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An efficient Pd(II)-based catalyst system for carboxylation of aromatic C–H bond by addition of a phosphenium salt

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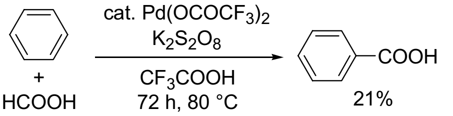
This article is dedicated to Professor Iwao Ojima on the occasion of his 60th birthday

Abstract—Addition of a phosphenium dramatically improved the reaction yields in the carboxylation of arenes by formic acid catalyzed by Pd(II). Control experiments revealed that the majority of the phosphenium triflate was converted to a mixed anhydride of phosphonic acid and formic acid (**7**), which however did not substitute for the phosphenium to improve the reaction yield.

Catalytic activation of aromatic C–H bonds leading to a new C–C bond formation is of considerable interest in organic synthesis.[1–5] Compared with Friedel–Crafts reaction, it would provide simple, clean, and economic methods for making many useful substituted aromatic compounds directly from simple arenes. Fujiwara and co-workers developed the electrophilic substitution of an aromatic hydrogen atom by Pd(II) to produce an arylpalladium species.[6] The arylpalladium was further allowed to react with CO,[7–9] CO_2,[10] O_2,[11,12] alkenes,[13,14] alkynes,[15] and nitrile[16] to form aromatic carboxylic acids, phenols, alkylarenes, alkenylarenes, and ketones, respectively. Recently, Grushin reported similar carboxylation of arenes by Rh-based catalyst system.[17] We recently reported the Pd-catalyzed carboxylation of aromatic C–H bonds by using formic acid as a carbonyl source (Eq. 1).[18] Given that CO and CO_2 are gaseous, formic acid is more favorable for handling to produce aromatic carboxylic acids.[19] Here we report an efficient catalyst system for carboxylation of aromatic C–H bond by using phosphenium salts as additives to achieve high yields in the Fujiwara-type carboxylation with formic acid as a carbonyl source.



(1)

Originally, phosphenium salts have been studied in comparison with its isoelectronic species, such as carbene and silylene since its discovery.[20–25] Phosphenium may behave as a σ-donor (Lewis base) and also as a π-acceptor (Lewis acid) due to the sp^2 lone pair electrons and a vacant p-orbital, respectively. In spite of their interesting properties, however, only few catalytic reactions by the use of phosphenium salts have been reported so far.[26,27] In fact, Baker showed his perspective[22] that some reactions whose mechanisms include the cationic transition-metal complexes would be accelerated by using strong electron-withdrawing ligands, such as phosphenium ions. Baker's insight prompted us to use phosphenium salts for our Pd-catalyzed carboxylation (Eq. 1), whose key step is the electrophilic substitution of aromatic hydrogen atom by Pd(II).[18] The catalytic activity was improved by the addition of phosphenium ion but no evidence was obtained to support the formation of palladium–phosphenium complex.

Crystallographic study of phosphenium triflate **1** was carried out to confirm the geometry around the central phosphorus atom of **1**.[28] Baker reported applications of phosphenium triflates for isolation of phosphenium-ligated rhodium[22] and platinum[25] complexes. In their

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Keywords: Electrophilic substitution; Phosphenium salt; Palladium; Carboxylation; Catalyst.

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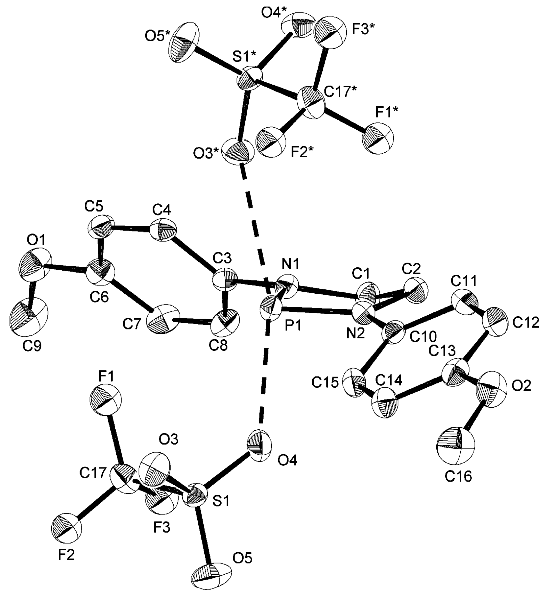
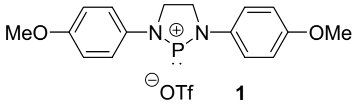
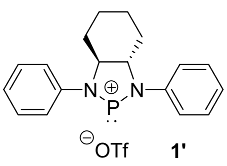


Figure 1. ORTEP drawing of phosphenium triflate **1** with the triflate anion of the other molecule. Dashed line is indicating the interactions between the central phosphorus atom and two oxygen atoms. (A minor part of disordered three fluorine atoms in triflate anion and hydrogens were omitted for clarity.)

reports, they suggested that the structure of phosphenium triflate **1** may consist of the weak coordination of the triflate to the phosphorus atom based on a previously reported structure of phosphenium triflate **1′**.[29] Single crystals suitable for X-ray analysis of **1** were grown from a toluene solution diffused with hexane at −30 °C under argon. As shown in Figure 1, solid state structure of **1** indicates that the central phosphorus atom has two kinds of weak interactions between the vacant p-orbital of cationic phosphorus and oxygen atoms of two triflate anions (P1–O4 = 2.4210(18) Å, P1–O3* = 2.8322(19) Å where O3* is one of oxygen atoms of triflate anion in the other molecule) (Table 1) to form pseudo-trigonal bipyramidal structure with a remaining lone pair as the 5th substituent in the equatorial position. Thus, the weak coordination of the triflate to the central phosphorus atom, that is similar to **1′**,[29] has been confirmed.



1

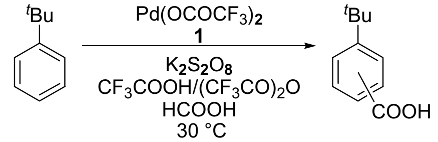


1′

Table 1. Selected interatomic lengths (Å) and angles (°) of **1**

P(1)–N(1)	1.628(2)	P(1)–N(2)	1.634(2)
P(1)–O(4)	2.4210(18)	P(1)–O(3*)	2.8322(19)
N(1)–C(1)	1.479(3)	N(2)–C(4)	1.485(3)
N(1)–P(1)–N(2)	93.74(10)	P(1)–N(1)–C(1)	114.01(16)
P(1)–N(2)–C(2)	114.32(16)	P(1)–N(1)–C(3)	122.47(16)
P(1)–N(2)–C(10)	124.64(16)	N(1)–P(1)–O(4)	93.48
N(2)–P(1)–O(4)	94.40	N(1)–P(1)–O(3*)	90.89
N(2)–P(1)–O(3*)	101.24		

Table 2. Optimization of conditions for carboxylation reaction[a]



Run	**1**/Pd	Time (h)	Yield[b] (%)
1	—	48	18[c]
2	0.55	24	32[c]
3	1.1	24	69[c]
4	2.2	24	22[c]
5	3.3	24	24[c]
6	1.1	48	84[d]
7	1.1	48	22[c,e]
8	1.1[f]	48	2[c]

[a] 5 mol % $Pd(OCOCF_3)_2$. 1.5 equiv $K_2S_2O_8$, $CF_3CO_2H/(CF_3CO)_2O$ solvent (10:1).

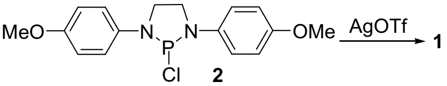
[b] Sum of the two isomeric carboxylic acid (*meta*/*para* = 1:3).

[c] Yields were determined by ^1H NMR using $C_2H_4Cl_2$ as an internal standard because of the presence of unseparable byproducts.

[d] Isolated yield.

[e] $Pd(OAc)_2$ was used.

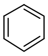
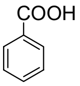
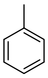
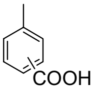
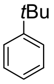
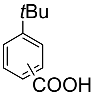
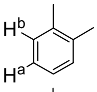
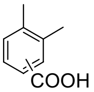
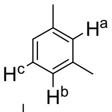
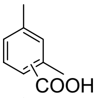
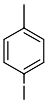
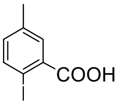
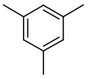
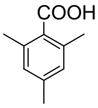
[f] **2** was used instead of **1**.



For the carboxylation of arenes, the reaction conditions were optimized with/without phosphenium salt **1**.[30] According to our previous report,[18] arenes and formic acid were used as substrates in the presence of $Pd(OCOCF_3)_2$ as a catalyst, $K_2S_2O_8$ as an oxidant, phosphenium salts as additive, and a mixture of $CF_3COOH/(CF_3CO)_2O$ as a solvent. Results are summarized in Table 2. In the absence of the phosphenium additive, the carboxylated product was obtained in 18% yield in 48 h (run 1). The **1**/$Pd(OCOCF_3)_2$ ratio was optimized in runs 2–5 and the highest yield of 69% in 24 h was achieved with 1.1 equiv of **1** to Pd (run 3). Longer reaction time of 48 h improved the yield up to 84% (run 6).[31] The use of $Pd(OAc)_2$ in place of $Pd(OCOCF_3)_2$ caused the drop of the yield to 22% (run 7). Addition of chlorophosphine **2** instead of phosphenium **1** resulted in almost no reaction. Thus, in the following studies, the reaction condition of run 6 was chosen as the standard condition.

The scope and generality of this reaction have been explored by using various commercially available arenes (Table 3). The reaction exhibited good yields and gave no byproducts for benzene and alkyl-substituted benzenes although electron-poor arenes, such as benzonitrile, nitrobenzene, and α,α,α-trifluorotoluene, did not react at all. Benzene was converted to benzoic acid as a sole product in 53% yield (run 1). In the cases of mono- and di-substituted arenes, carboxylation at the sterically less-hindered position took place predominantly (runs 2–5). Different steric factor of the alkyl group in the mono-substituted arenes did not affect the total yield of the carboxylated arenes, but did change the isomeric ratio of the products (runs 2 and 3). In the case of *m*-xylene, even sterically hindered C–H bond was activated

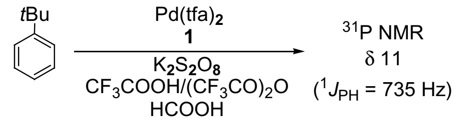
Table 3. Reaction scope of the carboxylation[a]

Run	Arene	Product	Yield
1			53[b]
2			89[c]
3			86[d]
4			83[e]
5			71[f]
6			80[b]
7			93[b]

[a] 11 mol % **1**, **1**/Pd = 1.1. 30 °C, 48 h, 1.5 equiv $K_2S_2O_8$, CF_3CO_2H/$(CF_3CO)_2O$ solvent (10:1).
[b] Single product was obtained.
[c] $o/m/p$ = 18:31:51.
[d] $o/m/p$ = 0:25:75.
[e] H^a/H^b = 83:17.
[f] $H^a/H^b/H^c$ = 14:9:77.

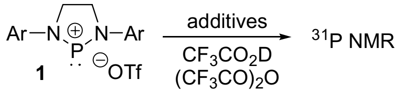
under the reaction condition (run 5). The reaction of mesitylene afforded 2,4,6-trimethylbenzoic acid as a sole product in a high yield even though mesitylene has only hindered C–H bonds. Hence, the present carboxylation reaction widely covers a range of substituted aromatic hydrocarbons with high yields.

In order to elucidate the role of phosphenium **1** in the catalytic reaction, an aliquot taken from the reaction mixture was analyzed by ^{31}P NMR spectroscopy. The only visible peak was at δ 11 with $^1J_{PH} = 735$ Hz (Eq. 2). For the purpose of characterization of this peak, several control experiments by ^{31}P NMR spectroscopy were carried out (Table 4). Although **1** exhibits a singlet peak of δ 185 in C_6D_6, a higher-field shift of the peak of **1** to δ 108 (accompanied by two small peaks of δ 132 and 4) in ^{31}P NMR spectrum was observed when the phosphenium was dissolved in the reaction media, that is, $CF_3COOD/(CF_3CO)_2O$ (run 1). Considering that the reaction of tris(dialkylamino)phosphines with acetic anhydride formed $P(OAc)_3$ via the P–N bond cleavage,[32] the peak at δ 108 could be assigned to $P(OCOCF_3)_3$ (**5**) (Scheme 1).[33,34] No change in chemical shifts and intensities of the three peaks in the existence of palladium, which implied that the formation of any phosphorus-containing palladium complex is less probable (run 2). An addition of formic acid made a significant chemical shift change to δ 11 with $^1J_{PH}$ of 739 Hz in ^{31}P NMR spectrum regardless to the existence of $Pd(OCOCF_3)_2$ and benzene (runs 3, 4, and 5). This peak was assigned to be mixed anhydride **7** as follows. Dissolving PCl_3 in HCOOH afforded a single peak at δ 11. The peak at δ 11 was also observed by an addition of HCOOH to $P(OCOCF_3)_3$ (**5**). Considering the P–H coupling constant and chemical shift of $HP(=O)(OAc)_2$ (δ_P 3, $^1J_{PH} = 620$ Hz),[35] one can expect that the peak of δ 11 is assignable to mixed anhydride **7**, which consists of phosphonic acid and formic acid although **7** was not able to be isolated.[36] Thus, phosphenium salt **1** seems to have transformed into **5** through **3** and **4** in $CF_3COOH/(CF_3CO)_2O$ solvent.



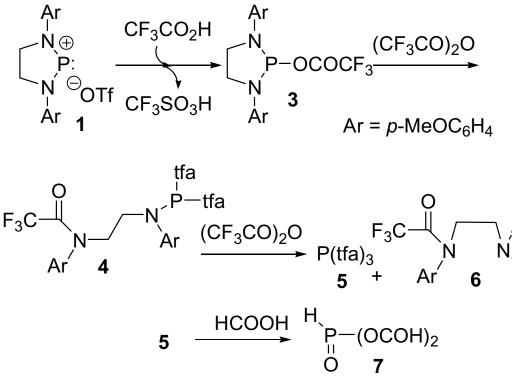
(2)

Table 4. The ^{31}P NMR chemical shift of phosphenium **1** with additives in $CF_3COOD/(CF_3CO)_2O$[a]



Run	Additives	δ_P (ratio)	$^1J_{PH}$ (Hz)
1	None	132, 108, 4.2 (1:8:1)	—
2	$Pd(tfa)_2$[b]	132, 108, 3.4 (1:7:1)	—
3	$Pd(tfa)_2$,[b] C_6H_6,[c] HCOOH[d]	11 (single peak)	739
4	C_6H_6,[c]HCOOH[d]	11 (single peak)	739
5	HCOOH[d]	11 (single peak)	739

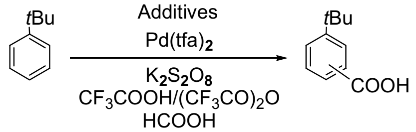
[a] **1** 55 μmol (24.8 mg), TFA-D 0.5 mL, TFAA 0.05 mL.
[b] 50 μmol.
[c] 1 mmol.
[d] 6 mmol (121 equiv).



Scheme 1. Sequential transformation of phosphenium in the reaction media.

For the catalytic reaction, however, the use of mixed anhydride **7** instead of phosphenium **1** did not reproduce the yield achieved with **1**. The carboxylation reaction by using phosphenium **1** took place in 69% yield (Table 5, run 1, the same as Table 2, run 3). In run 2, $P(OCOCF_3)_3$ (**5**) generated from PCl_3 and $AgOCOCF_3$ didn't lead to high yield although mixed anhydride **7** should be generated from **5** and formic acid. To assimilate a reaction condition to the optimized

Table 5. Examination of the transformation of phosphenium **1**



Run	Additives	Yields (%)
1	**1**	69
2[a]	**5**	Trace
3	**6**	Trace
4[a]	**5**, **6**	Trace

t-Butylbenzene 4 mmol, Pd(tfa)$_2$ 0.2 mmol, TFA-H 2.0 mL, TFAA 0.2 mL, HCOOH 1.0 mL, $K_2S_2O_8$ 6.0 mmol, **1** 0.22 mmol, **5** 0.22 mmol, **6** 0.22 mmol, 24 h, 30 °C.

[a] **5** was generated from PCl_3 + $AgOCOCF_3$.

one, independently synthesized diamide **6** was added to the reaction system (runs 3 and 4), but only trace amount of product was obtained. Thus, it ascertained that adding phosphenium **1**, not **7**, to the reaction system had some special effects.

In conclusion, we found a new phosphenium usage as an additive for the carboxylation reaction. Various arenes were converted to the corresponding arenecarboxylic acids in high yields. The mixed anhydride **7** was revealed to be the major species containing phosphorus atom under the carboxylation reaction. However, this was not an active species, and thus the origin of the phosphenium effect towards the better yields is now under investigation.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.027.

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28. Crystal data for **1** (CCDC No 255646) colorless prism, $0.50 \times 0.50 \times 0.20$ mm^3, $C_{17}H_{18}F_3N_2O_5PS$, $M = 450.36$, $T = 120(2)$ *monoclinic*, $P2_1/c$ $a = 13.531(3)$ Å, $b = 9.111(2)$ Å, $c = 15.898(4)$ Å, $\beta = 96.2910(9)°$.
29. Jones, V. A.; Sriprang, S.; Thornton-Pett, M.; Kee, T. P. *J. Organomet. Chem.* **1998**, *567*, 199–218.
30. Addition of two other phosphenium salts, which have 2,4,6-trimethylphenyl or 2,6-diisopropylphenyl group on each nitrogen atom instead of 4-methoxyphenyl group, to the reaction system resulted in poorer yields.
31. The yield of *t*-butylbenzoic acid was increased by time to time up to 48 h (see Supplementary data). During the reaction, no change in isomeric ratio of the products was observed.
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33. Garner, C. D.; Hughes, B. *Inorg. Chem.* **1975**, *14*, 1722–1724.
34. Although Ref. 33 did not reported the ^{31}P NMR chemical shift of $P(OCOCF_3)_3$, we confirmed it made from PCl_3 and AgOTf based on the procedure described in Ref. 33 as δ 108.
35. Sal'keeva, L. K.; Nurmagambetova, M. T.; Kurmanaliev, O. S.; Gazizov, T. K. *Rus. J. Gen. Chem.* **2003**, *73*, 183–186.
36. The solution of **7** evolved small bubbles, which likely to be CO gas due to the formyl group on the phosphorus. As the evolution of the bubbles proceeded, the S/N ratio of ^{31}P NMR spectrum changed to lower, indicating continuous decomposition of phosphorus-containing species in this condition.