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# The Oxidative Coupling of Methyl Benzoate

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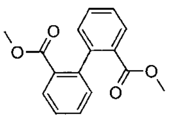
**The reaction of methyl benzoate (MBA) with pressurized (50 atm) artificial air (50 mol% $O_2$–$N_2$ mixture) at 150–200°C over a soluble palladium catalyst [$PdLL'_2$] ($L$ = phen, bipy, dppe; $L'$ = OAc, TFA) afforded isomeric dimethyl bibenzoic acid esters (DMBBA). Different factors affect the reactivity and regioselectivity of the process. The reactivity is enhanced by trifluoromethanesulfonic acid, arguably by activating the C–H bond of the aromatic ring by its protonation. The increase of temperature not only increases the reaction rate ($E_A = 5.5$ kcal/mol) but also favors a formation of an ortho-coupled product. Ligands with strong trans influence ($L$ = phen, bipy, or dppe) direct the oxidative coupling away from 2,$X'$-isomers ($X$ = 2, 3, or 4). Overall, electronic properties of a palladium catalyst are more important than steric restriction of the same catalyst for altering the activity and regioselectivity for MBA coupling.**

*Key Words:* **oxidative coupling; methyl benzoate; palladium; trifluoromethanesulfonic acid; triflic acid; 1,10-phenanthroline; C–H activation.**

## INTRODUCTION

The properties of some polymers may be changed in a systematic way to enhance, for example, their melt index and gas permeability. The effects of stereoregularity in improving the crystallinity and therefore thermal and mechanical properties are well established (1). One way of changing stereoregularity in polymers is to form a co-polymer with a monomer that introduces either randomness or regularity into the polymer chains. A comparison of symmetry patterns in polyesters was presented in the work (2) where the effect of stereoregularity upon the melting properties of polyethylenebibenzoate was discussed. For example, poly(ethylene-4,4′-bibenzoate), poly(ethylene-3,3′-bibenzoate), and poly(ethylene-2,2′-bibenzoate) are characterized by melting temperatures of 356, 156, and 132°C, respectively. In addition, when 4,4′-bibenzoic acid is incorporated as a co-polymer, it tends to produce highly crystalline or liquid-crystalline polymers, while use of the 3,4′-isomer produces relatively high-temperature amorphous materials (3). Molecular modelling studies, using MSI molecular mechanics software, of the homologous series of PET co-polyesters modified by 50 mol% bibenzoic acids predicted that the 2,$X'$ bibenzoates would possess the lowest molecular densities and lowest thermal properties, followed by the 3,3′ isomer and then the 3,4′ and 4,4′ isomers (4). In the present work, we report on our efforts to synthesize 3,4′- and 4,4′-dimethyl bibenzoic acid esters (DMBBA) monomers beginning with MBA.

Different pathways are known to produce DMBBA's. The direct esterification of biphenyl-4,4′-dicarcarboxylic (bibenzoic) acid by methanol (5) is maybe the oldest and simplest reaction, but it employs relatively expensive and not freely available bibenzoic acids. Other synthesis methods include the coupling of substrates over a transition metal catalyst. Iodo- (6–8), bromo- (9-11), or chlorobenzoic (12, 13) acid methyl esters produce DMBBA over Cu or Ni catalysts. Complexes [$Ni(PPh_3)_2Cl_2$] and [$Ni(dppe)Cl_2$] catalyze coupling of substituted benzoic acid methyl esters $R$–$C_6H_5COOMe$, where $R$ is trifluoromethanesulfonate, methanesulfonate, etc. (14–17). Azo derivatives (prepared *in situ* or before synthesis) of benzoic acid ester also have been used for preparation of DMBBAs over a copper catalyst (18–20). These methods, although straightforward, often lead to a mixture of byproducts that are difficult to separate and require a specific starting material.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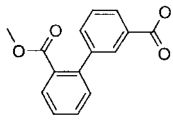
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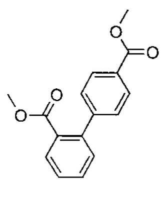
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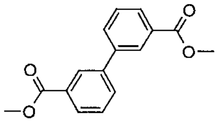
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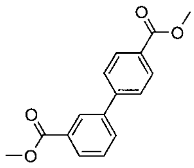
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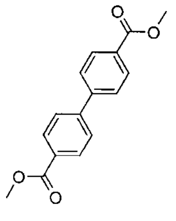
4,4′-DMBBA

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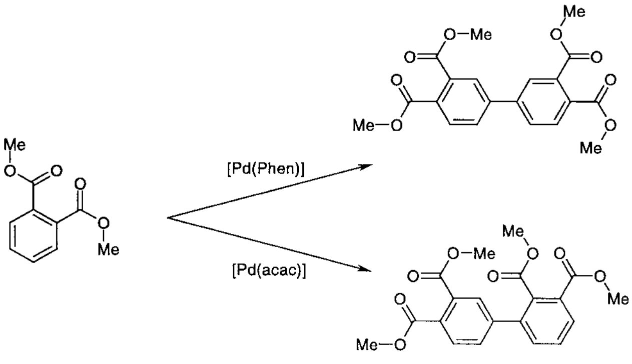
Van Helden and Verberg (21) have reported the oxidative coupling of benzene over palladium chloride and sodium acetate in acetic acid media giving rise to the biphenyl. Davidson and Triggs (22–25) reported the catalytic coupling of benzene derivatives by $Pd(CH_3COO)_2$ and $Pt(CH_3COO)_2$. This reaction is made catalytic by the presence of pressurized oxygen or other oxidants. Itatani and Yoshimoto (26) have shown that palladium-catalyzed coupling reactions in aromatic systems under oxygen pressure produced greatly enhanced yields. Attempts have been made to increase the performance of the catalytic system by studying the effect of additives. Iataaki and Yoshimoto (27) found that acetylacetone (Hacac) improved the reactivity of $Pd(CH_3COO)_2$ when present in equimolar amounts. The concentration of the catalyst as well as the pressure of oxygen play important roles in the coupling reaction (28). Yields and isomer distribution of coupled alkylbenzenes were attributed to the reaction variables such as temperature, additives, and the nature of the substitutes on a benzene ring (29). It was observed that the yield of ortho-substituted bitolyls increased with increasing temperature. Different oxidants were used to promote the oxidative coupling of aromatics on palladium; among them were sodium peroxydisulphate $Na_2S_2O_8$ (30) and thallium trifluoroacetate (31).



Eq. 1

Coupling of a substrate that is closely related to our study—dimethyl phthalate—has been reported (32, 33). It has been shown that 1,10-phenanthroline (phen) favors the regioselectivity to 3,4,3′,4′-tetramethylbiphenyltetracarboxylate when used in equimolar amounts with $Pd(CH_3COO)_2$. On the other hand, the 2,3,3′,4′-isomer was mainly formed with the Pd(II)/Cu(II)/Hacac system (Eq. [1]). Enhanced turnovers were obtained when the reaction was conducted by stepwise addition of the catalyst during the reaction.

These results suggested that the combined effects of electronic and steric might be operative to determine the distribution of isomers among the coupled products. In the followings, we examine in separate studies the effects upon reactivity and regioselectivity for changing the ligand size and the substituent groups on the ligands that coordinate to the Pd(II) ion.

## METHODS

MBA (99%), toluene (99.8%), palladium acetate, palladium acetylacetonate, and all ligands were purchased from Aldrich and used without further purification. $[Pd(phen)(OAc)_2]$ and $[Pd(phen)(TFA)_2]$ were prepared according to published procedures (34). Triflic acid (99 mol%) was purchased from Alfa-Aesar and used without further purification. Deuterated triflic acid (98 atom% deuterium incorporation) was obtained from Aldrich. Artificial air (50 mol% $O_2$) was purchased from Matheson.

Validation of GC-MS analytical pattern and identification of isomers was performed by direct comparison of their retention times (RTs) with the RT of pure DMBBAs. Dimethyl 4,4′-biphenyldicarboxylate (4,4′-DMBBA) was purchased from Aldrich. The other isomers were synthesized using known methods (35).

Some reactions were completed according to protocol 1 in a stainless steel 50-ml autoclave lined with Hastelloy-C276 (Autoclave Engineers, Erie, PA). A custom control unit fabricated by Autoclave Engineers controlled the reactor temperature. Samples were withdrawn from the unit through a diptube affixed to the reactor. Other reactions were completed according to protocol 2 under atmospheric pressure of air in a glass reactor (Ace Glass, four-neck reactor affixed with three standard taper joints, 240-ml volume). All samples were mixed with an internal standard (20–200 $\mu$l per 0.75 ml of internal standard and 1 ml of acetone) and analyzed on a HP 5890 Series II GC/HP 5972 MS. The internal standard was prepared by combining 200 $\mu$l of tridecane with 99.8 ml of hexane/acetone (50 vol% each). The partitioning agent was a Supelco SPB-5 column (30 m × 0.25 mm × 0.5 $\mu$m).

The reaction protocol 1 was as follows for the tests at elevated pressure. A desired amount of substrate (200–300 mmol) was added to the reactor at room temperature along with palladium acetate (0.3–0.5 mmol). The needed amount of ligand was added at this time, usually in equimolar amounts, to the Pd source. The reactor was pressurized with artificial air (50 mol% $O_2$) to a total pressure of 50 atm. The reactor heater was engaged and zero time for the reaction was determined when the temperature of the reactor achieved the setpoint (ca. 10 min after switching a heater on). The duration of the reaction was varied between 1 and 24 h. For protocol 2 the reactor pressure was 1 atm. The amount of substrate was 150–200 mmol and the amount of Pd ion was 0.1–0.2 mmol with equimolar amounts of the ligand. The reaction temperature was from room temperature to 150°C. Reaction times were 1–6 h.

Mass spectrometry of the deuterated products were completed on a VG Instruments mass spectrometer 70 SE. The products of the exchange experiments were examined for $^1$H-NMR in a Bruker 300-MHz instrument after being diluted in deuterated acetone.

## RESULTS

The coupling was completed at the reaction conditions described in protocol 1 with MBA as the substrate and for a reaction time of 4 h at 150°C. The turnover frequency (TOF), measured at 4-h reaction time, was $20 \pm 1$ 1/h and shows that the activity is similar to that reported previously (29). No isomer distribution data have been reported in the literature for MBA coupling.

*Effect of temperature.* Data of TOF were plotted versus reciprocal temperature on a semi-log plot to determine the activation energy. These data suggested that the activation energy for this reaction is 5.5 kcal/mol. Changing the reaction temperature can alter the regioselectivity; the 2,3′-, and 2,4′-DMBBA isomers appear to be favored by high reaction temperatures (Table 1).

*Effect of changing synthesis method.* The oxidative coupling of MBA has been carried out on $[\mathrm{Pd}LL'_2]$ complexes, prepared either in a preliminary step ($L = \mathrm{Phen}$, $L' = \mathrm{OAc}$, TFA) or in the reaction pot. The reaction conditions were as described according to protocol 1. No differences were found in the reactivity and regioselectivity between those two approaches.

*Effect of changing ligand.* The choice of ligands for $L$ included oxygen-containing ligands, such as acetylacetonate (acac), nitrogen-containing ligands, such as 2,2′-bipyridil (bipy) or phen, or phosphorus-containing ligands such as bis(diphenylphosphino)ethane (dppe). The ligands, $L'$, were either acetate, trifluoroacetate, or acetylacetonate ion. Reaction protocol 1 was used at a temperature of 150°C and for reaction times of 4 h. For $L = \mathrm{acac}$, phen, the regioselectivity was not a function of time for reaction times <4 h; however, for $L = \mathrm{dppe}$, the amount of $2,X'$-species was increased with time relative to the other isomers.

As might be seen from Table 2, the type of ligand that is coordinated to the Pd ion influences the activity and the regioselectivity of the reaction. These results prompted us to study the catalysis using the O- and N-containing ligands in more detail.

**TABLE 1**

**Effect of Reaction Temperature**

| | | Selectivity towards given DMBBA isomer, % | | | | | |
|---|---|---|---|---|---|---|---|
| Temp., °C | TOF,[a] 1/h | 2,2′- | 2,3′- | 2,4′- | 3,3′- | 3,4′- | 4,4′- |
| 100 | 9 | 1 | 23 | 10 | 35 | 26 | 5 |
| 150 | $20.0 \pm 1$ | 1 | 58 | 26 | 8 | 6 | 2 |
| 200 | 44 | 3 | 67 | 27 | 2 | 1 | 0.1 |

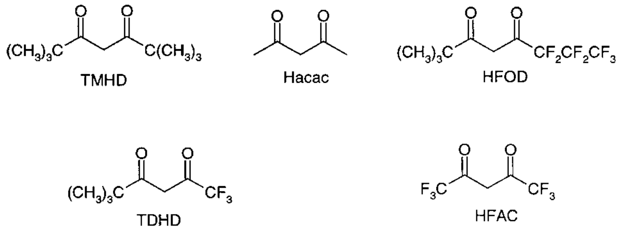
[a] Turnover frequency measured at 4-h reaction time.

**TABLE 2**

**Effect of Ligand upon the Activity and Regioselectivity**

| | | Selectivity towards given DMBBA isomer, % | | | | | |
|---|---|---|---|---|---|---|---|
| *L* | TOF, 1/h | 2,2′- | 2,3′- | 2,4′- | 3,3′- | 3,4′- | 4,4′- |
| acac | $20.0 \pm 1$ | 1 | 58 | 26 | 8 | 6 | 2 |
| phen | 1.4 | 0.3 | 15 | 7 | 18 | 38 | 21 |
| bipy | 1.9 | 2 | 54 | 17 | 13 | 12 | 2 |

*O-containing ligands.* Different $\beta$-diketones were used as O-containing ligands:



Tetramethylheptanedione (TMHD), 2,4-pentanedione (acetylacetone), 2,2′-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione (HFOD), trifluorodimethylhexanedione (TDHD), and hexafluoroacetylacetone (HFAC) were the obvious choices as ligands because they are offer a systematic change in the electronic properties while all coordinate to the Pd(II) through oxygen atoms. These reactions were completed at 150°C (protocol 1) using 0.5 mmol of $\mathrm{Pd}^{2+}$ and 330 mmol of substrate for 4 h. The data, Fig. 1, show a distribution of all six isomers. The 2,2′-isomer was formed

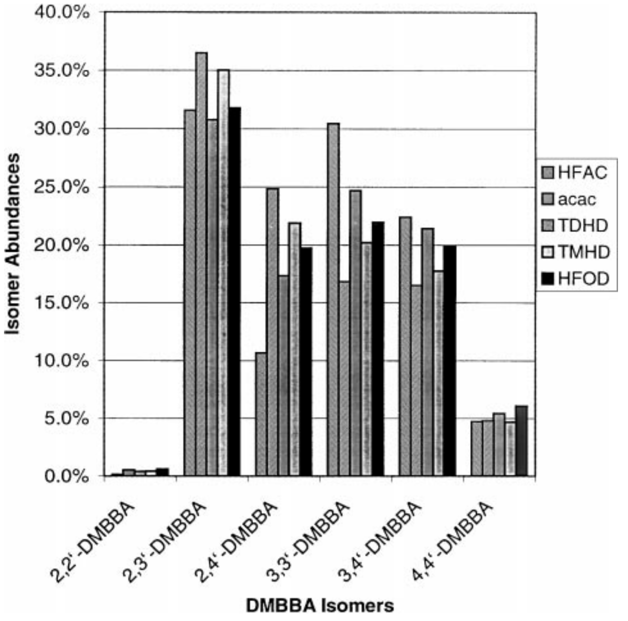


**FIG. 1.** O-containing ligand effect on the isomer distribution of MBA coupling.

only in very small quantities (0.1–0.5%), probably due to steric hindrance. The 4,4′-DMBBA showed an isomer yield of 4.0–6.1%. By far the most abundant product was 2,3′-DMBBA (up to 39.7%) together with 2,4′-, 3,4′-, and 3,3′-DMBBAs (11–26%, 15–22%, and 15–31%, respectively). The presence of electron-donating or electron-withdrawing substituents did not influence much the regioselectivity of the process.

We observed, however, a strong effect of the ligand environment upon the reactivity of the catalyst in the TOF, measured at 4-h reaction time. The TOF for $L =$ acac was $20 \pm 1$ and this system will be used as the base case for comparing the effects of electron-donating and -withdrawing effects.

The smallest turnover frequencies, TOFs were observed for $L =$ HFAC (16.1), whereas larger TOFs were observed for $L =$ TDHD (24), TMHD (26.1), and HFOD (30.3). These data show a mixed response of TOF to changing electron density to the acac ring. For example, the reactivity of the Pd catalysts is not a simple function of the number of F atoms in the ligand: the highest reactivity was observed for the ligand having 7 F atoms (HFOD), whereas the lowest reactivity was observed for the ligand having 6 F atoms (HFAC). Moreover, it appears that improved reactivity may also be realized when electron density is added to the ring by replacing Hs with –$CH_3$ groups (TMHD), even when Fs replace some of the Hs (TDHD). Data for these runs were repeated to ensure the accuracy of the results.

*Effects of acidity.* Our earlier results showed that triflic acid (HOTf) and $Pd^{2+}$ ion were effective catalysts for coupling toluene at room temperature (38). These data showed a combined selectivity of 3,4′- and 4,4′-dmbp of 80–95% when the reaction was completed at room temperature in the absence of pressurized oxygen. In the present work, we re-examined the effect of strong acidity on the catalysis of MBA coupling by combining 2 mmol of HOTf with 0.3 mmol each of $Pd(CH_3COO)_2$ and $Cu(CH_3COO)_2$ with 201 mmol of MBA at 80°C using air at 1 atm as the oxidant. The copper salt was added to ensure the reoxidation of palladium under low oxygen pressure. After 8 h the conversion was 2% (6.7 mol of dimer/mol of Pd, 0.8 mol of dimer/mol of Pd h). The product distribution showed only 2,2′-DMBBA and 2,3′-DMBBA. The major product was 2,2′-DMBBA (73%) after 3 h and this distribution decreased to 62% after 8 h. The hydrolysis product of methylbenzoate was found in low yields at 80°C and the yield of benzoic acid increased dramatically as the reaction temperature was increased to 150°C. This experiment was repeated with acac as the ligand in place of acetate. All other reaction conditions were the same. The conversion was lower (1%) after 8 h but the isomer selectivity was shifted to favor the 2,2′-DMBBA ester (88%) with the balance as the 2,3′-DMBBA ester. The last experiment was stoichiometric (in the absence of Cu(II) salt and under Ar), and acetic anhydride (2 mmol) was employed in addition to HOTf. Acetic anhydride could effectively tie up the by-product water formed during the oxidation and thereby maintain the acidity of the system. The selectivity to the 2,2′-DMBBA was 10%, whereas the selectivity to 2,3′-DMBBA was 90%. More study is needed to understand this change of reaction selectivity.

In a separate experiment, we combined 330 mmol of substrate with 5.5 mmol of $Pd(CH_3COO)_2$ and 5.5 mmol of HOTf at 65°C (protocol 1). The reaction was continued for 4 h to achieve a substrate conversion of 5%. A distribution of isomers was observed as follows: 2,2′- (0.8%), 2,3′- (33.3%), 2,4′- (21.6%), 3,3′- (19.2%), 3,4′- (18.7%), and 4,4′-DMBBA (6.3%).

The isomer distributions in these results are different from those we observed for the coupling of toluene in the presence of the same catalysts (38). MBA shows a carbonyl group that can interact with the Pd ion to form a Pd–O bond and facilitate an activation of an ortho proton through an ortho metallation reaction. It would result in a substantial yield of 2,$X'$-isomers. The possibility of similar activation of toluene is remote, which may explain the difference in the distribution of isomers between these two cases. The interaction of the Pd ion with the carbonyl oxygen could orchestrate coupling of the substrate through the transition state.

*N-containing ligands.* It has been shown (33) that the $[PdPhen(OAc)_2]$ catalyst demonstrates a regioselectivity for the coupling of dimethylphthalate that is different from that observed when $[Pd(CH_3COO)_2(acac)]$ was used. Moreover, the results shown in Table 2 support the use of N-containing ligands so as to change the regioselectivity. For this study, Table 3, we used 330 mmol of substrate, 0.5 mmol of the ligand (bipy or phen), and 0.5 mmol of $Pd^{2+}$ at a reaction temperature of 200°C for a duration of 4 h (protocol 1).

One effect for $L =$ bipy or phen was to decrease the reaction rate by an order of magnitude compared to the reactivity of the $[Pd(CH_3COO)(acac)]$ system. A second effect was the dramatic change in the regioselectivity for changing $L$ from an O- to an N-containing ligand. The 2,3′-isomer yield was 67% for the acac ligand, 43% for the bipy ligand, and only 11% for the phen ligand. Similar changes are noted for the decrease in the 2,4′-DMBBA isomer (27% to 21%

**TABLE 3**

**Effect of Ligand for the Reaction of MBA**

| | | Selectivity towards given DMBBA isomer, % | | | | | |
|---|---|---|---|---|---|---|---|
| $L$ | TOF,[a] 1/h | 2,2′- | 2,3′- | 2,4′- | 3,3′- | 3,4′- | 4,4′- |
| acac | 44 | 3 | 67 | 27 | 2 | 1 | 0.1 |
| bipy | 2.6 | 2 | 43 | 21 | 10 | 18 | 7 |
| phen | 1.4 | 0 | 11 | 5 | 18 | 43 | 23 |

[a] Turnover frequency measured at 4-h reaction time.

## TABLE 4

### Electronic Effects for Substituted 1,10-Phenanthroline

| $L$ | TOF,[a] 1/h | Selectivity towards given DMBBA isomer, % 2,2′- | 2,3′- | 2,4′- | 3,3′- | 3,4′- | 4,4′- |
|---|---|---|---|---|---|---|---|
| 5-Cl–Phen | 2.4 | 0 | 21 | 9 | 18 | 33 | 17 |
| 5-$NO_2$–Phen | 1.3 | 2 | 29 | 11 | 17 | 28 | 14 |
| Phen | 1.4 | 0 | 6 | 3 | 19 | 48 | 24 |
| 2,9-$Me_2$–Phen | 0.9 | 0.8 | 26 | 12 | 22 | 29 | 10 |
| 3,4,7,8-$Me_4$–Phen | 0.7 | 0.5 | 35 | 12 | 16 | 25 | 11 |

[a] Turnover frequency measured at 1.5-h reaction time.

to 5%) and for the increase in the 3,4′- (1% to 18% to 43%) or the 4,4′-DMBBA isomers (0.1% to 7% to 23%).

We were surprised that bipy did not change the regioselectivity as much as phen. Thus, we examined the kinetics of the reaction to determine if the distribution of isomers changed with time (Figs. 2–4). We compared the isomer distributions as a function of catalyst turnovers rather than reaction time since the reactivities of the systems were so much different (Table 4). The control system, $L=$ acac, showed very little change in the distribution of isomers with increasing extents of reaction to 62 turnovers (Fig. 2). The catalyst with $L=$ bipy or phen showed a transient in the regioselectivity at ca. 2–3 turnovers (Figs. 3 and 4). The rise of 3,3′-, 3,4′-, and 4,4′-DMBBA decreased rapidly, whereas the formation of 2,3′- and 2,4′-DMBBA became predominant.

In subsequent tests, we varied the $L$/Pd ratio to determine the effect of ligand excess (Figs. 5 and 6) for $L=$ bipy and phen. The yield of the 2,3′-DMBBA was shown to be a sensitive indicator of the regioselectivity in these systems (*vide supra*). When the formation of this isomer was low, the favored products were the 3,$X'$-DMBBA and 4,4′-DMBBA esters and conversely. Thus, we plotted the yield of the 2,3′-DMBBA isomer versus reaction extent expressed in turnovers to discover the effect of varying the initial ratio of $L$/Pd. These tests were conducted at 200°C for reaction times to 26 h, under pressurized artificial air (protocol 1), with 330 mmol of MBA and 0.5 mmol of $Pd^{2+}$ and for $L_2$/Pd ratios of 1–1.5. The regioselectivity changes quickly after 2 turnovers for L = bipy when bipy/Pd = 1 (Fig. 5). When the bipy/Pd ratio is 1.25, the initial relative formation of 2,3′-DMBBA ester decreases from 10% to 5% and then begins to increase after 4 turnovers have been completed. The yield of this isomer versus turnover becomes identical to that observed with bipy/Pd = 1 when the turnovers are more than 6. Increasing the bipy/Pd ratio to 1.5 shows the same trend in 2,3′-DMBBA selectivity, but the rapid increase in this isomer yield is delayed until 5.5 turnovers have been completed. This test was repeated for phen with phen/Pd = 1, 1.1, and 1.5 (Fig. 6). The 2,3′-DMBBA formation increased after 3 turnovers when phen/Pd = 1, whereas this isomer

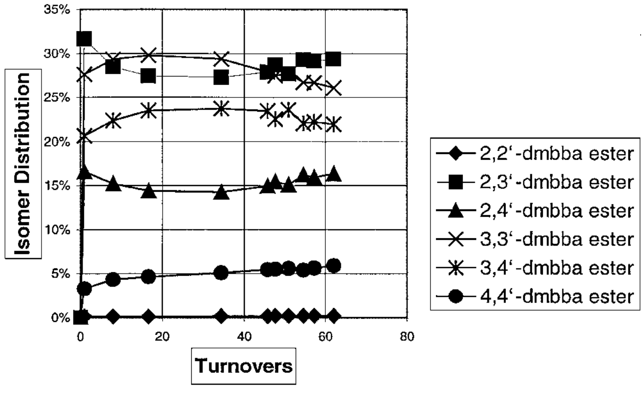


**FIG. 2.** Kinetics of MBA coupling over $Pd(OAc)_2$/Hacac at 150°C.

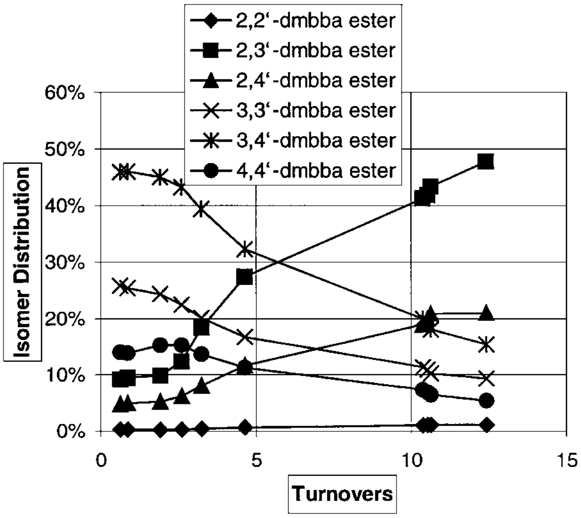


**FIG. 3.** Kinetics of MBA coupling over $Pd(OAc)_2$/bipy at 200°C.

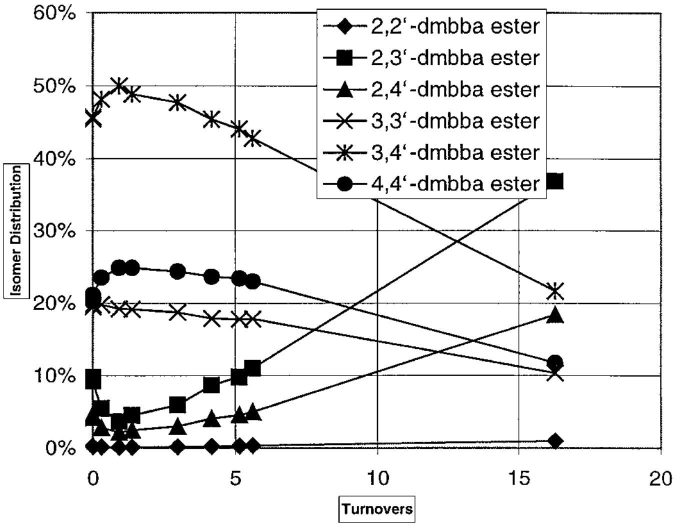


**FIG. 4.** Kinetics of MBA coupling over $Pd(OAc)_2$/phen at 200°C.

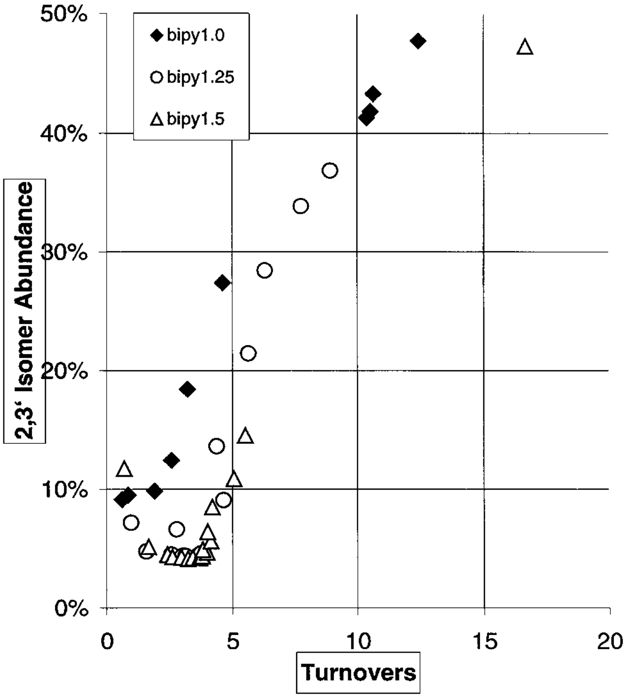


**FIG. 5.** Effect of adding excess bipy ligand on the regioselectivity.

yield increased rapidly after 6 turnovers when the phen/Pd ratio was 1.1 or 1.5.

The addition of excess ligand to the Pd catalyst apparently delayed the onset of the rise in the 2,3′-DMBBA formation. We interpret the rapid increase in the 2,3′-DMBBA yield as an indication that the ligand has become ineffective in directing the selectivity of the catalysis, possibly by its oxidation so that it is no longer coordinated to the metal. In the case of the bipy system, we observed the appearance of the characteristic fragmentation pattern of *N*,*N*-bipyridyldioxide in the GC/MS trace at the same time that the 2,3′-DMBBA yield increased rapidly with time. The appearance of this oxide of bipy coincident with the increase in the 2,3′-DMBBA yield suggests that the bipy was oxidized and thus no longer coordinated to the Pd ion.

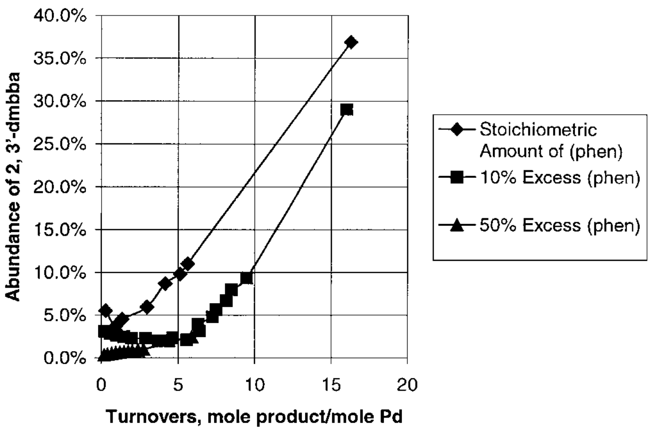


**FIG. 6.** Effect of adding excess phen ligand on the regioselectivity.

The apparent reactivity of these systems decreases with increasing $L$/Pd ratio when $L =$ bipy or phen. When this ratio is 2.0, the reaction was inhibited. These same results were reported by others using phen when the substrate was dimethylphthalate (32, 33).

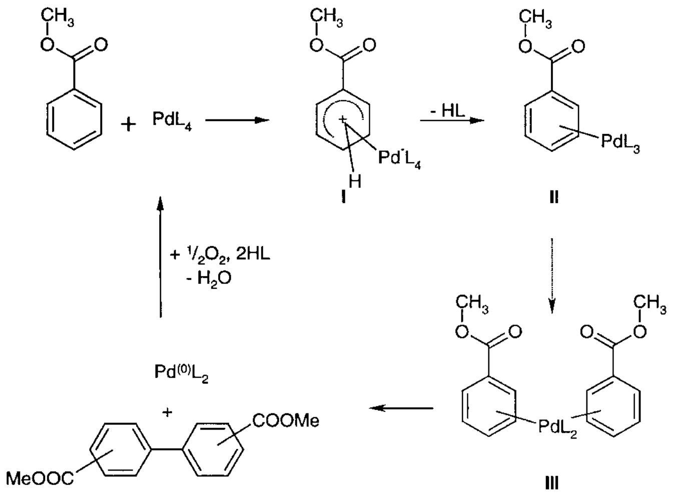
*Effect of substituents on 1,10-phenanthroline ligand.* We examined further the electronic effects by changing $L$ to 1,10-phenanthroline ligands having different substituent groups on the rings (Table 4). These groups included electron-withdrawing groups such as chloro and nitroso located at the 5-position on the ligand and electron-donating groups such as methyl located at the 2- and 9-positions or at the 3-, 4-, 7-, and 8-positions.

The reaction temperature was 200°C (protocol 1), 0.5 mmol of $Pd^{2+}$, 330 mmol of substrate, and 90-min reaction time. This reaction time was sufficiently short to allow an assumption that the ligands were not oxidized.

The Pd catalyst chelated by the unsubstituted 1,10-phenanthroline shows the highest combined selectivity to 3,4′- and 4,4′-DMBBA ester (72%), whereas the systems having electron-donating or -withdrawing groups show higher selectivities to 2,3-DMBBA. Contrary to the case with substituted acetylacetonates, the TOF was not a very strong function of the substituent groups on the phen ring as it varied by a factor of 2–3 from the least active to the most active system.

## DISCUSSION

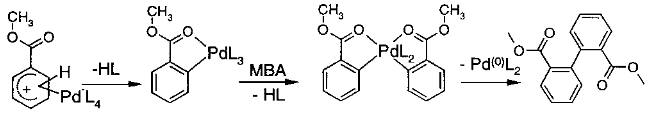
These results presented here may be explained within the framework of the existing theories for oxidative coupling of arenes at metal centers. Several earlier papers suggested a mechanism for the oxidative coupling of arenes. We show here the application of this tentative mechanism to MBA:



The first step of the aromatic coupling reaction is believed to be an electrophilic substitution of a proton from an aromatic nucleus by palladium with the formation of isomeric Pd–C- bonded species **II**. This substitution is thought to go through a relatively stable intermediate—the Wheland complex **I**. Then, the organopalladium species **II** may undergo the second electrophilic substitution (28) or disproportionate with the formation of an intermediate, **III**. The latter experiences a reductive elimination of a coupled product to create a zero-valent palladium complex, which can be reoxidized by oxygen with release of a water molecule. The rate-determining step is the formation of an aryl–palladium intermediate as suggested by the data for the H–D kinetic isotope effect observed for the coupling of toluene (28, 29) and for the cross-coupling of benzene with ethylene (30).

For such a mechanistic pathway of the oxidative coupling of aromatic compounds, it is known that electron-releasing substituents on the aromatic ring promote the reaction (21, 36). However, the electrophilic properties of the palladium (2+) cation are responsible for the ease of substitution during the first step of the process and, therefore, weakly coordinated ligands favor the reaction. The best results so far were achieved with such ligands as acetate (29), trifluoroacetate (31), and trifluoromethanesulfonate (triflate) (38) anions. Another important factor upon the reactivity of the system is its acidity. It has been shown that strong acids, such as perchloric (22, 24) or triflic (38), increase the rate of toluene coupling dramatically.

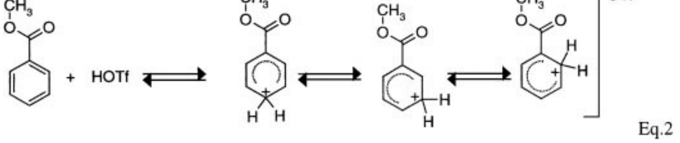
The effect of temperature on the regioselectivity suggests that increasing temperatures favor the formation of the ortho-coupled products. The possible explanation for the preferential formation of 2,2′- and 2,3′-isomers of DMBBA may lie in the ability of palladium to form ortho-metallated complexes (37) when a ligand has an additional electron-donating center. Those species are quite stable and for obvious reasons would direct the coupling onto the 2-position. Moreover, the ortho-palladated triaryl phosphite complex is a highly active catalyst (39) in biaryl coupling reactions of Suzuki or Stille. The stability of the ortho-palladated intermediate may shift the equilibrium, leading to the formation of aryl-palladium carbon-bounded species. The tentative scheme of the reaction is presented here (Scheme 1). This chelation by the substrate may be frustrated when the ligand *L* is implementing a strong labilizing effect (trans effect). At lower temperatures, we suggest that acac effectively precludes this chelation by the C=O group of MBA, and at higher temperatures, possible decomposition of the Pd–acac catalyst leads to the formation of the $Pd^{2+}$ ion which could be easily ortho-metallated by the substrate.



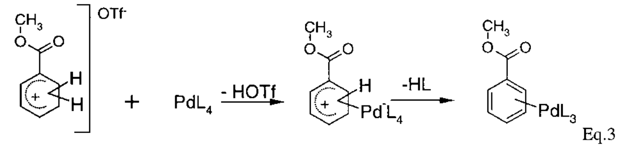
**SCHEME 1**

One piece of evidence to support this hypothesis is the effect of a weakly coordinating ligand, such as the triflate anion, on the regioselectivity of this system. When acac is replaced by $OTf^-$, the 2,2′- and 2,3′-DMBBA isomers are formed in high proportions (90%), even at room temperature. Thus, ortho coupling of the substrate may be favored by weakly coordinated and labile ligands. This effect can be minimized by using ligands bipy and phen. Indeed, the yields of 2,*X*′-DMBBA esters were very low when *L* was either bipy or phen, provided that the ligand remained intact (i.e., at low turnovers). We observed dramatic increases in the 2,*X*′-DMBBA yields that accompanied the destruction of the bipy ligand, as made evident by the appearance of *N*,*N*-bipyridyldioxide.

The enhanced reactivity at room temperature when HOTf is added to the system can be explained by the facilitation of the Wheland complex and consecutive aryl–palladium intermediate formations through initial activation of the C–H bond by its protonation, similar to the process described earlier for toluene (38). The formation of the carbo cation was examined using hydrogen–deuterium exchange between deuterated triflic acid (DOTf) and MBA-$d_0$. A blank experiment between DOTf and MBA in which no $Pd^{2+}$ was present showed the significant H–D exchange (MS analysis). Isotope cluster abundance calculations for MBA ($m/e$ of parent ion $= 136$) suggest that the relative amount of $m/e = 137$ equals 9.21% in the natural product, when $m/e = 138$ is about 0.78% of the intensity of the $m/e = 136$ peak. After a treatment with DOTf, such distribution is changed with an increase of $m/e = 137$ to 25.6% and $m/e = 138$ increased to 5.2%, again relative to $m/e = 136$. This enhancement clearly indicates that H–D exchange has occurred and therefore the C–H bond of the phenyl group can be labilized by a super acid. We may speculate that the equilibration (Eq. [2]) is followed by fast transmetallation to form for a first instance a Wheland complex and then aryl–palladium species (Eq. [3]).



Eq.2



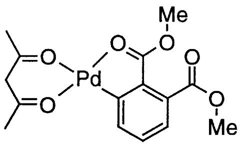
Eq.3

Indirect support for such an hypothesis is the fact that complexes of osmium $[Os(NH_3)_5L](OTf)_2$ (where *L* is an inactivated arene or polyaromatic hydrocarbon) are readily protonated by HOTf to generate stable arenium, naphtalenium, and anthracenium cations (40).

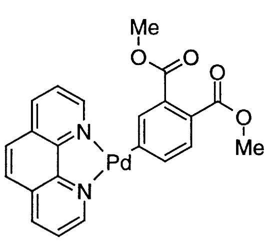
The relative ease of formation of the aryl-palladium intermediate may contribute to the decrease of a potential barrier of the reaction and therefore increase the overall rate of the coupling. Indeed, MBA undergoes such transformation at only 65°C in the presence of HOTf. The natural drawback, though, is that HOTf may protonate preferentially the oxygens of the ester group and thus facilitate side reactions. As a matter of fact, when the reaction was carried out at 150°C, the major product was benzoic acid—the result of routine hydrolysis of an ester by water formed in equimolar amounts during the catalytic coupling reaction.

It is known that the strength of the HOTf is enhanced in the acetic acid media, so it was interesting to check the influence of acetic acid onto the $Pd(OAc)_2$ catalyzed coupling. We did not notice any increase of the rate of reaction or its yield, but the regioselectivity was changed dramatically. The major product was 2,3′-DMBBA at a selectivity of 90%. The 2,2′-isomer was formed with a selectivity of 8%, and four others show 2%. When acetic acid is present, the second arylation may be directed onto the meta position resulting in 2,3′-DMBBA. The reasons for that are to be investigated.

*Effect of nitrogen ligands.* Considering the possible ortho metallation and its effect on the selectivity of the reaction, preventing it may be a way to discourage the formation of 2,$X'$-isomers ($X = 2$, 3, or 4) and therefore direct the process toward 3,3′-, 3,4′-, and 4,4′-DMBBAs. To repress the formation of ortho-metallated species, the Pd–O bond must be labilized. The success of controlling the selectivity of dimethyl phthalate coupling by a Pd–phen catalyst (32, 33) prompted us to explore the trans-effect hypothesis as a way to control the regioselectivity in MBA coupling. Indeed, in the case of the Pd–acac catalyst, the coupling onto the 2-position is facilitated by the possible formation of a chelated, five-membered intermediate (**IV**), which directs the process further toward the 2,$X'$-coupled products.



**IV**



**V**

$Pd(phen)(OAc)_2$ as a catalyst may discourage the formation of such intermediates because of the high trans effect of the phen–ligand and direct the coupling to the different products (because of steric factors), preferably with no involvement of the 2-position (**V**).

Among different known ligands with a strong trans effect, it is difficult to find ones that would withstand the actual experimental conditions, especially high temperature combined with the high pressure of oxygen. Nevertheless, we attempted to use one such ligand, bis(diphenylphosphino)ethane [dppe], to confirm the trans effect. When we used dppe for a short-term experiment, the formation of the 3,3′-DMBBA ester prevailed over the rest of the isomers. The bipy and phen ligands were effective in directing the coupling to the 3,4′- and 4,4′-DMBBA ester isomers when the reaction times were short. At longer reaction times, the regioselectivity changed rapidly to favor the 2,$X'$-DMBBA ester, perhaps as a result of the decomposition of the ligands. Addition of excess ligand delayed the onset of the transient in regioselectivity but at the expense of lower reactivity. Indeed, if more than 1.8 mol of ligand/mol of $Pd^{2+}$ was present initially, the reaction rate was nearly zero. This last result suggests that the active catalyst must contain at least one labile anion, such as the acetate anion.

We now compare the effects of the ligands on the properties of the Pd ion for the coupling of methyl benzoate. Acetylacetonate binds to the Pd ion as a negatively charged ligand whereas phenanthroline binds with the Pd ion as a neutral molecule. Moreover, the coordination mode and properties of these molecules as ligands are different. Strong $\sigma$-donor effects of the phen molecule decreases the electrophility of $Pd^{2+}$ and electron-donating substituents may contribute to such phenomena. In other words, an increase of electron density on Pd leads to a decrease of the catalyst reactivity. In the case of negatively charged acac, additional electron density on it may lead to its partial dissociation and thus create an additional accessible coordination place on Pd, which may contribute to an increase of reactivity.

## CONCLUSION

Electronic properties of a palladium homogeneous catalyst are more important than steric restrictions of the same catalyst for altering the activity and regioselectivity for MBA coupling. The activity of these Pd catalysts can be improved by using a strong acid such as HOTf and weakly coordinating ligands such as the triflate anion. The regioselectivity under these conditions favors the formation of 2,2′- and 2,3′-DMBBA esters. On the other hand, bidentate ligands such as 1,10-phenanthroline direct the oxidative coupling of MBA away from 2,2′-, 2,3′-, and 2,4′-isomers but with a much lower activity than the weakly coordinating ligands. An excess of phen or bipy extends the lifetime of the catalyst and permits the catalyst to achieve greater turnover numbers with enhanced regioselectivity away from the 2,$X'$-DMBBA ester isomers.

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