New developments in transition metal-catalyzed synthetic reactions via C–H bond activation*

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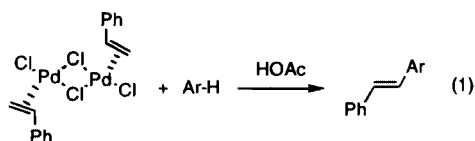
Abstract: Several novel and useful reactions involving transition metal-catalyzed C–H bond activation discovered in our laboratory have been summarized here, which includes olefin arylation, hydroarylation of alkynes, carboxylation of arenes and alkanes, and acetoxylation and aminomethylation of alkanes. Possible mechanisms of these reactions have been suggested.

INTRODUCTION

Catalytic activation of C–H bonds of alkanes and arenes, leading to direct transformations into various functionalized chemicals, is of considerable interest to chemical industries and remains a challenge to chemists, especially of the least reactive alkanes. The success of such processes would provide simple, economic, and clean methods for making many chemicals directly from hydrocarbons [1,2]. Heterogeneous catalysts are commonly employed in petrochemical industries for production of chemical intermediates from hydrocarbons under severe conditions. By comparison, there are relatively few examples of alkane and arene functionalizations catalyzed by homogeneous transition-metal compounds. Homogeneous catalysis offers several advantages, such as high selectivity (either regio-, stereo-, or enantio-) and mild reaction conditions, over heterogeneous process. It is especially attractive to fine chemical industries. Herein, we will briefly summarize the synthetic reactions involving C–H bond activation developed mainly in our laboratory.
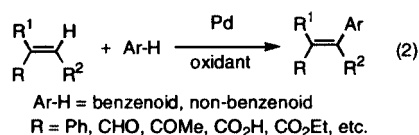
PD-CATALYZED COUPLING OF ARENES WITH OLEFINS

In 1967, we reported Pd(II)-mediated coupling reaction of arenes with olefins in refluxing HOAc (eq. 1) [3a]. In the presence of oxidants such as Ag(I), Cu(II), O_2, t-BuO_2H, and $PhCO_3Bu$-t, the reaction proceeds catalytically to Pd [3b–f]. The reaction is general to arenes and olefins (eq. 2). The reaction is one of the earliest examples of direct arylation of olefins via aromatic C–H bond activation. Recently, we found that a high turnover number (up to 280) could be obtained in the presence of a catalytic amount of benzoquinone as co-catalyst [3f].


$$\text{(1)}$$

$$R^1 \underset{R}{\overset{H}{=}} R^2 + Ar\text{-}H \xrightarrow[\text{oxidant}]{Pd} R^1 \underset{R}{\overset{Ar}{=}} R^2 \quad (2)$$

Ar-H = benzenoid, non-benzenoid
R = Ph, CHO, COMe, CO$_2$H, CO$_2$Et, etc.

σ-Aryl-Pd complexes formed via electrophilic substitution of aromatic C–H bonds by cationic $^+$PdOAc species were proved to be the intermediates in the catalytic cycle (Scheme 1). The complexes have been isolated as stable trinuclear Pd compounds with dialkylsulfide ligands (**1** in Scheme 2) [3j]. The reaction has been extended to intramolecular couplings [4a,b]. Recently, asymmetric arylation of substituted cyclic olefins catalyzed by Pd-chiral sulfonylamino-oxazoline complexes has been reported [4c].
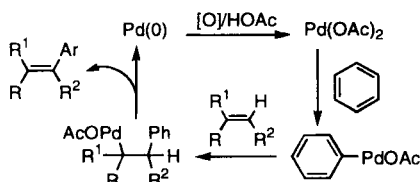

**Scheme 1** Mechanism for Pd-catalyzed coupling of arenes with olefins.
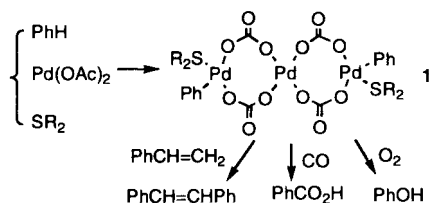
Scheme 2 Reactions involving α-aryl-Pd complexes.

PD- AND PT-CATALYZED HYDROARYLATION OF ALKYNES

In our attempt to extend the coupling reaction of arenes with alkenes to alkynes, we found that the reaction of arenes with alkynes gave addition products instead of coupling products in trifluoroacetic acid (TFA) (Scheme 3) [2b]. The reaction is regio- and stereoselective, and very general with respect to arenes and alkynes, affording *cis*-arylalkenes in most cases. Various arenes including those bearing OH or Br groups underwent the addition reaction to various terminal and internal alkynes (eq. 3) [5]. In some cases, the Pt(II) catalyst showed better selectivity than Pd(II) catalysts. The reactions of heteroaromatic compounds such as furans, pyrroles, and indoles proceed under very mild conditions (even in acetic acid or neutral solvents such as CH$_2$Cl$_2$ at room temperature) [6].
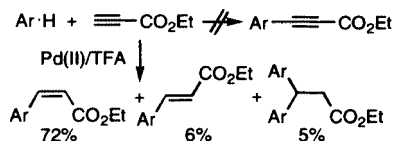
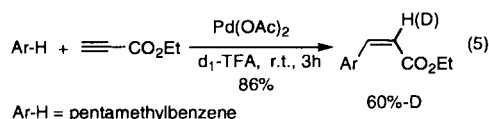**Scheme 3** Pd-catalyzed addition reaction (Ar-H = 1,4-dimethoxybenzene).

Ar-H + R—≡—R^1 $\xrightarrow[\text{or CH}_2\text{Cl}_2]{\text{Pd(II) or Pt(II)}}$ (structure) (3)
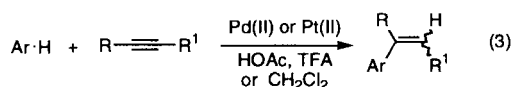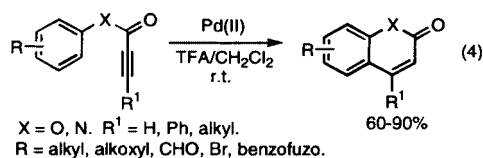
Ar-H = substituted benzenes, furans, pyrroles, indoles, thiophenes.
R = H, alkyl, Ph, CO$_2$Et.
R^1 = H, alkyl, Ph, CO$_2$Et, COOH, COMe, CHO.

The intramolecular version of this reaction provides a general method for preparation of biologically active heterocycles such as coumarins and quinonlinones (eq. 4) [2b,7]. The reaction tolerates various functional groups such as Br, CHO, etc.

(equation 4 structures) $\xrightarrow[\text{r.t.}]{\text{Pd(II)} \atop \text{TFA/CH}_2\text{Cl}_2}$ (4)

X = O, N. R^1 = H, Ph, alkyl.
R = alkyl, alkoxyl, CHO, Br, benzofuzo.
60-90%

Ar-H + ≡—CO$_2$Et $\xrightarrow[\text{86\%}]{\text{Pd(OAc)}_2 \atop d_1\text{-TFA, r.t., 3h}}$ (structure) (5)

Ar-H = pentamethylbenzene
60%-D

Isotope experiments reveal that D-atoms have been incorporated to the vinyl position of adducts either in inter- (eq. 5) or intramolecular reactions. Thus, a possible mechanism involving σ-aryl-Pd complexes similar to those involved in the coupling of arenes with olefins has been suggested (Scheme 4). We also found that a methoxyl substituent greatly increased the reactivity of phenylacetylene in the reaction with pentamethylbenzene (Scheme 5), suggesting possible involvement of vinyl cationic species (such as **2** in Scheme 5) in the reaction.
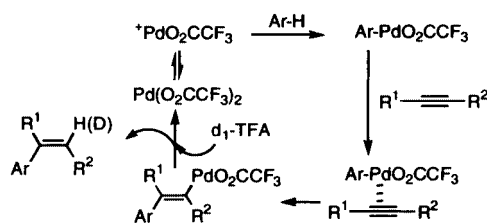
Scheme 4 Possible mechanism for Pd-catalyzed hydroarylation of alkynes.
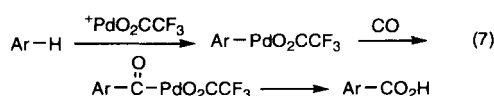
R = H   31% / 48 h
R = OMe   70% / 1 h
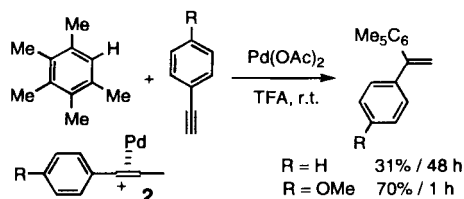
Scheme 5 Pd-catalyzed reaction of phenylacetylenes with pentamethylbenzene.

PD-CATALYZED CARBOXYLATION OF ARENES

The reaction of σ-aryl-Pd complexes **1** (Scheme 2) with CO affords aromatic acids in HOAc [3j], implying the possibility for preparation of aromatic acids directly from arenes, an attractive route for industry. Indeed, we found in the presence of oxidants such as $K_2S_2O_8$, the carboxylation of arenes proceeds catalytically to Pd under mild conditions (room temperature and 1 atm CO) in TFA (eq. 6) [8]. Benzene and chlorobenzene were converted to the corresponding benzoic acids quantitatively in the presence of 10% $Pd(OAc)_2$ [8c,d]. Naphthalene and substituted benzenes afford the mixture of several regio-isomers with α-naphthoic acid and *para*-substituted benzoic acids as the main products, respectively.
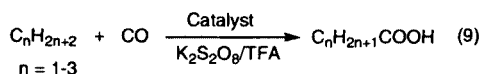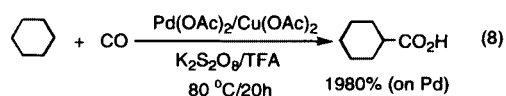
$$Ar-H + CO \xrightarrow[K_2S_2O_8 /TFA]{Pd(OAc)_2 \ \text{r.t.}} Ar-CO_2H \quad (6)$$

$$TON = 8\text{-}33$$
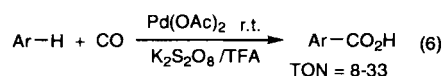
Ar = benzene, chlorobenzene, naphthalene,
toluene, anisole, etc.

$$Ar-H \xrightarrow[O]{^+PdO_2CCF_3} Ar-PdO_2CCF_3 \xrightarrow{CO} \quad (7)$$

$$Ar-\overset{O}{\overset{\|}{C}}-PdO_2CCF_3 \longrightarrow Ar-CO_2H$$

Similarly, the reaction proceeds via electrophilic metallation of aromatic C–H bonds by cationic $^+PdO_2CCF_3$ species to give σ-aryl-Pd complexes, which undergo CO insertion to afford aroylpalladium(II) complexes (eq. 7). The subsequent reductive elimination provides aromatic acids via acid anhydride and Pd(0). Pd(0) would be reoxidized to Pd(II) by $K_2S_2O_8$.
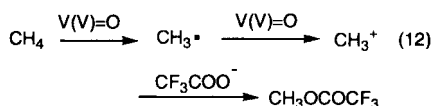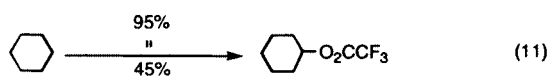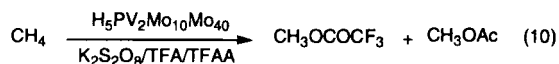
CARBOXYLATION OF ALKANES

Alkanes also undergoes the carboxylation reaction with CO (20–40 atm) in the presence of Pd catalysts in TFA at 80 °C; the Pd(II)/Cu(II) system works efficiently [9]. The first example of alkane caboxylation was performed on cyclohexane, affording cyclohexanecarboxylic acid in 1980% yield based on Pd (4.3% based on cyclohexane, eq. 8) [9a]. Gaseous alkanes such as methane, ethane, and propane were also carboxylated to give the corresponding acids (eq. 9). In 1992, we reported the first synthesis of acetic acid from methane in relatively low yield [9b]. Recently, we found that V-catalysts are very active in alkane carboxylation; methane can be converted to acetic acid almost quantitatively with $VO(acac)_2$ as catalyst [9c]. Also interestingly, $CaCl_2$ exhibits high activity in catalytic conversion of methane to acetic acid but relatively low TON [9d].

$$\text{(hexagon)} + CO \xrightarrow[K_2S_2O_8/TFA \atop 80\ ^\circ C/20h]{Pd(OAc)_2/Cu(OAc)_2} \text{(hexagon)}-CO_2H \quad (8)$$

$$1980\% \ \text{(on Pd)}$$

$$C_nH_{2n+2} + CO \xrightarrow[K_2S_2O_8/TFA]{Catalyst} C_nH_{2n+1}COOH \quad (9)$$

$$n = 1\text{-}3$$

α-Pd-catalyzed carboxylation of alkanes may proceed in a similar fashion to the carboxyation of arenes, involving electrophilic attack of cationic $+PdO_2CCF_3$ species to alkanes to give alkyl-Pd(II)-O_2CCF_3 species. For the V-catalyzed reaction, the involvement of radical species has been suggested. The V(V)=O species could abstract H· from CH_4 to form methyl radical CH_3·, which could react with CO to give acetyl radical CH_3CO·. The oxidation of CH_3CO· to CH_3CO^+ by V(V)=O would give acetic acids [9c].
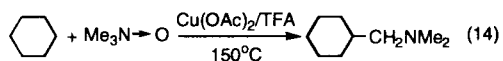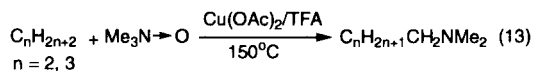
OXIDATIVE ACETOXYLATION OF ALKANES

Various transition-metal catalysts have been investigated for conversion of alkanes to alcohol derivatives [10], especially for converting abundant but the least reactive methane to methanol derivatives. Recently, we found that the V-containing heteropolyacids are very active in this transformation (eqs. 10, 11). Methane is converted to methyl trifluoroacetate along with a small amount of methyl acetate in 95% yield in a mixture of TFA/TFAA (80 °C, 20h) [10a]. Also, simple $Cu(OAc)_2$ is found to be very active as catalyst in this reaction [10b]. A possible mechanism involving the formation of methyl radicals via abstraction of H· by V(V)=O from methane and subsequent oxidation of methyl radical to methyl cations has been suggested (eq. 12).

$$CH_4 \xrightarrow[\text{K}_2\text{S}_2\text{O}_8/\text{TFA/TFAA}]{\text{H}_5\text{PV}_2\text{Mo}_{10}\text{Mo}_{40}} CH_3OCOCF_3 \ + \ CH_3OAc \quad (10)$$

$$\bigcirc \xrightarrow[45\%]{95\%} \bigcirc\text{-O}_2\text{CCF}_3 \quad (11)$$

$$CH_4 \xrightarrow{\text{V(V)=O}} CH_3\cdot \xrightarrow{\text{V(V)=O}} CH_3^+ \quad (12)$$
$$\xrightarrow{\text{CF}_3\text{COO}^-} CH_3OCOCF_3$$

CU-CATALYZED AMINOMETHYLATION OF ALKANES

Direct catalytic introduction of amino groups to alkanes should be a very important reaction. However, few reports are available on such transformation. In continuing studies on exploring synthetic reactions via C–H bond activation, we have found the Cu-catalyzed reaction of alkanes with *N,N*-dialkylmethylamine *N*-oxide in TFA affords *N,N*-dialkylaminomethylated alkanes (eqs. 13 and 14) [2a,11a,b]. Aminomethylation of ethane with trimethylamine *N*-oxide gave *N,N*-dimethyl-propylamine (1460% on Cu and 14.6% on *N*-oxide) as the sole product. The reaction of propane with trimethylamine *N*-oxide gave *N,N*-dimethylisobutylamine (1400% on Cu, 14% on *N*-oxide).

$$C_nH_{2n+2} + Me_3N\!\rightarrow\!O \xrightarrow[150^\circ C]{\text{Cu(OAc)}_2/\text{TFA}} C_nH_{2n+1}CH_2NMe_2 \quad (13)$$
$$n = 2, 3$$

$$\bigcirc + Me_3N\!\rightarrow\!O \xrightarrow[150^\circ C]{\text{Cu(OAc)}_2/\text{TFA}} \bigcirc\text{-CH}_2\text{NMe}_2 \quad (14)$$

Possible involvement of reactive species such as the Manich iminium base, alkyl radicals, and alkyl-Cu species has been suggested as intermediates in this reaction [2a].

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