

# Catalytic Functionalization of Arenes and Alkanes via C–H Bond Activation

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## ABSTRACT

Several novel synthetic reactions of arenes and alkanes discovered and investigated in our laboratory are summarized here. These include olefin arylation, hydroarylation of alkynes, hydroxylation of arenes, carboxylation of arenes and alkanes, and aminomethylation and acetoxylation of alkanes. Most of these reactions are catalyzed by highly electrophilic transition metal cationic species generated in situ in an acid medium, involving electrophilic metalation of C–H bonds of arenes and alkanes which lead to the formation of aryl–metal and alkyl–metal  $\sigma$ -complexes.

## Introduction

Hydrocarbons, especially alkanes, are the main feedstocks for the chemical industry from oil and natural gas. Therefore, direct and catalytic transformation of alkanes and arenes to various useful chemicals via C–H activation, especially of the least reactive alkanes, is of considerable interest to chemical industries and remains a challenge to chemists.<sup>1</sup> The development of catalytic systems for the catalytic functionalization of saturated as well as aromatic, olefinic, and acetylenic hydrocarbons constitutes an extremely important field of contemporary chemistry. The

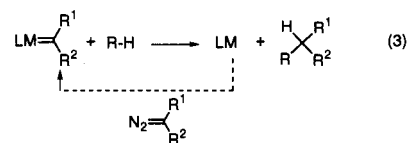
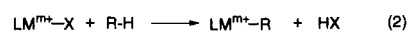
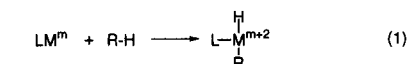
Chengguo Jia obtained his Ph.D. in 1993 from the Institute of Chemistry, Chinese Academy of Sciences (Beijing, China), under the guidance of Prof. Y. Y. Jiang. After postdoctoral studies with Prof. H. Mimoun and P. Mueller at the University of Geneva (Switzerland) 1993–1995 and with Prof. R. C. Larock at Iowa State University 1995–1996, he was employed as a senior research engineer by Research Institute of Petroleum Processing, China Petrochemical Co. (Sinopec), in 1996. Since 1998, he has been working on Pd-catalyzed synthetic reactions with Prof. Y. Fujiwara in Kyushu University as a research fellow of the Japan Society for the Promotion of Science. His research interests cover polymer-supported synthesis and catalysts, zeolite catalysts and transition-metal-catalyzed organic synthesis.

Tsugio Kitamura received his Ph.D. from Kyushu University in 1982 under the direction of Prof. H. Taniguchi. He joined the faculty as a research associate at Kyushu University in 1982. Since 1993, he has been an associate professor at Kyushu University. In 1986–1988, he worked as a postdoctoral fellow with Prof. P. J. Stang at the University of Utah. His research interests involved the mechanistic and synthetic chemistries on vinyl cations. His current interests are in the field of chemistry of hypervalent main group elements (iodine and sulfur) and transition metals such as palladium.

Yuzo Fujiwara received his Ph.D. from Osaka University under the supervision of Prof. I. Moritani. He worked as an NSF postdoctoral fellow with Prof. G. M. Whitesides at MIT from 1972 to 1974. After working as a research associate at Osaka University, he was promoted to associate professor at Kyushu University in 1977, and full professor at Hiroshima University in 1988. Prof. Fujiwara moved to Kyushu University in 1995. Prof. Fujiwara has very broad research interests in developing new synthetic reactions based on the chemistry of both d- and f-block transition metals, especially palladium and rare earth metals. He has been the recipient of several scientific awards, including Japan Rare Earth Society Awards in 1992 and Chemical Society of Japan Award in 2000.

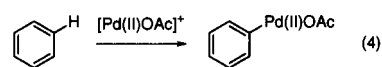
success of such processes would provide potentially economic and clean methods for making many chemicals directly from hydrocarbons.<sup>2</sup> One of the main reasons for the challenge arises from the high strength of C–H bonds in alkanes and arenes (e.g., methane, 105 kcal/mol; benzene, 110 kcal/mol).

Over the past 20 years, there has been a massive effort to achieve selective C–H bond activation by transition metal complexes.<sup>1</sup> The catalytic reactions involving the oxidative addition to C–H bonds (eq 1)<sup>3a–c</sup> and electrophilic substitution (eq 2)<sup>3d–f</sup> of C–H bonds of alkanes by highly reactive metal complexes have been shown to be very promising approaches to the application of the reactions of C–H bonds of alkanes to the synthesis of carboxylic acid, amine, and alcohol derivatives.



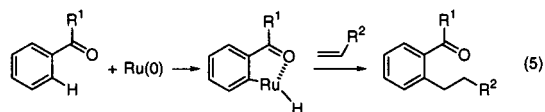
Recently, an alternative method has been described to achieve asymmetric intermolecular C–H activation of a range of alkanes and tetrahydrofuran through a C–H insertion mechanism (eq 3) by rhodium carbenoids derived from methyl aryldiazoacetates and a dirhodium complex.<sup>4</sup> The reaction has very good chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity, favoring C–H insertion into secondary and tertiary sites.

The study of aryl C–H bond activation by transition metal compounds began in the 1960s and followed the successful development of acid-catalyzed and acid-promoted Friedel–Crafts arene alkylation and acylation chemistry in the early part of the 20th century. In 1967, we reported that Pd(II) complexes could mediate the coupling of arenes with olefins in refluxing HOAc.<sup>5a</sup> This reaction involves the electrophilic substitution of aromatic C–H bonds by Pd(II) species (eq 4) and is one of the earliest examples of aromatic C–H bond activation by transition metal compounds.<sup>5b</sup> However, while there are



many examples of stoichiometric aryl C–H bond activation by transition metal compounds,<sup>1</sup> there are relatively few catalytic systems that are synthetically practicable. Activation of aromatic C–H bonds by ortho-chelation, an oxidative addition using low-valent transition metal compounds followed by additions to C–C multiple bonds, is a promising example of such catalysis (eq 5).<sup>1b,7</sup> However,

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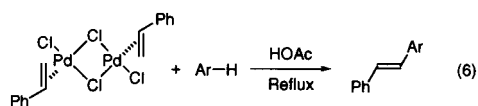


synthetically useful catalytic arene C–H activation by transition metals remains uncommon. In most cases, the direct use of aromatic compounds in synthesis relies on the presence of a more reactive group than a C–H bond. For example, it is common to employ activation of the C–X (X = Cl, Br, or I) bond of aryl halides to transfer aryl groups.<sup>6</sup> While this chemistry can be very successful and catalytically efficient, the manufacture of aryl halides is not an environmentally friendly process. Moreover, reactions that activate C–X bonds of aryl halides typically produce halide salts as byproducts. Thus, it is probable that the development of practical catalytic ways to directly activate C–H bonds of arenes and the successful development of such catalytic reactions would lead to a future where the bulk synthesis of aryl derivatives proceeded by such C–H bond activation.

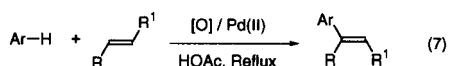
In general, it is more difficult to achieve selective functionalization of alkanes than arenes. The alkanes are unreactive to most conventional reaction systems. The products from alkanes are more reactive than alkanes, which causes the selectivity problems. For several decades, we have been involved in the search for efficient catalytic systems for activation of C–H bond of arenes and alkenes, and the synthetic application of these reactions. Herein, we will give a brief account of the synthetic reactions involving C–H bond activation which were recently discovered and developed mainly in our laboratory. We will also discuss the related research results reported by other groups.

## Pd-Catalyzed Coupling of Arenes with Olefins

With the initial discovery of the stoichiometric coupling reaction of Pd(II)-olefin complexes with arenes (eq 6),<sup>5a</sup> the reaction has been made catalytic in the presence of catalytic amounts of Pd(OAc)<sub>2</sub> and an oxidant such as Ag(I), Cu(II), O<sub>2</sub>, *t*-BuO<sub>2</sub>H, and PhCO<sub>3</sub>Bu-*t* (eq 7).<sup>5b,8</sup> The catalytic reaction is very general to substrates, and a broad spectrum of arenes, heteroarenes, and olefins is compatible with the reaction (yield, 10–90%; turnover number, TON, 3–280). The reaction is one of the earliest examples of direct arylation of olefins via aromatic C–H bond activation.



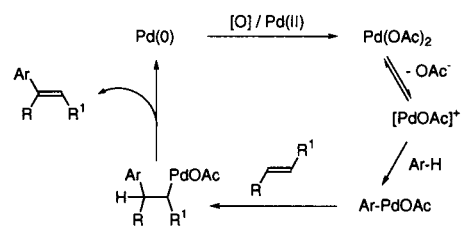
Ar = phenyl, *p*-tolyl, 2,5-dimethylphenyl  
Yield: 15–26% on Pd-complex



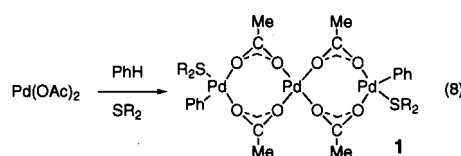
ArH : benzoid and non-benzoid  
R = H, CH<sub>3</sub>, Ph. R<sup>1</sup> = Ph, CO<sub>2</sub>Et, COMe, CHO, CO<sub>2</sub>H, CN  
Yield: 10–90% on olefin  
TON: 3–280

$\sigma$ -Aryl–Pd complexes formed via electrophilic substitution of aromatic C–H bonds by cationic [PdOAc]<sup>+</sup> species have been proved to be the intermediates in the catalytic cycle (Scheme 1). The complexes have been isolated as

Scheme 1. Mechanism for Pd-Catalyzed Coupling of Arenes with Olefins

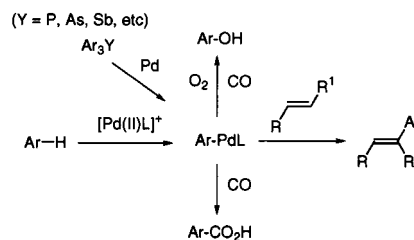


stable tripalladium(II) complexes with dialkylsulfide ligands (**1** in eq 8).<sup>8c</sup> Complex **1** reacts with styrene and CO to give stilbene and benzoic acid, respectively.<sup>8c</sup>



Similar aryl complexes from triarylsarsene, -stibine, or -bismuth have been used in the synthesis (Scheme 2).<sup>9</sup>

Scheme 2. Reaction of Aryl–Pd Complexes



The reaction of aryl halides or triflates with Pd(0) also affords similar aryl–Pd(II) complexes.<sup>6</sup>

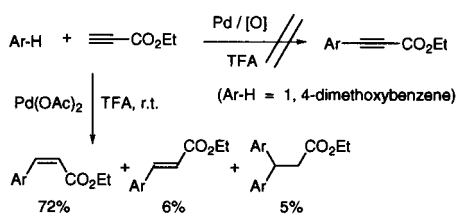
Recently we have found that a high turnover number (up to 280) could be obtained in the presence of a catalytic amount of benzoquinone as cocatalyst and *t*-BuOOH as oxidant.<sup>8d</sup> By this reaction, one can prepare ethyl 3-phenylcinnamate efficiently from ethyl cinnamate and benzene. The application to the synthesis of styrene, an important monomer, from benzene and ethylene is underway. The first asymmetric version of this reaction has been reported in arylation of substituted cyclic olefins catalyzed by Pd–chiral sulfonylamino–oxazoline complexes.<sup>10</sup>

## Pd- and Pt-Catalyzed Hydroarylation of Alkynes

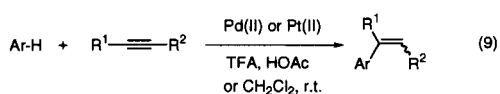
In our attempt to extend the coupling reaction of arenes with alkenes to alkynes, we found that the reaction of arenes with ethyl propiolate gave addition products instead of coupling products in trifluoroacetic acid (TFA) (Scheme 3).<sup>11</sup>

The reaction is regio- and stereoselective, and very general with respect to arenes and alkynes, affording *cis*-

Scheme 3. Reaction of Arenes with Alkynes in TFA

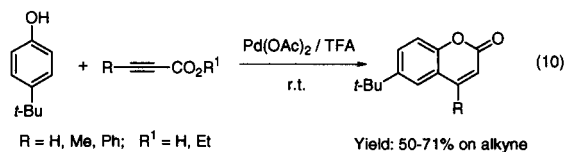


arylalkenes in most cases (yield, 50–98% on alkyne). Various arenes, including those bearing OH or Br groups, underwent the addition reaction to various terminal and internal alkynes (eq 9).<sup>11b</sup> The reaction of electron-rich arenes (donor) with electron-poor alkynes (acceptor) affords good yields, indicating the reaction is electrophilic in nature. In some cases, the Pt(II) catalyst showed lower activity but better selectivity than Pd(II) catalysts.

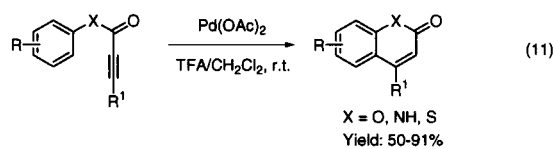


R<sup>1</sup> = H, Ph, CO<sub>2</sub>Et, alkyl  
R<sup>2</sup> = H, Ph, CO<sub>2</sub>Et, CHO, COMe, alkyl  
Ar-H: arenes and heteroarenes  
Yield: 50-98% on alkyne

The reactions of heteroaromatic compounds such as furans, pyrroles, and indoles with alkynoates proceed under very mild conditions (in acetic acid or even in neutral solvents such as CH<sub>2</sub>Cl<sub>2</sub> at room temperature).<sup>11d</sup> The present reaction provides a very convenient method for functionalization of arenes and heteroarenes. The reaction of a phenol with alkynoates affords coumarins (yield, 50–71% on alkyne) (eq 10). A similar reaction carried out in formic acid at room temperature for the synthesis of coumarins has been reported by Trost and Toste.<sup>12</sup> Interestingly, Pd(0), rather than Pd(II), is involved in this reaction.

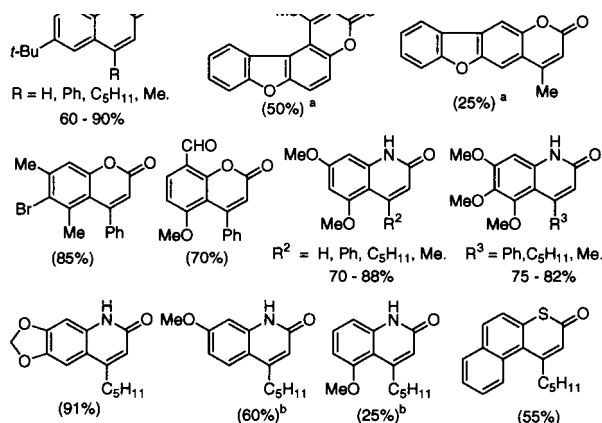


The intramolecular version of this reaction provides a general method for the preparation of biologically active heterocycles such as coumarins, quinonlinones, and thio-coumarins (yield, 50–91%) (eq 11, Scheme 4).<sup>11c</sup> The reaction tolerates various functional groups such as Br, CHO, etc.



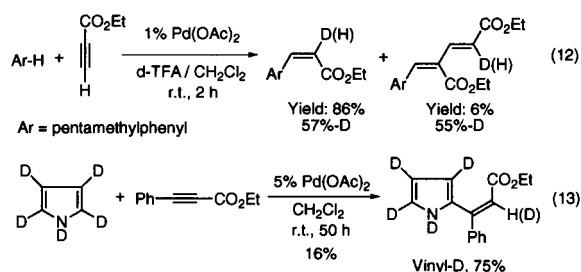
Isotope experiments reveal that D atoms have been incorporated into the vinyl position of adducts either in inter- (eq 12) or intramolecular reactions when the reaction was run in TFA-*d*.<sup>11b,c</sup> The reactions of heteroarenes with alkynoates in AcOD gave similar results.<sup>11d</sup>

Scheme 4. Typical Heterocyclic Compounds from Pd-Catalyzed Intramolecular Hydroarylation (Eq 11)



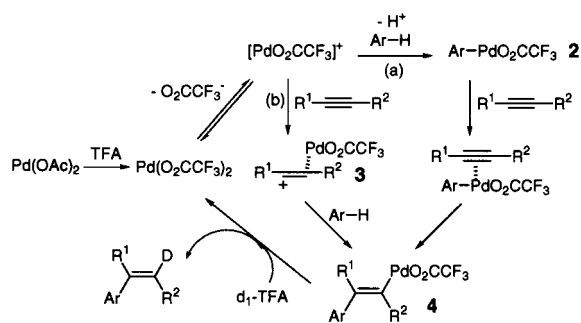
<sup>a,b</sup> The two regioisomers from the same starting materials, respectively. (The numbers in parenthesis refer to the yield.)

Also, the addition of heteroaromatic C–D bonds to C–C triple bonds (eq 13) and a large isotope effect ( $k_{\text{H}}/k_{\text{D}} = 3$ ) between pyrrole and pyrrole-*d*<sub>5</sub> in the reaction with ethyl phenylpropiolate have been observed.<sup>11d</sup>



Thus, a possible mechanism involving  $\sigma$ -aryl–Pd complexes (2) similar to those involved in the coupling of arenes with olefins has been suggested (route a in Scheme 5).

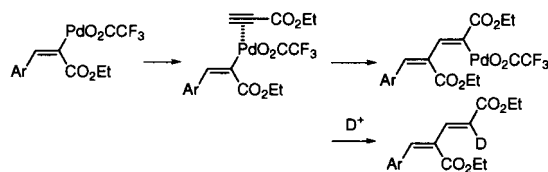
Scheme 5. Possible Mechanism for Inter- and Intramolecular Hydroarylation



Similar aryl–Pt(II) complexes have been synthesized from cationic Pt(II) complexes but have not been used for organic synthesis.<sup>13a,b</sup> The facile formation of such Pd–aryl complexes from Pd(II) and arenes in TFA has been indicated by the coupling reaction of arenes with arenes,<sup>13c,d</sup> and also demonstrated by formation of aromatic acids from simple arenes with carbon monoxide (Scheme 2),<sup>14</sup> and both at room temperature. Although the trans-insertion of aryl–Pd complexes to C–C triple bonds is not

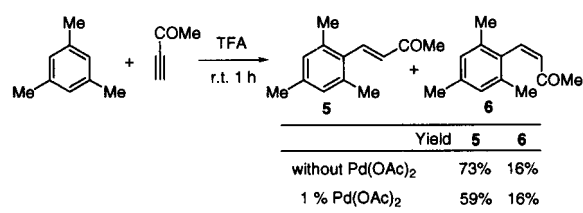
well understood, a similar trans-insertion has been reported in several reactions of alkynes,<sup>15,16</sup> including photoinduced trans-hydrophenylation of alkynes by benzene with a Rh catalyst.<sup>15</sup> The formation of vinyl–Pd complexes (**4**) has been suggested by the formation of adducts of two alkynes and one arene (Scheme 6).<sup>11b</sup> The use of TFA as

Scheme 6. Formation of the Adduct of Two Alkynes and One Arene



solvent facilitates the generation of highly cationic  $[\text{Pd}(\text{II})\text{-O}_2\text{CCF}_3]^+$  species to form  $\sigma$ -aryl–Pd complexes through electrophilic substitution of aromatic C–H bonds. On the other hand, the involvement of vinylcationic species (such as **3**, route b in Scheme 5) in the reaction cannot be ruled out.<sup>11c,17,18</sup> In this context, we have found that the reaction of 3-butyne-2-one with mesitylene can occur without  $\text{Pd}(\text{OAc})_2$  (Scheme 7), clearly indicating the involvement of

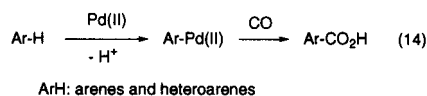
Scheme 7. Reaction of Mesitylene with 3-Butyn-2-one



vinylcationic species generated from alkynes and  $\text{H}^+$  in this reaction. The yield difference in the presence and in the absence of  $\text{Pd}(\text{OAc})_2$  may be explained by the competition between  $[\text{Pd}(\text{II})\text{-O}_2\text{CCF}_3]^+$  and vinylcationic species in electrophilic substitution of aromatic C–H bonds.

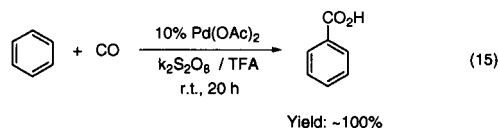
## Pd-Catalyzed Carboxylation of Arenes

The reaction of  $\sigma$ -aryl–Pd complexes **1** (see the structure in eq 8) with CO affords aromatic acids in HOAc (eq 14),<sup>8c</sup> implying the possibility for synthesis of aromatic acids directly from arenes—a very attractive route for industry. In 1980, we reported the first direct carboxylation of arenes with CO in the presence of a stoichiometric amount of  $\text{Pd}(\text{OAc})_2$ .<sup>14a</sup> The reaction can be made catalytic in the presence of oxidants such as  $\text{O}_2$ , *t*-BuOOH, alkyl halides, or  $\text{K}_2\text{S}_2\text{O}_8$ .<sup>14b–e</sup> The reaction can be used to carboxylate arenes and heteroarenes such as furan and thiophene.<sup>14c</sup>



The reaction provides a very convenient and atom-economic method for synthesis of aromatic acids directly from simple arenes, offering a useful alternative to the carbonylation of aryl halides with CO catalyzed by transition metal compounds.<sup>19</sup> Recently, we found that the carboxylation of arenes proceeds in high yields when TFA

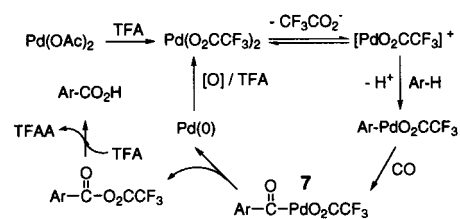
is used as solvent in the presence of  $\text{K}_2\text{S}_2\text{O}_8$  as oxidant under mild conditions (room temperature and 1 atm of CO) in TFA (eq 15).<sup>1e,14d,e</sup> Benzene and chlorobenzene were converted to the corresponding benzoic acids quantitatively in the presence of 10%  $\text{Pd}(\text{OAc})_2$ .



The reaction is electrophilic and results in ortho–para orientation when the benzene is substituted by an electron-donating group. Thus, naphthalene and substituted benzenes afford a mixture of several regioisomers with  $\alpha$ -naphthoic acid and para-substituted benzoic acids as the main products, respectively. Electron-rich arenes such as *p*-xylene give high yields (15730% based on Pd) of 2,5-dimethylbenzoic acid in the presence of  $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2$  as the catalytic system.<sup>1e</sup>

A possible mechanism for the reaction is outlined in Scheme 8.<sup>14d</sup> The reaction proceeds via electrophilic

Scheme 8. Mechanism for Pd-Catalyzed Carboxylation of Arenes

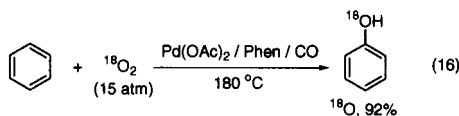


metallation of aromatic C–H bonds by cationic  $[\text{PdO}_2\text{-CCF}_3]^+$  species to give  $\sigma$ -aryl–Pd complexes, which undergo CO insertion to afford acylpalladium(II) complexes (**7** in Scheme 8). The subsequent reductive elimination provides aromatic acids via reductive elimination of Pd and acid anhydride exchange.  $\text{Pd}(0)$  would be reoxidized to  $\text{Pd}(\text{II})$  by  $\text{K}_2\text{S}_2\text{O}_8$ . The presence of TFA facilitates the generation of the highly electrophilic cationic  $[\text{PdO}_2\text{CCF}_3]^+$  species. Therefore, in the presence of TFA, the reaction occurs at room temperature.<sup>14d,e</sup>

## Hydroxylation of Arenes

The reaction of  $\sigma$ -aryl–Pd complexes **1** (see the structure in eq 8) with  $\text{O}_2$  and CO affords phenol (as well as benzoic acid) (Scheme 2),<sup>8c</sup> indicating the possibility of producing phenol from benzene. We succeeded in synthesizing phenol from benzene in the presence of carbon monoxide and a catalytic system:  $\text{Pd}(\text{OAc})_2/1,10$ -phenanthroline in HOAc.<sup>20</sup> We have confirmed the oxygen transformation from  $\text{O}_2$  to phenol by isotope reactions (eq 16).<sup>20b</sup> The reaction also involves the formation of  $\sigma$ -aryl–Pd complexes from electrophilic substitution of aromatic C–H bonds by  $[\text{AcOPd-Phen}]^+$  species, which should react with  $\text{O}_2$ .<sup>20b,c</sup> The combination of CO and 1,10-phenanthroline with  $\text{Pd}(\text{OAc})_2$  is crucial to the reaction. The reaction requires carbon monoxide as the co-reductant; thus, the catalytic system is similar to monooxygenases in some aspects.<sup>21</sup>

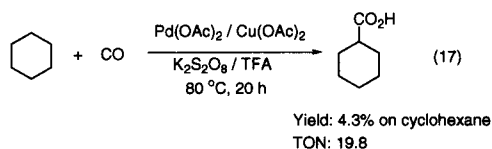




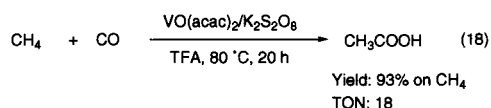
Although the yield of phenol (5.6% on benzene) and the turnover number (10–15 to Pd) are still not high, the reaction represents a completely new approach for phenol synthesis. The direct synthesis of phenols from arenes is of the greatest interest to chemical industry, and the findings of other new catalytic systems have been reported but not industrialized yet.<sup>22</sup>

## Carboxylation of Alkanes

Encouraged by the success of arene carboxylation, we challenged ourselves to investigate the carboxylation of alkanes in the presence of a catalytic amount of the highly electrophilic transition metal cationic species generated in situ in trifluoroacetic acid.<sup>23</sup> With a catalytic system similar to that used in carboxylation of arenes, the first example of catalytic alkane carboxylation based on transition metal compounds was reported in 1989, which was performed on cyclohexane with CO (20–40 atm) with a Pd(II)/Cu(II) catalytic system in TFA at 80 °C, affording cyclohexanecarboxylic acid in 1980% yield based on Pd (4.3% based on cyclohexane, eq 17).<sup>23a,b</sup>



Gaseous alkanes such as methane, ethane, and propane were also carboxylated to give the corresponding acids.<sup>23,24</sup> In 1992, we reported the first synthesis of acetic acid from methane in relatively low yield.<sup>23</sup> Recently, we found that V-catalysts are very active in alkane carboxylation,<sup>24a</sup> and methane can be converted to acetic acid almost quantitatively with VO(acac)<sub>2</sub> as the catalyst (eq 18). Also interestingly, CaCl<sub>2</sub> exhibits high activity in catalytic conversion of methane to acetic acid but relatively low TON.<sup>24b</sup>

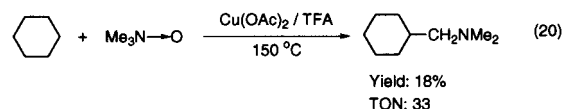
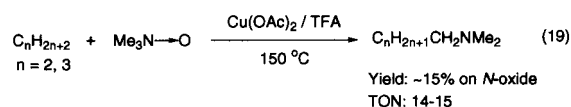


Pd-catalyzed carboxylation of alkanes may proceed in a fashion similar to the carboxylation of arenes, involving electrophilic attack of cationic [PdO<sub>2</sub>CCF<sub>3</sub>]<sup>+</sup> species to C–H bonds of alkanes to give alkyl–Pd(II)–O<sub>2</sub>CCF<sub>3</sub> species. The similar Pt species, alkyl–Pt(II)–O<sub>2</sub>CCF<sub>3</sub>, have been characterized as stable species in strong acids.<sup>3b,25</sup> For the V-catalyzed reaction, the involvement of radical species has been suggested.<sup>24a</sup> The V(V)=O species could abstract H• from CH<sub>4</sub> to form methyl radical CH<sub>3</sub>•, which could react with CO to give acetyl radical CH<sub>3</sub>CO•. The oxidation of CH<sub>3</sub>CO• to CH<sub>3</sub>CO<sup>+</sup> by V(V)=O would give acetic acid.

Similar catalytic systems using transition metal compounds in perfluorocarboxylic acids or other protic media for C–H and C–C bond activation have been reported by Sen.<sup>3f,26</sup>

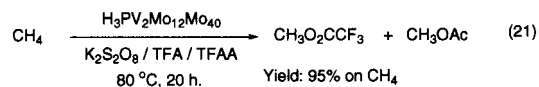
## Aminomethylation and Acetoxylation of Alkanes

Direct and catalytic introduction of amino or hydroxyl groups to alkanes with C–N or C–O bond formation should be very important reactions. However, few reports are available on such transformations.<sup>1,3f</sup> In continuing studies on exploring synthetic reactions via C–H bond activation, we have found that the reaction of alkanes with *N,N*-dialkylmethylamine *N*-oxides in TFA affords *N,N*-dialkylaminomethylated alkanes in the presence of Cu(OAc)<sub>2</sub> as the catalyst (eqs 19 and 20).<sup>27</sup>



Aminomethylation of ethane with trimethylamine *N*-oxide gave *N,N*-dimethylpropylamine (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). Possible involvement of reactive species such as the Mannich iminium base, alkyl radicals, and alkyl–Cu species have been suggested as intermediates in this reaction.<sup>27a</sup>

Various transition metal catalysts have been investigated for conversion of alkanes to alcohol derivatives in strong acids by many research groups,<sup>1,3f,28,29</sup> 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 (eq 21).<sup>30</sup> Methane is converted to methyl



trifluoroacetate in 95% yield along with a small amount of methyl acetate in a mixture solvent of TFA/TFAA (80 °C, 20 h). Heteropolyacids as catalysts in various catalytic reactions have been well documented.<sup>31</sup> Also, simple Cu(OAc)<sub>2</sub> has been found to be very active as a catalyst in this reaction.<sup>30b</sup> A possible mechanism involving the formation of methyl radical via abstraction of H• by V(V)=O from methane and subsequent oxidation of methyl radical to methyl cation has been suggested.<sup>30a</sup>

Sen et al. reported the first electrophilic activation and conversion of methane to a methanol derivative by H<sub>2</sub>O<sub>2</sub> in TFA,<sup>32</sup> using the Pd(II)/TFA system which we employed in our earlier reports.<sup>33</sup>

Periana et al. reported highly efficient esterifications of methane using the Hg(II)/H<sub>2</sub>SO<sub>4</sub> and Pt(II)/H<sub>2</sub>SO<sub>4</sub> catalyst systems. The reactions are electrophilic in nature to give esters in high yields (43 and 72% yields, respectively).<sup>34</sup>

## Conclusion

In summary, the electrophilic activation of aromatic and alkyl C–H bonds, leading to some very useful synthetic reactions, has been discussed here. Most of these reactions are catalyzed by highly electrophilic transition metal cationic species generated in situ in an acid medium. These reactions provide a novel strategy for catalytic functionalization of alkanes and arenes with C–C, C–O, and C–N bond formation.

By utilizing our new hydroarylation of alkynes, one can prepare biologically active heterocycles such as coumarins, quinolinones, and thiocoumarins in high yields under very mild conditions. And the processes for the syntheses of styrene from benzene and ethylene, phenol from benzene and O<sub>2</sub>, acetic acid from methane and CO, and methanol from methane will be industrialized in the near future, when efficiencies of the metal catalysts (turnover number) are improved.

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