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Direct Synthesis of Dimethylbiphenyls by Toluene Coupling in the Presence of Palladium Triflate and Triflic Acid

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A direct coupling reaction of toluene for synthesis of dimethylbiphenyl is reported in the presence of a strong acid, such as trifluoromethane sulfonic acid (TfOH) and Pd(II) triflate [Pd(TfO)$_2$] at room temperature. The presence of both Pd(TfO)$_2$ and TfOH is necessary for coupling of toluene at room temperature, and the reaction rate is promoted by H$^+$ with a labile anion such as OTf$^-$.

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INTRODUCTION

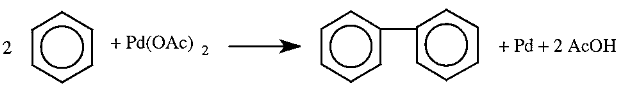
The unique properties of biphenyls, their oligomers, and polymers have stimulated much work attempting to develop new materials (1). Copper has been used for the synthesis of biphenyls and biaryls from halogen-substituted benzene and other aromatics (Ullmann reaction) (1). The chemistry is well established for aryl coupling from halogen-substituted aromatics catalyzed by nickel or palladium (1–3). Others reported the coupling of aryl-ligands from organometal complexes (4, 5). Friedel and Crafts reported direct coupling of two aromatic molecules by treatment with a Lewis acid such as $AlCl_3$ at elevated temperatures a century ago. This reaction, later known as the Scholl reaction, was seldom useful in synthesis due to poor product yields and selectivity (6), although high product yields may be obtained in some *intramolecular* Scholl reaction (7).

Other examples of coupling by functionalized aryl substrates include the Kharasch reaction using an aryl Grignard reagent, ArMgX, and an aryl halide Ar′X in the presence of a suitable catalyst (8a). A related reaction, the Negishi reaction, uses arylzinc reactants together with aryl halides or triflates (8a). The Stille reaction employs arylstannates and aryl halides or triflates (8a) and it is extremely versatile for coupling a wide range of aryl reagents. The Suzuki reaction is known for tolerating a wide range of aryl substrates (8a).

The catalysts for these four reactions (Karasch, Negeshi, Stille, and Suzuki) include palladium and nickel metal complexes. Typically, a divalent metal is used to generate the active metal complex *in situ*. All four reactions suffer from the need to functionalize the aromatic before it can be coupled. Moreover, as a result of this functionalizing, solid waste products are generated in stoichiometric proportions. Some of these wastes are considered toxic (e.g., Stille reaction). Thus, there is a need to develop a catalytic reaction of the aryl substrates without reactive functional groups on the substrate.

COUPLING OF UNFUNCTIONALIZED ARYL SUBSTRATES

The oxidative coupling of aryl substrates proceeds by the effect of transition metal catalysts without the direct participation of a functional group (8b, 9). One important metal catalyst, Pd, is known to couple aryl substrates via a reactive σ-aryl–Pd complex (10) as shown in Eq. [1].



[1]

The reaction tolerates monosubstituted aryls Ar–X, where $X =$ Me-, MeO-, MeOOC-, -CF_3, -Cl, -F, MeOCO-, and -NO_2, and disubstituted aryls ArX_2, where $X =$ Me- and MeOOC- (11). Electron donating groups accelerate the reaction rate, whereas electron withdrawing groups have the opposite effect (9). The reaction conditions are mild (150–200°C) and the catalyst may be generated *in situ* from equimolar amounts of Pd(AcO)$_2$ and pentanedione. The isomer selectivity may be altered for the coupling of dimethylphthalate when 1,10-phenanthroline (phen) is substituted for pentanedione (acac) (12); however, for some substrates the reactivity is less with the phen ligand than with the acac ligand (13).

The conventional technology using Pd(II)(AcO)$_2$ and pentanedione (11, 14) is catalytic for the substrates shown in Table 1 when air is used as the oxidant at 150°C. Whereas the toluene coupling rate is 18.5 turnovers/h at

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TABLE 1

Performance of $Pd(AcO)_2$/2,4-Pentanedione Catalysts[a]

Substrate	Turnover rate, 1/h
Benzene	7.8
Toluene	18.5
o-Xylene	14.3
m-Xylene	10.3
p-Xylene	1
1,3,5-Trimethyl benzene	0
Naphthalene	11.3
Methyl benzoate	21.3
o-Dimethyl phthalate	13
Chlorobenzene	1
Fluorobenzene	5.8
Nitrosobenzene	6.3

[a] Reaction conditions: 50 ml of substrate, 0.5 mmol each $Pd(AcO)_2$ and 2,4-pentanedione, temperature 150°C, artificial air at 750 psig (50 mol% O_2). Ref. (14).

150°C, we estimate that the coupling rate would be only 0.00021 turnovers/h at 20°C using an activation energy (22.3 kcal/mol) derived from data in Ref. (11). This activation energy is similar to that reported by another group (12), 17.9 kcal/mol, for the coupling of dimethyl phthalate over $Pd(OAc)_2$ in the presence of 1,10-phenanthroline and $Cu(OAc)_2$. The electrochemical coupling of a related compound, anisole (15), proceeds at a rate of 0.44 mmol anisole consumed/h at 20°C in trifluoroacetic acid ($HOOCCF_3$). Several groups describe the oxidative coupling of aromatics completed in the presence of trifluoroacetic acid (16, 17) and perchloric acid (17). However, another group reports that these reactions do not occur in the presence of HCl and H_2SO_4 (14). These apparently conflicting results prompted us to seek further evidence on the effect of acids upon the reaction rate when the anion was either the trifluoroacetate or the triflate. In the present communication, we report the direct toluene coupling to form dimethylbiphenyls (DMBP) in the presence of palladium (II) triflate [$Pd(CF_3SO_3)_2$], further denoted as $Pd(TfO)_2$, and triflic acid (TfOH) without an oxidant. The results of this reaction are also reported using trifluoroacetic acid (TFA) and acetic acid (HOAc) in place of the triflic acid. The oxidant was omitted from these studies to minimize side reactions and the effects of catalyst reoxidation on the results.

EXPERIMENTAL

Trifluoroacetic acid (Alfa-Aesar), triflic acid (Alfa-Aesar), and acetic acid (Aldrich) were used without further purification. $Pd(TfO)_2$ was synthesized from wet palladium (II) nitrate [$Pd(NO_3)_2$, Alfa-Aesar] or palladium(II) acetate [$\{Pd(AcO)_2\}_3$, Aldrich] (18) with excess TfOH at room temperature. Evaporation of the liquid from the reaction mixture under vacuum at 150°C gave $Pd(TfO)_2$ as a dry solid of lavender color. The $Pd(TfO)_2$ solid is highly air sensitive and should be stored in well-capped bottles under inert gas. Sorption of moisture from air can change the metal triflate to a deliquescent solid. Moisture can also cause decomposition, possibly hydrolysis, of $Pd(TfO)_2$. Details of the synthesis and characterization with IR, NMR, TG-DTA, XRD, and elemental analysis of the $Pd(TfO)_2$ will be reported elsewhere (19).

The toluene coupling reaction was carried out in a round-bottom flask under a dry nitrogen flow at atmospheric pressure and room temperature (20°C). The required amount of palladium salt (e.g., $Pd(TfO)_2$ in the triflic acid runs), usually ca. 2 mol% of toluene, was added to the reactor first. After purging the $Pd(TfO)_2$-loaded reactor with dry nitrogen for 5 min, 70 to 250 mmol of dry toluene (99%, Aldrich) was then added under nitrogen flow. The reactor with $Pd(TfO)_2$ and toluene was placed in a bath of cold water, and TfOH was added in an amount equal to a multiple of the moles of reacting toluene (0.74–1.17 mmol acid/mmol toluene). Once TfOH was loaded, the reaction mixture was stirred vigorously with a magnetic stirring bar. Usually, the addition of TfOH caused a temperature increase to 35°C, but the temperature returned to 20°C within 5 min. After reaction for 2–4.5 h, ice was added directly to the reaction mixture to terminate the reaction. This protocol was essentially the same when either trifluoroacetic acid or acetic acid was used, except that the palladium salt was $Pd(AcO)_2$.

Analysis of the organic phase was performed on a HP 5890 Series II GC-MS with Supelco SPB-5 capillary column (30 m × 0.25 mm × 0.5 μm). Identification of 4,4′-, 3,4′-, and 3,3′-DMBP from 2,2′- and other DMBP isomers was possible by their fragmentation patterns in the MS spectra. However, identification of the 2,2′-, 2,3′-, and 2,4′-DMBP isomers was difficult using their MS spectra. The identification of the 4,4′- and 3,3′-DMBP was confirmed by using authentic solutions in toluene. Since it was difficult to obtain all the isomers of DMBP at present time, identifications of the other isomers were made by assuming that their elution from the column followed the sequence of their boiling points. We estimated the isomer yields from GC/MS peak areas assuming that all the isomers of DMBP have the same response factor as 4,4′-DMBP.

Samples from the hydrogen/deuterium exchange reactions were examined for ^{1}H-NMR in a Bruker 300 MHz instrument after diluting in deuterated acetone. Perdeuterated toluene [C_7D_8] was obtained from Aldrich. The mass spectra of the samples were completed using a VG Instruments mass spectrometer 70 SE.

RESULTS

Table 2 shows the results of the toluene coupling reaction in the presence of $Pd(TfO)_2$ or $Pd(AcO)_2$ with TfOH at

TABLE 2

Toluene Coupling in the Presence of Palladium Salts and Triflic Acid at 20°C[a]

Catalyst:	$Pd(TfO)_2 + TfOH$	$Pd(TfO)_2 + TfOH$[b]	$Pd(AcO)_2 + TfOH$	$Pd(TfO)_2$[c]	$Pd(AcO)_2$	TfOH
TfOH/toluene (molar)	0.91	0.74	0.95	0	0	1.08
Pd/toluene (molar)	0.020	0.014	0.027	0.016	0.02	0
Reaction time/min	120	120	270.00	120	180	120
Conversion, %	5.61	5.43	7.58	0.72	∼0	∼0
Product selectivity, %						
2,2′-DMBP	0.62	0.66	0.11	1.13		
2,3′-DMBP	3.25	2.69	2.23	6.01		
2,4′-DMBP	2.68	1.98	1.30	6.64		
3,3′-DMBP	5.21	4.59	2.64	0.03		
3,4′-DMBP	58.25	49.29	29.17	14.66		
4,4′-DMBP	15.76	19.44	14.15	5.05		
Total DMBPs	85.77	78.65	49.60	32.39	No DMBPs	No DMBPs
Trimer	8.87	15.33	12.49	0.28		
Methylacetophenone	0.12		37.91	Trace		
Unknowns	5.24	6.02	Trace	67.33[d]		

[a] The results represent composition of the organic phase after work-up with water.

[b] $Pd(TfO)_2$ synthesized from $Pd(NO_3)_2$ by wet method.

[c] The reaction was carried out at 20°C for 4 h, followed by heating the reactor to 60°C and then reacted at 60°C for another 40 min.

[d] The main by-products are ethylbenzene; benzaldehyde; propylbenzene; benzylalcohol; 1-methyl, 4-phenylmethylbenzene; and 1-methyl,2-phenylmethylbenzene.

20°C. Two kinds of $Pd(TfO)_2$ were used for the reaction: one was synthesized from palladium acetate (column 1), and the other from palladium nitrate (column 2). These results suggest that the source of Pd(II) in making $Pd(TfO)_2$ does not have a significant effect in the catalysis for the toluene coupling reaction. Toluene coupling was also attempted, respectively, with [$Pd(AcO)_2$/HOTf], $Pd(TfO)_2$, $Pd(AcO)_2$, or TfOH alone, and the results are also shown in Table 2 (columns 3–6).

The toluene coupling reaction in TfOH alone is inactive (column 6) and $Pd(TfO)_2$ alone induces very low conversion of toluene (0.72%) perhaps as a result of its low solubility in toluene. Product selectivity in the presence of $Pd(TfO)_2$ but without TfOH is also different from the case in which both $Pd(TfO)_2$ and TfOH were present; with $Pd(TfO)_2$ the major products are phenylmethyl toluenes (column 4). While $Pd(AcO)_2$ alone is also inactive for the formation of DMBP (column 5), $Pd(AcO)_2 + TfOH$ promote the toluene coupling reaction (column 3 vs. column 2) with less activity than $Pd(TfO)_2 + TfOH$ (3.8% in 4.5 h versus 4.2% yield DMBP in 2 h). Formation of $Pd(TfO)_2$ has been reported from the reaction of $Pd(AcO)_2$ with TfOH (18, 19). Thus, the toluene coupling with $Pd(AcO)_2 + TfOH$ may be the result of $Pd(TfO)_2$ formed *in situ* from $Pd(AcO)_2 + TfOH$. The formation of 4-methylacetophenone in the system with $Pd(AcO)_2 + TfOH$ provides support for the *in situ* synthesis of $Pd(TfO)_2$ as 4-methylacetophenone is the product of toluene acylation by acetic acid in the presence of TfOH (20). It is interesting that the activity of $Pd(AcO)_2 + TfOH$ is less than that of $Pd(TfO)_2 + TfOH$. Water molecules, formed as a coproduct of 4-methylacetophenone through TfOH-catalyzed acylation of toluene by acetic acid, may be responsible for the lower activity of $Pd(AcO)_2 + TfOH$, since $Pd(TfO)_2$ was found to decompose in water (19). Moreover, Sood showed that the carbonylation rate of toluene catalyzed by HOTf at room temperature decreased dramatically as the [H_2O] was added to the reaction mixture [21].

The amount of $Pd(TfO)_2$ used for the reaction has a significant effect on the toluene coupling reaction (Table 3, columns 1–3). Though the product selectivity is not changed with increasing amounts of $Pd(TfO)_2$ in the reaction mixture at levels of ∼1.5–8 mol%, the conversion of toluene increases (from 5.6 to 22%) in proportion to the amount of $Pd(TfO)_2$ in the reaction system (Fig. 1). The slope of this curve gives the number of moles toluene reacted per mole of Pd(II). The reaction rate was 1.7 turnovers/h for this reaction promoted by $Pd(TfO)_2$/TfOH at room temperature compared to the estimated production rate of 0.00021 turnovers/h for the reaction catalyzed by $Pd(AcO)_2$/2,4-pentanedione at the same temperature (*vide supra*). Efforts are being made to optimize the amount of $Pd(TfO)_2$ and of TfOH for this reaction.

The reaction was also completed using either trifluoroacetic acid or acetic acid under similar reaction conditions (Table 4). These reaction conditions were 20°C, 2 mol% $Pd(AcO)_2$ using a substrate to acid ratio of 1 mol/mol. The Pd salt was completely soluble in either triflic or trifluoroacetic acid. With triflic acid, we observed 0.83 turnovers in 30 min for a turnover frequency of 1.7 h^{-1}. At longer reaction times (120 min) we observed a turnover rate of 1.55 h^{-1}. We observed a reactivity of 0.48 turnovers over

TABLE 3

Effect of Palladium Triflate on Toluene Coupling Reaction at 20°C[a]

Catalyst:	$Pd(TfO)_2$ + TfOH	$Pd(TfO)_2$ + TfOH	$Pd(TfO)_2$ + TfOH	Pd + TfOH	Isomerization of 4,4′-DMBP
TfOH/toluene (molar)	0.91	0.87	1.00	1.17	1.00
Pd/toluene (molar)	0.020	0.039	0.072	0.040	0
Reaction time/min	120	120	120	120	120
Conversion, %	5.61	12.05	21.97	1.52	> 60%
Product selectivity, %					
2,2′-DMBP	0.62	0.54	1.04	trace	0.04
2,3′-DMBP	3.25	3.89	7.54	0.86	0.45
2,4′-DMBP	2.68	3.72	8.66	0.08	0.66
3,3′-DMBP	5.21	3.05	2.75	1.14	1.44
3,4′-DMBP	58.25	49.58	48.96	7.82	51.27
4,4′-DMBP	15.76	23.45	23.09	2.59	38.32
Total DMBPs	85.77	84.23	92.04	12.49	92.18
Trimer[b]	8.87	14.01	4.88	86.78[c]	7.82
Methylacetophenone	0.12	0.17			
Unknowns	5.24	1.59	3.07	0.73	

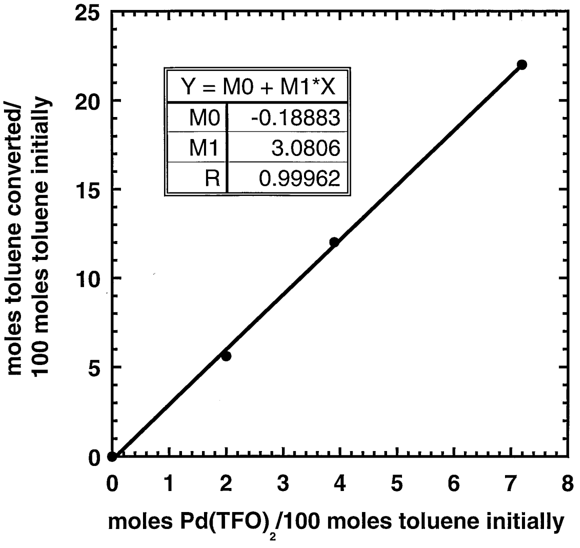
[a] The results represent composition of the organic phase after work-up with water.

[b] Compounds with molecular weight at 246–248 and 276–278.

[c] Only compounds with molecular weight at 246–248.

the Pd^{2+} catalyst in 6 h when the acid was trifluoroacetic acid (turnover frequency = 0.08 h^{-1}). The palladium salt was very slow to dissolve into acetic acid requiring 24 h. No product was observed 48 h after mixing the acetic acid with the substrate and $Pd(AcO)_2$.

Attempts were made to make that reaction catalytic under oxygen pressure and high temperature (100–150°C). Under these conditions triflic acid catalyzes several side reactions which result in a formation of copious amount of black tar of unknown nature suggesting that some high molecular weight products are produced. Under N_2 at elevated temperature (above 80°C) HOTf similarly caused a formation of many uncharacterized species. On the other hand, experiments at 50°C gave similar results as at 20°C. The rate of coupling reaction seems to be so great that the majority of dimethylbiphenyls is formed nearly instantly even at room temperature.



Y = M0 + M1*X	
M0	-0.18883
M1	3.0806
R	0.99962

FIG. 1. Conversion of toluene as a function of $Pd(TfO)_2$ in starting mixture. Reaction conditions: $T = 20°C$; TfOH/toluene = 0.87–1.00 M; reaction time = 120 min; N_2 at 1 atm.

Hydrogen/deuterium exchange between the perdeuterated substrate (99.9 mol% toluene-d_8) and the protons of the acids (triflic or trifluoroacetic acid) at room temperature was used as a probe to the possible interactions between the acid and substrate. We speculated that the acid may protonate the substrate to form an intermediate prior to the palladation reaction. Moreover, this protonated intermediate would engage the palladium ion in a facile transmetallation reaction faster than the unprotonated substrate. The necessary condition for this hypothesis is to show that the substrate is protonated by the acid. We tested this hypothesis with acids of different strength: trifluoroacetic acid and triflic acid.

The ^1H-NMR of the triflic acid/substrate mixtures are shown in Fig. 2. Figure 2A shows the spectrum of triflic acid and toluene-d_8 after mixing for 2 h at room temperature; no Pd(II) ion was present in this mixture. The acid layer shows a sharp peak at 2.1 ppm indicative of the methyl hydrogens on the undeuterated toluene impurity. Two, large broad peaks are observed between 7 and 10 ppm. Pure triflic acid shows a sharp resonance at 10.5 ppm whereas the ring hydrogens of toluene show peaks at 7–7.3 ppm. The mass spectrum of the same sample is also shown in Fig. 2. Here, we observe a distribution of m/e showing the largest peaks at $m/e = 97$ and 98. The NMR and mass spectrum of

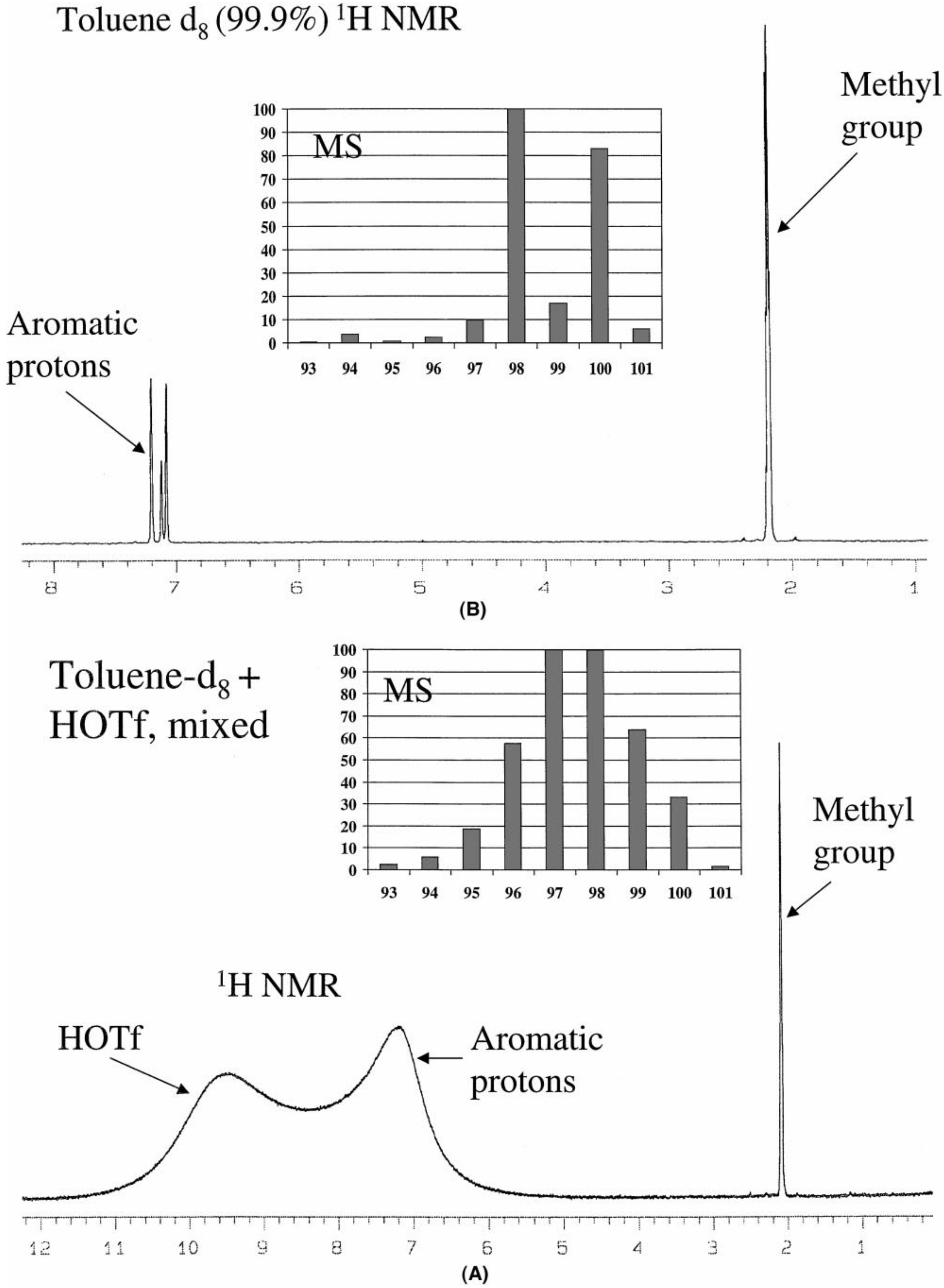


FIG. 2. Hydrogen/deuterium exchange reaction at room temperature. (A) NMR and MS of triflic acid/perdeuterated toluene. (B) NMR and MS of perdeuterated toluene reactant. Reaction conditions: $T = 20°$C; acid/substrate 1 mol/mol; reaction time 2 h; air at 1 atm.

TABLE 4

Comparison of Toluene Coupling Catalysts

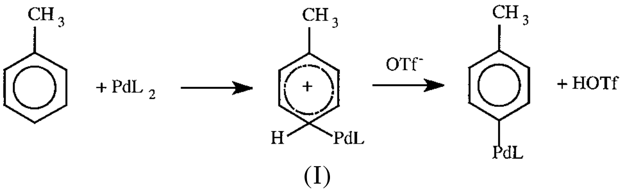
Investigators:	Iataaki and Yoshimoto (11, 14)	Van Helden and Verberg (9a)	Unger and Fouty (31)		Davidson and Triggs (9b, 9c)		Ferrers *et al.* (16)	This work	This work	This work
Reaction conditions										
Catalyst	$Pd(OAc)_2$	$PdCl_2$	$PdCl_2$	$PdCl_2$	$Pd(OAC)_2$	$Pd(OAC)_2$	$Pd(OAc)_2$	$Pd(OTf)_2$	$Pd(OTf)_2$	$Pd(OTf)_2$
Cocatalyst	H(acac)	HOAc	NaOAc	NaOAc	$HClO_4$	$HClO_4$	H(TFA)	HOAc	H(TFA)	HOTf
Temperature, °C	150	100	200	110	50	100	25	20	20	20
Duration, min	360	300	120	180	90	60	1440	1440	480	120
Pd/substrate (mol/mol)	0.002	0.08	0.1	0.1	0.09	0.09	0.025	0.02	0.02	0.039
Cocatalyst/substrate (mol/mol)	0.002	0.4	0.49	0.49	1.32	1.32	7.2	1	1	0.87
Substrate conversion, %	14.2	6	2.8	5.4	0.033	0.09	1.2	0	0.960	12.1
Turnover rate, 1/h	11.83	0.15	0.14	0.18	0.002	0.010	0.020	0.00	0.060	1.55
Isomer distribution										
2,2′-DMBP	2		Trace	Trace	0.7	0.5	1.9	—	—	0.6
2,3′-DMBP	12	25	12.5	12.7	4.6	4.8	6.7	—	—	4.6
2,4′-DMBP	8		12.2	13.4	11.4	9.4	21.0	—	—	4.4
3,3′-DMBP	32	30	18.8	17.2	6.9	9.8	7.6	—	—	3.7
3,4′-DMBP	34	35	35.3	35.2	34.2	38.3	32.4	—	—	58.8
4,4′-DMBP	12	20	21.4	21.2	42.2	37.3	30.5	—	—	27.9

the unreacted, perdeuterated toluene is shown in Fig. 2B. Notice that the NMR peaks are sharp and coincide with the expected chemical shifts for the toluene-d_0 impurity. The mass spectrum shows the expected distribution of m/e for the toluene-d_8. The peak at 100 is the parent ion of toluene and the peak at 101 is the ^{13}C natural abundance. These data suggest that the average proton incorporation into the substrate is one when the substrate is mixed with triflic acid at room temperature. Thus, most of the substrate must have been protonated by the triflic acid. The NMR and mass spectrum of the mixture trifluoroacetic acid and perdeuterated toluene after contact for 2 h at room temperature are identical to that observed for the deuterated substrate, Figure 2B. The NMR spectrum shows no interaction between the trifluoroacetic acid protons and the protons in the toluene-d_0 impurity. The mass spectrum of the mixture is identical to that of toluene-d_8. Therefore, very little of the substrate is protonated by trifluoroacetic acid.

DISCUSSION

The general mechanism has been reported for aryl coupling by transition metals, such as Au(III), Pd(II), Pt(IV), and Rh(III) and nontransition metals, such as Hg(II), Tl(III), and Pb(IV) (8). The reaction proceeds by substitution of the hydrogen in the arenes by the electrophilic metal ions. All of these reactions appear to proceed through a Wheland complex.

Several authors (9, 14, 22) have reported the reaction mechanism shown below for the Pd-catalyzed, aryl-coupling reaction.



(I)

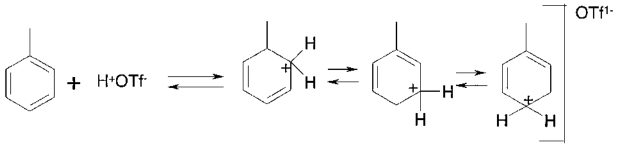
[2]

$$2(I) \rightarrow Ar_2Pd + PdL_2 \quad [3]$$

$$Ar_2Pd \rightarrow Ar\text{–}Ar + Pd^0 \quad [4]$$

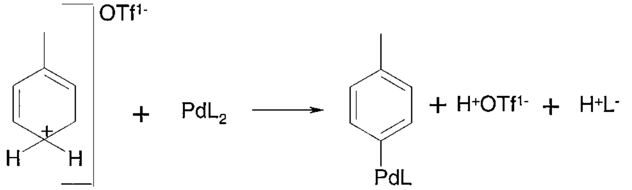
For the case of $PdCl_2$/NaOAc in acetic acid, the reaction rate is correlated by a rate equation, which is first order in Pd(II) ion and arene. After the metallation step, the acetate resides in the coordination sphere of the palladium. Activation of aromatics in acidic media has been achieved by Pd(II) acetate or Pd(II) trifluoroacetate via the formation of Ar–Pd–L intermediate. This science has been applied to the catalytic carboxylation of aromatics with CO and O_2, and for synthesis of aryl olefins from aromatics and olefins (20, 23). Electrophilic attack of $Pd(AcO)_2$ or $Pd(CF_3COO)_2$ on the benzene ring was considered for the formation of Ar–Pd(AcO) or Ar–Pd(CF_3COO) intermediate. $Pd(CF_3COO)_2$ showed a much higher catalytic activity than $Pd(AcO)_2$ in the carbonylation of aromatics; this observation was explained by the more favored electrophilic property of the $Pd^+(CF_3COO)$ ion derived from $Pd(CF_3COO)_2$ than that of the $Pd^+(AcO)$ ion derived from $Pd(AcO)_2$ (23). We suggest an additional reason for the lower reactivity of the $Pd(AcO)_2$. The trimeric form of this metal complex may offer steric hindrance to the approach of the substrate to the Pd ions. Thus, the ensemble size of the Pd complex residing in the reaction medium is important. The trimer, $[Pd(AcO)_2]_3$ is stable in benzene (24), whereas an equilibrium between the trimer and dimer is found in glacial acetic acid (25) at room temperature. This equilibrium is shifted to the dimer when excess OAc^- is added.

In the present study, we propose that the first step of the reaction mechanism is the protonation of the substrate by the strong acid to form the equilibrium:



[5]

The strength of the acid determines the position of the equilibrium. We speculate that significant amounts of the substrate become protonated by triflic acid since the D/H exchange results show that triflic acid interacts with the substrate by a fast equilibration reaction (NMR data). The next step of the mechanism involves a transmetallation reaction between the Pd salt (PdL_2) and either the substrate (Eq. [2]) or the protonated substrate (Eq. [6]).



[6]

We hypothesize that the acceleration of the reaction by triflic acid vis-à-vis trifluoroacetic acid rests upon the effect of the strong acid on the rate of the transmetallation step involving the protonated species (Eq. [6]) as opposed to the unprotonated species (Eq. [2]). The isotope effect has been measured for the coupling of benzene with perdeuterobenzene. A large isotope effect (k_H/k_D) was found to be 2.1–2.5 at 150°C under oxygen pressure. At room temperature the isotope effect was 4.1–5.1 under atmospheric pressure (26a) and near 4.5 when the reaction temperature was 90°C (26b). Other researchers show that the rate-determining step in the Pd-catalyzed, cross-coupling of benzene with ethylene is associated with a strong primary kinetic isotope effect ($k_H/k_D = 5$) (27). Thus, it is possible to speculate that C–H bond breaking may be the rate-determining step in the Pd-catalyzed coupling of toluene. Moreover, the value of the isotope effect suggests that more than one step in the reaction mechanism involve C–H bond scission. On the basis of these data, it has been suggested that the mechanism for Pd-catalyzed coupling of aromatic compounds proceeded through a two-step hydrogen abstraction as shown below using benzene as the model aromatic compound:

$$Pd(AcO)_2 + C_6H_6 \rightarrow C_6H_5\text{–}Pd\text{–}OAc + AcOH \quad [7]$$

$$C_6H_5\text{–}Pd\text{–}OAc + C_6H_6 \rightarrow C_6H_5\text{–}Pd\text{–}C_6H_5 + AcOH \quad [8]$$

$$C_6H_5\text{–}Pd\text{–}C_6H_5 \rightarrow C_6H_5\text{–}C_6H_5 + Pd(0)\ (\text{fast}) \quad [9]$$

The last step is a reductive elimination (Eq. [9]) that should proceed very quickly (28) when compared to the other mechanism steps. We believe that this same mechanism may explain our data. The palladation reaction (Eq. [2] or Eq. [6]) clearly involves the activation of a C–H bond as well as the activation of the Pd–L bond. It is known that the triflate anion (TfO^-) is a more labile anion than acetate and trifluoroacetate anions (CH_3COO^- and CF_3COO^-). The use of triflate anion to produce highly electron-deficient metal complexes has been well documented in inorganic synthesis (29, 30). Thus, the reaction rate could be altered by changing the anion provided that removal of the ligand from Pd is the rate-determining step. As shown earlier, the rate-determining step is probably C–H bond activation. Thus, we favor a mechanism for which the protonation of the substrate results in a species that is more facile in the palladation reaction.

These early researchers (14) did describe the reoxidation of the Pd^0 by the following sequence

$$Pd(0) + O_2 + \text{Aryl–H} \rightarrow \text{Aryl–Pd–OOH} \quad [10]$$

$$\text{Aryl–Pd–OOH} + \text{H(acac)} \rightarrow \text{Aryl–Pd–acac} + \text{HOOH} \quad [11]$$

Metallic Pd is reoxidized by the action of molecular O_2 and another substrate molecule to form the peroxide intermediate (R–Pd–OOH). Pentanedione reacts with the peroxide intermediate to form the aryl–Pd–L and hydrogen peroxide. Our results suggest that Pd "black" does not catalyze this reaction because Pd + TfOH induced little conversion of toluene (column 4, Table 3). A series of experiments have been completed for another substrate (methyl benzoate) using a soluble Pd^0 complex: $Pd_2(dba)_3$ where (dba) is dibenzylidene acetone (13). In the absence of molecular O_2, this catalyst is inactive for coupling methyl benzoate; therefore, we suggest that it is equally inactive toward coupling toluene. Kashima *et al.* (26) also reported data for the effect of varying the concentration of palladium acetate on the reaction rate of toluene coupling in the presence of an oxidant. The overall yields of bitolyl increase with increasing catalyst concentration up to 1.4×10^{-2} M palladium acetate. Further increases in the catalyst concentration to 2.7×10^{-2} M did not increase the bitolyl yields. These results suggest that not all of the Pd^0 formed during the reaction, is reoxidized to Pd^{2+} at high catalyst concentration.

The slope of the toluene conversion curve vs. Pd(II) amount (Fig. 1) may be explained by the mechanism reported by the UBE group (14). This mechanism suggests that three molecules of toluene will be sequestered for every Pd(II) ion initially present in the reaction mixture when the Pd(0) is not reoxidized. Our results agree with this mechanism since the slope of the toluene conversion curve is 3.08 in the stoichiometric mode (i.e., no reoxidation of the Pd).

Under the reaction conditions used in the present study, the main coupling product is 3,4′-DMBP. At shorter reaction times (30 min), the selectivity to 3,4′- and 4,4′-DMBP are nearly equal in agreement with the results of Davidson and Triggs who observed the regioselectivity in the coupling of toluene in acetic acid/perchloric acid (9). Since the reaction occurs in the presence of TfOH, isomerization of the 4,4′-DMBP to thermodynamically favorable 3,4′- and other DMBP isomers may account for the higher selectivity of 3,4′-DMBP. In order to confirm this point, we investigated the reaction of 4,4′-DMBP dissolved in toluene at 10 mol% in the presence of TfOH (TfOH/toluene = 1) but *without* the palladium salt. It was found that ca. 60% of the 4,4′-DMBP was transformed to 3,4′-DMBP in 2 h; formation of other isomers of DMBP was less than 5% of 3,4′-DMBP. Thus, isomerization of the products by strong acid could explain some of the regioselectivity demonstrated by this catalyst.

We compare our results (Table 4) to those appearing in the open literature. The reactivity of the $Pd(TfO)_2$/TfOH is the greatest of those listed in Table 4 when one considers the values of the turnover rate and the temperature of the reaction. The $Pd(AcO)_2$/H(acac) system shows a smaller turnover rate (0.00021 h^{-1}) than the present work, when one corrects for the effect of temperature (*vide supra*). All other entries show turnover rates smaller than the present work using triflic acid regardless of temperature.

The regioselectivity is also summarized in Table 4 for these systems. The effect of the triflic acid is to favor the selectivity to 3,4′- and 4, 4-′DMBP (total = 85%), whereas the other systems using weaker acids as cocatalysts ($HClO_4$ and CF_3COOH) show smaller yields of these two components (66–75 and 52%, respectively). The systems in acetic acid show a combined selectivity to 3,4′- and 4,4′-DMBP in the range of 48–55%.

CONCLUSIONS

A direct coupling reaction of toluene for synthesis of DMBP has been reported in the presence of a strong acid and Pd(II) at room temperature. The presence of both $Pd(TfO)_2$ and TfOH is shown to be crucial for an effective coupling of toluene at room temperature. Moreover, the reaction rate is promoted by H^+ when the anion is labile such as OTf^- so that the overall reactivity of the Pd(II)/HOTf system is greater than that reported by others for the Pd(II) system in weaker acids such as acetic or trifluoroacetic acid. The regioselectivity is altered by increasing acid strength to favor coupling in the 3- and 4-positions.

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