0.11 : 1 : 0.76	53%
4	FeCl <sub>3</sub>	DCE	-	65%	0.73 : 1 : 1.23	34%
5	FeCl <sub>3</sub>	DCE	DMG	67%	0.61 : 1 : 0.79	42%
6	FeCl <sub>3</sub>	DCE	TMEDA	73%	0.29 : 1 : 0.49	56%
7	NiCl <sub>2</sub>	-	-	66%	0.24 : 1 : 0.54	56%
8	NiCl <sub>2</sub>	-	DMG	65%	0.22 : 1 : 0.53	57%
9	NiCl <sub>2</sub>	-	TMEDA	88%	0.48 : 1 : 0.52	50%
10	Ni(acac) <sub>2</sub>	-	-	67%	0.31 : 1 : 0.60	52%

<sup>a</sup> Determined by GC; <sup>b</sup> Determined by GC; <sup>c</sup> Defined as a proportion of a-TMBP in all isomers of TMBPs. DCE = 1,2-dichloroethane, DMG = dimethyl glycol ether, TMEDA = N,N,N',N'-tetramethylethyldiamine, acac = acetyl acetone.

The Ni-catalyzed cross-coupling under neat conditions demonstrates good yield with selectivity more than 50%, following which separation of a-TMBP out of the product is next challenge. Most of 3,3'-TMBP and 4,4'-TMBP are able to be removed by iterative recrystallization. However, the method for purification usually leads to lower isolation yield with residual 3,3'-TMBP and 4,4'-TMBP in the product, which significant weakens the potential profits on lower cost (the price is very low for industrial mixture of two isomers of chlorinated 1,2-xylenes). Therefore, considering to advances in the cross-coupling, we move on to investigate Kumada cross-coupling between Grignard reagents and aryl chlorides. The primary optimizations for the synthesis of a-TMBP are based on

(3,4-dimethylphenyl)magnesium bromide and 3-chloro-1,2-xylene, in which a-TMBP is from cross-coupling while 4,4'-TMBP from homo-coupling (Table 2).

**Table 2.** Cross-coupling (3,4-dimethylphenyl)magnesium bromide with 3-chloro-1,2-xylene



Entry	catalyst <sup>a</sup>	ligand	conversion <sup>b</sup>	homo-coupling <sup>b</sup>	cross-coupling <sup>b</sup>	selectivity <sup>c</sup>
1	CoCl <sub>2</sub>	PPh <sub>3</sub>	68%	68%	0%	-
2	MnCl <sub>2</sub>	PPh <sub>3</sub>	0%	-	-	-
3	FeCl <sub>3</sub>	PPh <sub>3</sub>	54%	51%	3%	17:1
4	FeF <sub>3</sub>	PPh <sub>3</sub>	4.3%	-	-	-
5	Fe(acac) <sub>3</sub>	PPh <sub>3</sub>	56%	53%	3%	17:1
6	Fe(acac) <sub>3</sub>	TMEDA	67%	64%	3%	21:1
7	NiCl <sub>2</sub>	PPh <sub>3</sub>	99%	27%	62%	1:2.3
8	NiCl <sub>2</sub>	-	73%	40%	33%	1: 0.8
9	Ni(acac) <sub>2</sub>	PPh <sub>3</sub>	73%	23%	50%	1:2.2
10	NiF <sub>2</sub>	PPh <sub>3</sub>	98%	6%	92%	1:15
11	NiF <sub>2</sub>	-	42%	14%	29%	2.1:1
12	NiF <sub>2</sub>	dppe	36%	36%	0%	-
13	NiF <sub>2</sub>	PCy <sub>3</sub>	12%	8.0%	4%	2: 1
14	NiF <sub>2</sub>	TMEDA	27%	19%	8%	2.3: 1
15	NiF <sub>2</sub>	BDMAE	27%	17%	10%	1.7 : 1

<sup>a</sup> Catalyst loadings not optimized; <sup>b</sup> Determined by GC, calculated based on 4-bromo-1,2-xylene; <sup>c</sup> Defined as ratio of homo-coupling to cross-coupling. PPh<sub>3</sub> = triphenylphosphine, acac = acetyl acetone, TMEDA = N,N,N',N'-tetramethylethyldiamine, dppe = 1,2-(diphenylphosphino)ethane, PCy<sub>3</sub> = tricyclohexylphosphine, BDMAE = 2,2'-bis(dimethylamino)ethyl ether.

Common metal salts and ligands that are easy to access are evaluated on catalysis in Kumada cross-coupling for the synthesis of a-TMBP. We find that Co, Fe, and Ni are effective for triggering the coupling. However, there is sole product from homo-coupling of Grignard reagent on using CoCl<sub>2</sub> as catalyst with triphenylphosphine (PPh<sub>3</sub>) as ligand (Table 2, entry 1). MnCl<sub>2</sub> does not promote the coupling (Table 2, entry 2). Iron(III)-catalyzed conversions toward homo-coupling of Grignard reagent are predominated over cross-coupling (Table 2, entry 3-6), of which FeF<sub>3</sub> is not as effective in yield and selectivity as literature.<sup>13</sup> The presence of TMEDA as ligand give higher yield as well as selectivity to homo-coupling (Table 2, entry 6). Good to excellent results are obtained from Ni(II)-catalyzed couplings on yield and cross-coupling selectivity. The reaction catalyzed by

NiCl<sub>2</sub>-PPh<sub>3</sub> gives yield 99% and selectivity on cross-coupling with 2.3 times over homo-coupling, in which PPh<sub>3</sub> is crucial for high yield and selectivity (Table 2, entry 7, 8). Ni(acac)<sub>2</sub> demonstrates similar selectivity but lower yield (Table 2, entry 9). An exciting result comes from NiF<sub>2</sub>-catalyzed coupling (Table 2, entry 10), which produces the product in yield 98% and excellent selectivity on cross-coupling with 15 times to homo-coupling. However, in absence of PPh<sub>3</sub>, the reaction displays yield only 42% and poor selectivity (Table 2, entry 11), suggesting vital importance of PPh<sub>3</sub> in manipulating conversion and selectivity. Other ligands including 1,2-(diphenylphosphino)ethane (dppe), tricyclohexylphosphine (PCy<sub>3</sub>), TMEDA, and 2,2'-bis(dimethylamino)ethyl ether (BDMAE) show poor results in facilitating NiF<sub>2</sub>-catalyzed couplings (Table 2, entry 12-15). The yield and selectivity of the cross-coupling catalyzed by Ni(II) salts are tightly dependent on anion and ligand.

The selective oxidation of a-TMBP in liquid-phase catalyzed by Co/Mn/Br combination is most potential due to its lower reagent consuming, less wastes, clean, and easy to process. In a suitable Ti-autoclave (anti-corrosion in acidic oxidative environment), a-TMBP and a combination of catalysts (Co 1 mol%, Mn 0.5 mol%, Br 0.5 mol%) in acetic acid is stirred and heated under air or oxygen diluted with nitrogen to give biphenyl-2,3,3',4'-tetracarboxylic acid (a-BPTA) in yield up to 86% (Scheme 2). No methyl groups are detected in <sup>1</sup>H NMR spectra of the crude product, indicating completion of the catalytic oxidation. Trace of decarboxylated a-BPTA can be found in the crude product. Dehydration of a-BPTA is then performed by heating in acetic acid anhydride to give desired a-BPDA in quantitative yield. High pure a-BPDA suitable for preparation of isomeric PIs is obtained from further purification by sublimation.

### Summary

We present here a practical synthesis of a-BPDA, a key dianhydride for isomeric polyimides. The synthetic approach starts with catalytic Kumada cross-coupling of Grignard reagent of one isomer and another isomer of halogenated 1,2-xylenes. The conditions of cross-coupling are investigated on solvents, additives and catalyst combination. Aerobic oxidation in liquid-phase is carried out under catalysis by Co/Mn/Br system to give a-BPTA that is converted to dianhydride by heating in acetic acid anhydride. The synthesis is easy to process in large scale with lower material cost and waste output in comparison with classic isolation-based methods.<sup>7, 14</sup> Further researches on high selectivity in coupling from a mixture of chlorinated 1,2-xylenes are more valuable and in progress.

### Experiments

All reagents are commercial available. GC analysis is performed on Shimadzu GC2010 with XXX column, and peaks in GC spectra are determined by comparison with authentic samples. NMR measurements are conducted on Bruker DPX-400 400 MHz with CDCl<sub>3</sub> or DMSO-*d*<sub>6</sub> as solvent and TMS as internal standard. Structures of both TMBPs and BPDA are confirmed by <sup>1</sup>H NMR by comparison with authentic samples. Followings are typical experiments.

Coupling under neat conditions: To a three-necked flask under nitrogen, was added magnesium turnings (0.37 g, 15.4 mmol), 4-chloro-1,2-xylene (5 mL) and 3-chloro-1,2-xylene (5 mL), iodine (10 mg, 3.6 × 10<sup>-3</sup> mmol) and THF (1.41 mL, 17.4 mmol) at room temperature. The suspension was then stirred and heated to 110 °C for 8-10 hours when magnesium is completely consumed. After cooling to 60 °C, NiCl<sub>2</sub> (99.7 mg, 0.77 mmol) was introduced into the reaction mixture and stirred for another 12 hours. After quenched with saturated aqueous ammonium chloride, organic layer was separated out for GC analysis. Total yield of three TMBPs were 66%, and molar ratio of 3,3'-TMBP, a-TMBP and 4,4'-TMBP was 0.24 : 1 : 0.54.

Cross-coupling of 3-chloro-1,2-xylene with 4-bromo-1,2-xylene: To a three-necked flask under

nitrogen, was added magnesium turnings (0.29 g, 12.0 mmol), 4-bromo-1,2-xylene (1.85 g, 10.0 mmol) and THF (8 mL) at room temperature. The suspension was then heated to slightly reflux till to disappearance of magnesium when Grignard reagent was formed. In another three-necked flask under nitrogen, was added NiCl<sub>2</sub> (90 mg, 0.7 mmol), triphenylphosphine (0.204 g, 0.72 mmol) and THF (2 mL). The mixture was stirred for 30 minutes to form catalysts, to which was added 3-chloro-1,2-xylene (0.982 g, 6.7 mmol) and the Grignard reagent solution. The reaction suspension was then heated to reflux for 8 hours and poured into saturated aqueous ammonium chloride (10 mL). Organic layer was separated out and aqueous phase was extracted with ethyl acetate. The combined organic layer was dried with magnesium sulfate followed by removal of solvents by evaporator. The crude product containing a-TMBP and 4,4'-TMBP was obtained in yield of 99% by GC analysis. Further crystallization of the crude to give desired isomer in yield of 53%.

Oxidation and dehydration: (*Cautious: Conditions for oxidation is corrosive and dangerous, it is responsibility of researchers who implement the experiment for safeguard*) In a Ti-autoclave, was added a-TMBP (21.03 g, 0.10 mol), cobalt acetate (0.177 g, 1.0 mmol), manganese(II) acetate (0.086 g, 0.5 mmol), sodium bromide (0.051 g, 0.5 mmol) and acetic acid (100 mL). The autoclave was sealed after introduction of air to have the pressure at 0.5 MPa. The reaction system was heated to above 100 °C and kept at the temperature for 6 hours. After cooling to room temperature and disposing of pressure, the resulted mixture was poured into 10% aqueous hydrochloride and standing for 24 hours. The precipitates were collected by filtration and dried in vacuo at 60 °C to give crude a-BPTA, which was dissolved in acetic acid anhydride (100 mL) and heated for 12 hours. Most of volatiles were removed in vacuo, and toluene was added to the residual syrup. The precipitates were collected to give a-BPDA in yield of 86%.

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