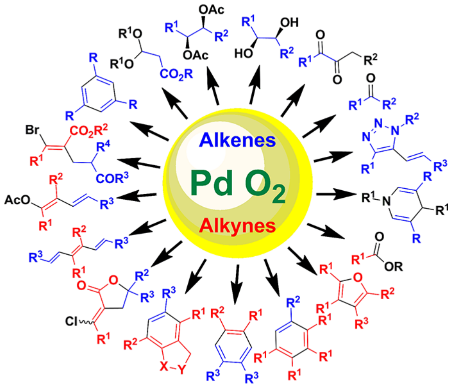
ACCOUNTS
of chemical research

Palladium-Catalyzed Oxidation of Unsaturated Hydrocarbons Using Molecular Oxygen

WANQING WU AND HUANFENG JIANG*
School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China

RECEIVED ON FEBRUARY 13, 2012

CONSPECTUS



Oxidation reactions are central components of organic chemistry, and modern organic synthesis increasingly requires selective and mild oxidation methods. Although researchers have developed new organic oxidation methods in recent years, the chemistry community faces continuing challenges to use "green" reagents and maximize atom economy. Undoubtedly, with its low cost and lack of environmentally hazardous byproducts, molecular oxygen (O_2) is an ideal oxidant. However, relatively limited methodologies are available that use O_2 efficiently in selective organic transformations.

Recently, the use of metal catalysts coupled with the reduction of O_2 has become an attractive approach for aerobic oxidation. In particular, Pd complexes have shown great potential for the development of versatile aerobic reactions because of their ability to directly couple O_2 reduction. As a result, these complexes have attracted tremendous research attention and afford new opportunities for selective oxidation chemistry.

In this Account we highlight some of our progress toward the synthetic goal to functionalize the unsaturated hydrocarbons largely through the appropriate choice of Pd catalysts and O_2. We have focused on developing simple and efficient methods to construct new carbon-carbon and carbon-heteroatom bonds with O_2 as the oxidant and/or reactant. We have demonstrated Pd-catalyzed oxidation of carbon-carbon double bonds, Pd-catalyzed oxidation of carbon-carbon triple bonds, and Pd-catalyzed oxidative cross-coupling reactions of alkenes and/or alkynes with high selectivity. O_2 plays a critical role in the success of these transformations. Most of the reactions can tolerate a range of functional groups, and some can occur under aqueous conditions. Depending on the specific process, we propose several mechanistic scenarios that describe the in situ generation of different intermediates and discuss the plausible reaction pathways.

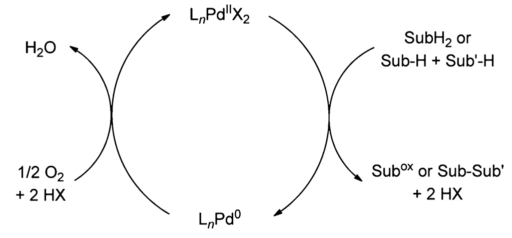
These methods provide new strategies for the green synthesis of diverse 1,2-diols, carbonyls, lactones, conjugated dienes, trienes, and aromatic rings. These products have potential applications in natural product synthesis, materials science, and bioorganic chemistry. Given our new mechanistic understanding, we are optimistic that additional Pd-catalyzed aerobic oxidative transformations will be developed that are both more economical and environmentally friendly.

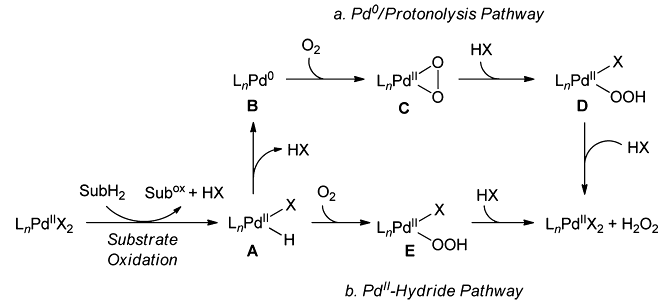
I. Introduction

Oxidation reactions are crucial for both heteroatom introductions and functional group transformations in organic synthesis. The development of selective and practical oxidation reactions employing "green" oxidants is one of the key issues in modern organic chemistry. Molecular oxygen (O_2) is no doubt the best choice due to its inexpensive and environmentally benign nature. Although a number of industrial processes feature catalytic methods for aerobic oxidation, the synthetic scope and utilities of O_2 for more complex molecules are still limited.[1]

Over the past decades, transition-metal-catalyzed reaction has emerged as one of the most attractive and powerful strategies for efficient assembly of new chemical bonds.[2] Particularly, Pd catalysis, which mainly includes cross-coupling reactions initiated by Pd^0 and oxidative transformations started with Pd^{II}, has found widespread use in organic synthesis since the discovery of the Wacker process in the late 1950s.[3] However, the relative reduced attention to Pd-catalyzed oxidations is possibly due to the requirement for a stoichiometric oxidant such as Cu^{II}, Ag^{I} salts, and benzoquinone to regenerate the active catalyst, which usually

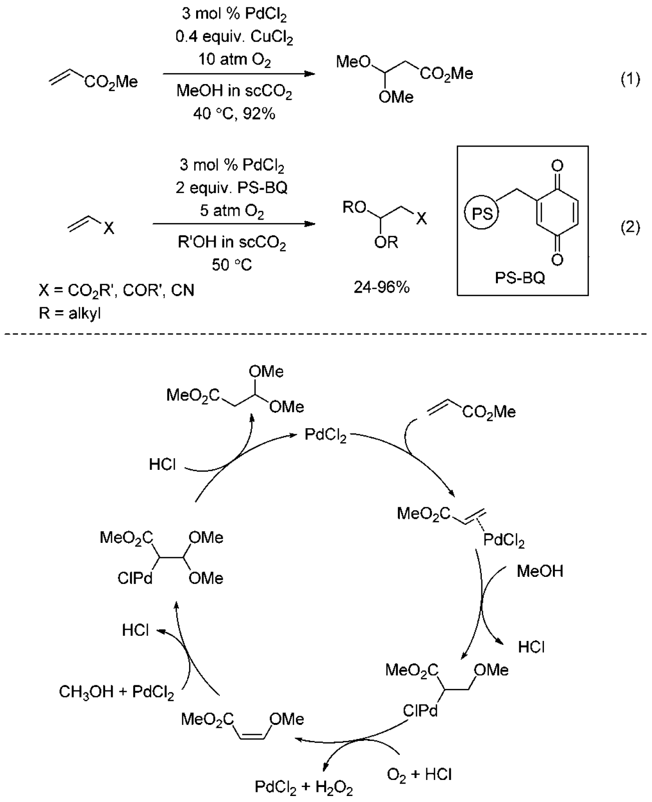
10.1021/ar3000508


SCHEME 1. Simplified Catalytic Cycle of Pd-Catalyzed Oxidation Reactions


SCHEME 2. Proposed Pathways for the Oxidation of Pd Complexes with O_2

leads to the complexity of the reaction system and a decrease in atom economy. Clearly, the most advantageous is the direct utilization of O_2.[4]

In general, Pd oxidative catalysis can be divided into substrate oxidation with Pd^{II} and O_2-coupled regeneration of the active Pd^{II} species (Scheme 1). Two mechanisms have been proposed for the interaction of Pd complexes with O_2 (Scheme 2).[4] The first possible pathway involves formation of Pd^0 species B by reductive elimination of HX from complex A and subsequent oxygenation of B to give an η^2-peroxido Pd^{II} species C, which undergoes protonation to generate a Pd^{II} hydroperoxide intermediate D. Finally, a second protonation leads to the formation of H_2O_2 and the active Pd^{II} catalyst (Scheme 2, pathway a). The other mechanistic possibility is the direct insertion of O_2 into the Pd−H bond of a Pd^{II} hydride intermediate A to produce a Pd^{II} hydroperoxide species E, followed by protonolysis to release H_2O_2 and regenerate the Pd^{II} catalyst (Scheme 2, pathway b). It should be noted that palladium remains in the +2 oxidation state throughout the catalytic cycle in this case. Direct O_2-coupled turnover remarkably enhances the appeal of Pd-catalyzed oxidative reactions. As a result, the scope of these transformations has expanded considerably during the past decade, affording new opportunities for selective aerobic oxidation methods, thus has a significant impact on the future of oxidation chemistry.[5]

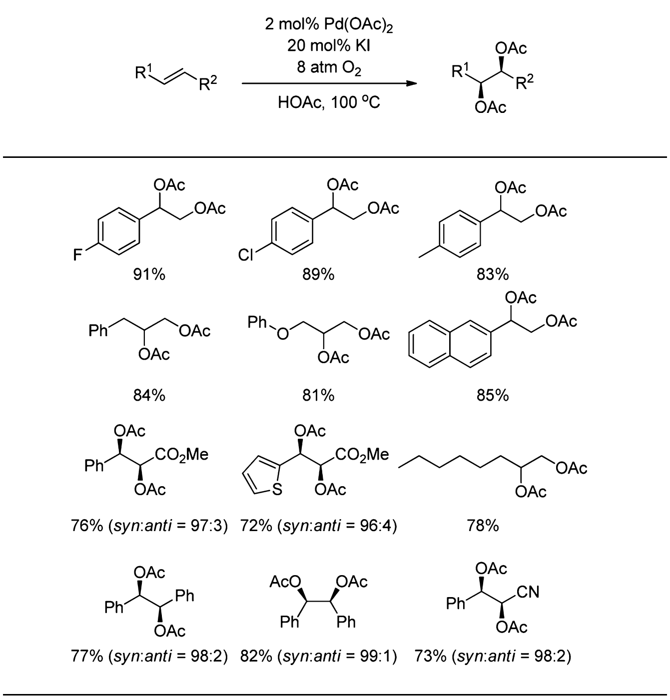

SCHEME 3. Pd-Catalyzed Oxidative Acetalization of Alkenes and Proposed Mechanism

Developing green and sustainable chemistry for organic synthesis has been a long-term objective of our group. We have explored some unconventional reaction media that can potentially simplify synthesis and maximize resource utilization, such as supercritical carbon dioxide ($scCO_2$)[6] and ionic liquids.[7] Our research efforts also focus on the development of new and efficient aerobic oxidation methods. This present Account describes our recent progress on Pd-catalyzed oxidative transformations of unsaturated hydrocarbons, particularly alkenes and alkynes. Emphasis will be placed on the role of O_2 and the mechanistic understanding of these processes. The new transformations will provide a platform to enable further oxidation reaction development.

II. Pd-Catalyzed Oxidation of Carbon−Carbon Double Bonds

A. Oxidative Acetalization of Alkenes. The acetalization of alkenes with alcohols by the Wacker system is among the most important reactions for olefin functionalization. Many acetals, such as alkyl 3,3-dialkoxypropanoates, β-ketoacetals, and β-cyanoacetals, are useful intermediates in organic synthesis and have been utilized to construct a variety of valuable compounds. In 1999, we first reported our

TABLE 1. Pd-Catalyzed Diacetoxylaton of Alkenes



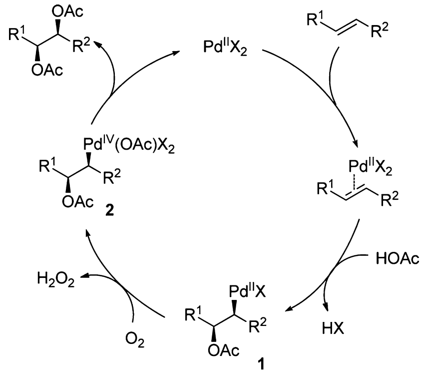
investigation on the Pd-catalyzed aerobic acetalization of terminal olefins with electron-withdrawing groups in $scCO_2$ (Scheme 3, eq 1).[8] Additional studies showed that polystyrene-supported benzoquinone (PS-BQ) was a successful substitute for the cocatalyst $CuCl_2$ (or CuCl) (Scheme 3, eq 2).[9] A catalytic cycle for the acetalization reaction was proposed accordingly. (Scheme 3).

B. Diacetoxylation, Dihydroxylation and Oxidative Cleavage of Alkenes. Transition metal-catalyzed oxidative difunctionalization of alkenes continues to be a fascinating and useful area of research.[10] Reactions for vicinal alkene oxidation with a combination of Pd and a strong oxidant were first explored by Bäckvall.[11] His suggestion of the involvement of Pd^{IV} intermediate was instructive for subsequent development of the field. Our recent work in this area with O_2 as the sole oxidant includes diacetoxylation[12] and dihydroxylation[13] of alkenes.

The detailed investigation on alkene diacetoxylation led to a discovery that $Pd(OAc)_2$ and O_2 were critical for the success of the reaction. The presence of a halide, particularly KI, would also promote the transformation. This method was found to have a broad substrate scope. Under the optimal conditions, all the tested alkenes converted cleanly to the corresponding diacetates in high yields (Table 1).

A possible Pd^{II}/Pd^{IV} catalytic cycle was proposed in Scheme 4. First, a Pd^{II} catalyst underwent *cis*-acetoxypalladation with olefin to afford an organopalladium intermediate **1**. The extremely high diastereoselectivity observed in the diacetoxylation of 1,2-disubstituted alkenes provided strong evidence in support of this step. Then, **1** was oxidized by O_2 to yield a Pd^{IV} intermediate **2**,[14] followed by reductive elimination to form the second C−O bond and regenerate the Pd^{II} catalyst. An alternative Pd^{II}/Pd^{0} mechanism was less probable due to the result that no desired product was detected without O_2 upon the treatment of stoichiometric $Pd(OAc)_2$. I_2 oxidizing Pd^{II} to Pd^{IV} could also be excluded, since the diacetoxylation reaction did not occur when using a stoichiometric amount of I_2 as the oxidant. We speculated that KI might serve as a ligand and thereby promote the oxidation of Pd^{II} to Pd^{IV}.

SCHEME 4. Plausible Catalytic Cycle for Alkene Diacetoxylation

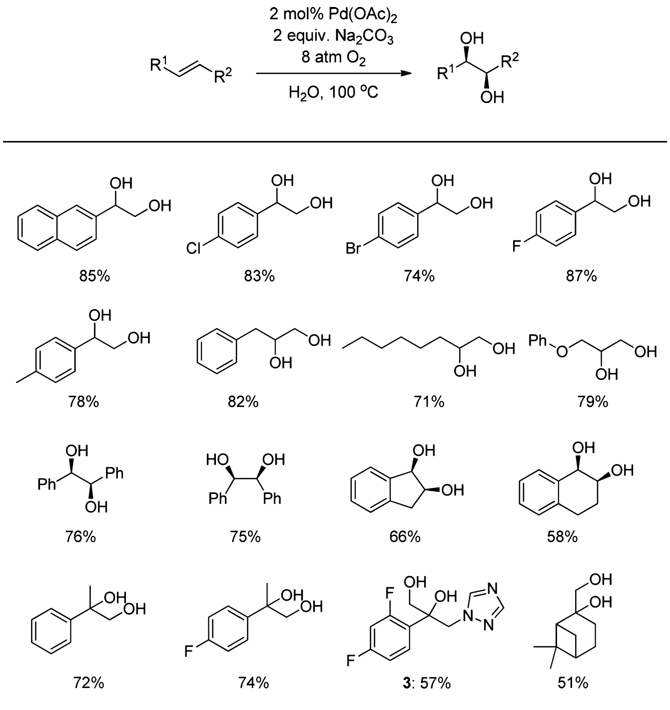


This work opened up a new avenue for the green synthesis of 1,2-diacetates, and its high diastereoselectivity made it a potentially attractive method for the preparation of *cis*-1,2-diols. The encouraging result prompted us to begin exploring the $Pd(OAc)_2/O_2$ system in alkene dihydroxylation.[13] Our studies revealed that the addition of Na_2CO_3 was essential to the transformation. The optimized system was successfully applied to dihydroxylation of a number of alkenes, including those bearing synthetically useful functional groups (Table 2). It is noteworthy that product **3** is a key intermediate for triazole antifungal agents.[15]

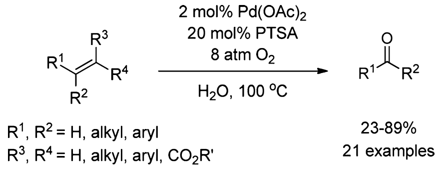
Interestingly, when a Brønsted acid (PTSA) was utilized as the additive, the oxidative cleavage reaction occurred instead of the dihydroxylation, affording the corresponding aldehyde or ketone products.[13] A variety of alkenes, including aromatic alkenes with electron-rich or electron-withdrawing groups, α,β-unsaturated alkenes, linear aliphatic alkenes, 1,2-disubstituted, and 1,1-disubstituted olefins, were reacted efficiently under the optimal conditions (Scheme 5).

What is the reason that 1,2-diols were formed under basic conditions whereas C−C double bond was cleaved in the presence of an acid? With the assumption that the

TABLE 2. Pd-Catalyzed Alkene Dihydroxylation



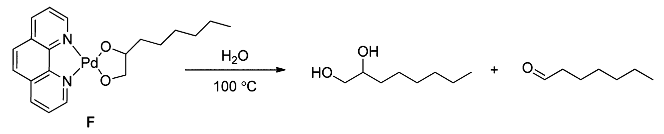
SCHEME 5. Pd-Catalyzed Oxidative Cleavage of Alkenes



Pd-catalyzed dihydroxylation protocol was accompanied by overoxidation under the treatment of acid, we set out to study the oxidative cleavage of 1,2-diols. With 0.2 equiv amount of PTSA, the cleavage reaction of *trans*-1,2-diphenylethane-1,2-diol gave benzaldehyde in 94% yield, which dropped to 46% when the reaction proceeded without any additives. However, only trace cleavage product was observed in the presence of Na_2CO_3. In comparison, the reaction provided no conversion without a Pd catalyst. These observations were consistent with our speculation.

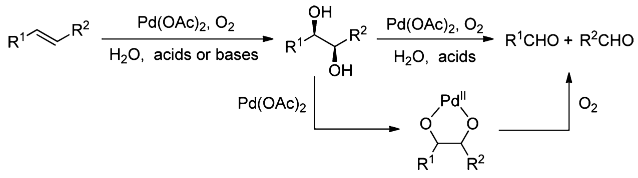
In an attempt to further rationalize the reaction pathway, a dioxo-Pd^{II} complex, (1,10-phenanthroline)(1,2-octanediolato)Pd^{II} F was prepared (Table 3). Treatment of complex F with PTSA or Na_2CO_3 in H_2O at 100 °C produced 1,2-octanediol with good yield, while only 17% yield was obtained in the absence of any additives, indicating that acid or base could promote the hydrolysis of dioxo-Pd^{II} complex. To gain the cleavage product of complex F, several oxidants were examined. It was found that the employment of O_2 was critical for the aldehyde formation, while other oxidants, such as $CuCl_2$, $Cu(OAc)_2$, and benzoquinone, had no effect on the cleavage reaction. These results suggested that 1,2-diols or dioxo-Pd^{II} complexes might be the precursors for the formation of carbonyl compounds and O_2 played an important role in these processes.

TABLE 3. Hydrolysis and Cleavage Reaction of Dioxo-Pd^{II} Complex F



additive	oxidant	yield of diol (%)	yield of aldehyde (%)
		17	n.d.
PTSA		88	n.d.
Na_2CO_3		84	n.d.
PTSA	O_2 (8 atm)	4	91
Na_2CO_3	O_2 (8 atm)	21	72

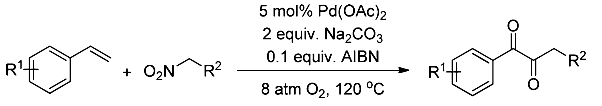
SCHEME 6. Possible Pathway of the Alkene Cleavage

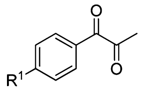
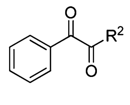


Accordingly, a possible pathway was proposed for the alkene cleavage reaction (Scheme 6): 1,2-diol was formed and then transferred into a dioxo-Pd^{II} intermediate, which underwent C$-$C bond cleavage to produce aldehydes under O_2 atmosphere. To highlight the synthetic value of these reactions, the dihydroxylation and oxidative cleavage reaction of styrene were successfully scaled up to 100 mmol, and the isolated yields (based on complete alkene consumption) remained at 81% and 83%, respectively.

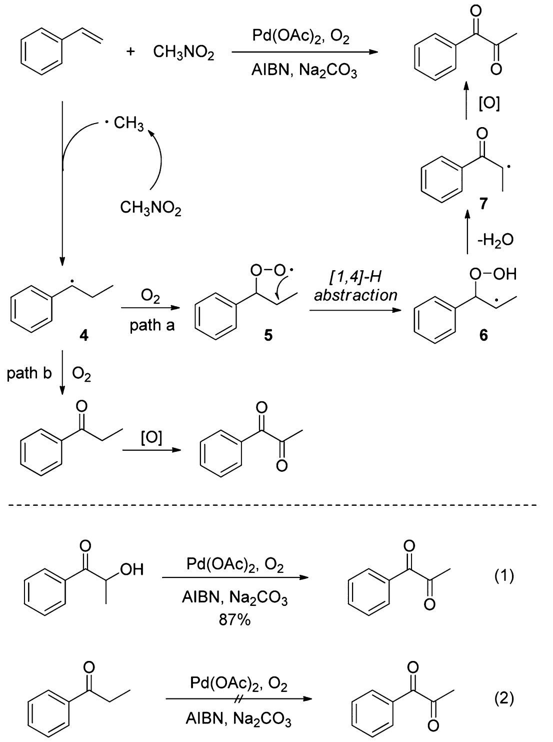
C. Carbonation-Diketonization of Alkenes. Functionalization of the C$-$N bond is one of the most challenging targets in modern organic synthesis. Although some significant progress on C$-$C bond formation reactions via C$-$N bond cleavage has been achieved recently with sulfonamides, anilines, or amides as the coupling partners, little attention is paid to nitroalkanes.[16] In connection with our interest in the search for new alkene oxidations, we have developed a Pd-catalyzed carbonation$-$diketonization reaction of terminal alkenes with O_2 as the oxidant to synthesize 1,2-diketone derivatives.[17] Here, the employment of 2,2′-azobisisobutyronitrile (AIBN) was crucial for this transformation, while the use of 2,2,6,6-tetramethylpiperidine-1-oxyl

TABLE 4. Pd-Catalyzed Carbonation-Diketonization of Terminal Alkenes with Nitroalkanes



	R^1 = 4-H 67% R^1 = 4-F 75% R^1 = 4-Cl 73% R^1 = 4-Br 69% R^1 = 4-CN 62% R^1 = 4-CF_3 72%	R^1 = 4-Me 61% R^1 = 4-*t*Bu 69% R^1 = 4-Ph 61% R^1 = 3-Cl 64% R^1 = 2-Cl 32%
	R^2 = Et 63% R^2 = *n*Pr 58% R^2 = *i*Pr 31% R^2 = *n*Bu 56%	

SCHEME 7. Plausible Reaction Pathways and Control Experiments



(TEMPO) or 2,3-dichloro-5,6-dicyanobenzo quinone (DDQ) as the additive failed to give the product, which indicated that a radical pathway was possibly involved. Moreover, among various bases screened, Na_2CO_3 was the most effective for this process. With the optimized reaction conditions, both electron-poor and electron-rich aromatic alkenes proceeded well in acceptable yields. The scope of the reaction was further expanded to a variety of nitroalkanes. For example, nitroethane, 1-nitropropane, 1-nitrobutane and 2-nitropropane could also react with styrene to give the desired 1,2-diketones (Table 4).

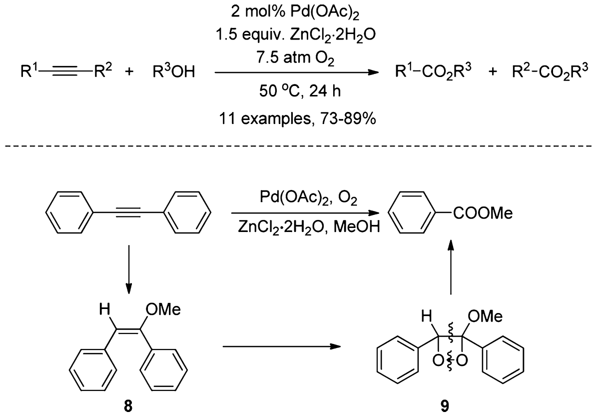
The isotopic labeling study with $^{18}O_2$ clearly demonstrated that the oxygen atoms of the 1,2-diketone products originated from molecular oxygen. According to the experimental results, a preliminary reaction pathway was proposed, as shown in Scheme 7. Initially, a methyl radical would be generated from nitromethane in the presence of $Pd(OAc)_2$ and Na_2CO_3, which selectively added to styrene to produce intermediate **4** and then attacked by O_2 forming superoxide radical **5**. Next, **5** underwent [1,4]-H abstraction to generate hydroperoxide **6**, which subsequently converted to ketone radical **7**. According to the Russell mechanism,[18] the oxidation of ketone radical **7** with O_2 led to the formation of α-hydroxylketone as well as 1,2-diketone in equal yields, the former of which could be further converted to 1,2-diketone under the reaction conditions (Scheme 7, eq 1). The participation of pathway b could be completely excluded (Scheme 7, eq 2).

III. Pd-Catalyzed Oxidation of Carbon–Carbon Triple Bonds

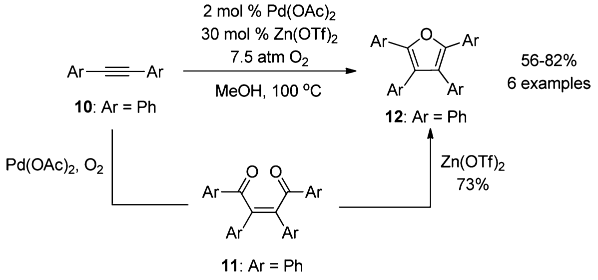
A. Oxidative Cleavage of Alkynes. The cleavage of C–C triple bonds is one of the most challenging subjects in organic chemistry.[19] Except for metathesis of alkynes, there are very few examples for the metal-catalyzed C–C triple bond cleavage reactions.[20] In 2008, we disclosed a new Lewis-acid-promoted and Pd-catalyzed oxidative cleavage reaction of alkynes using O_2 as the sole oxidant.[21] A broad range of alkynes could be applied to this cleavage reaction, affording different carboxylic esters in various alcohols with good yields (Scheme 8). Under the treatment of $Pd(OAc)_2$, 1,2-diphenylethyne was first hydroalkoxylated to form 1-methoxy-1,2-diphenylethene (**8**), which was subsequently attacked by Pd activated molecular oxygen to generate a cyclic peroxide **9**. Fragmentation of **9** produced methyl benzoate and benzaldehyde, the latter of which could undergo further oxidation and esterification to yield the benzoate. The detection of **8** by GC analysis was consistent with our assumption of the reaction pathway.

B. Oxidation and Cyclization of Alkynes. Polysubstituted furans are known to be versatile building blocks for natural products and pharmaceuticals.[22] During the course of condition screening of the alkyne oxidative cleavage, a small amount of tetrasubstituted furans were detected. This observation encouraged us to investigate the reaction conditions for the synthesis of furan derivatives.[23] We examined various Lewis acids toward the oxidation and found that $Zn(OTf)_2$ was highly effective. Other oxidants, such as DDQ,

SCHEME 8. Pd-Catalyzed Triple Bond Cleavage Reactions and Possible Pathway



SCHEME 9. $Pd(OAc)_2/Zn(OTf)_2$-Catalyzed Oxidation-Cyclization of Alkynes

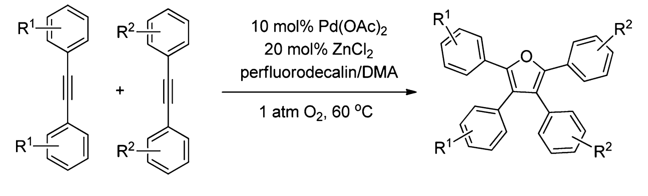


oxidant	yield of **12** (%)
O_2 (7.5 atm)	77
DDQ (2 mmol)	12
BQ (2 mmol)	11
H_2O_2 (2 mmol)	53

BQ, and H_2O_2, just led to a decrease in the yield. A series of aromatic alkynes worked well in this system to afford the desired furans (Scheme 9). The proposed catalytic pathway was initiated by the oxidation of **10** in the presence of $Pd(OAc)_2$ and O_2 forming the 1,4-dione **11**, followed by cyclocondensation with $Zn(OTf)_2$ to generate furan **12**. Actually, we proposed **11** as a key intermediate not only because 1,4-dione was observed via GC analysis during the reaction, but also it could undergo a cyclization without $Pd(OAc)_2/O_2$ to give the final product.

However, this method has some limitations including harsh reaction conditions and narrow substrate scope. We then successfully employed fluorous solvent as medium to solve these problems.[24] Under the optimized conditions, intermolecular reactions between diverse alkynes provided corresponding tetrasubstituted furans with improved yields and selectivity relative to the previous results (Table 5). The intramolecular version was also successfully demonstrated.

TABLE 5. $Pd(OAc)_2/ZnCl_2$-Catalyzed Oxidation-Cyclization of Alkynes



$R^1 = R^2 = H$ 94%	$R^1 = R^2 = 4$-*n*Bu 89%	$R^1 = H$, $R^2 = 4$-*n*Bu 50%
$R^1 = R^2 = 4$-Br 86%	$R^1 = R^2 = 3$-Cl 74%	$R^1 = 4$-Me, $R^2 = 4$-*n*Bu 52%
$R^1 = R^2 = 4$-F 83%	$R^1 = R^2 = 3$-F 69%	$R^1 = 4$-CF_3, $R^2 = 4$-F 54%
$R^1 = R^2 = 4$-CF_3 95%	$R^1 = R^2 = 3$-Me 65%	
$R^1 = R^2 = 4$-OMe 80%	$R^1 = R^2 = 2$-F 46%	
$R^1 = R^2 = 4$-Me 90%		

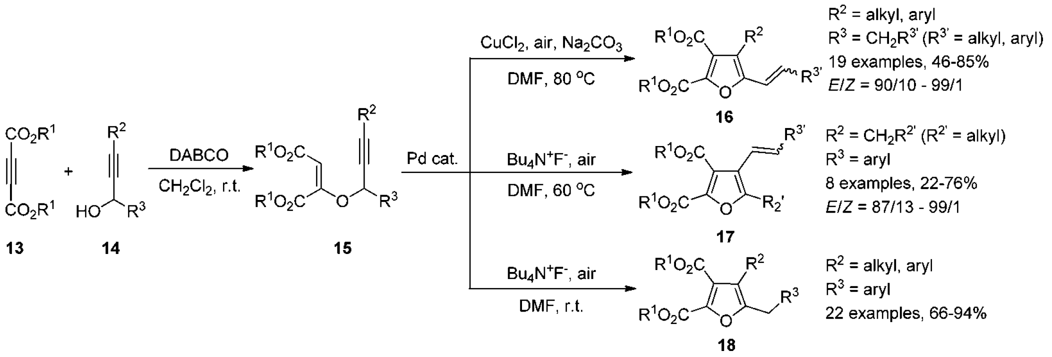
Very recently, our group has developed another facile method for the one-pot synthesis of polysubstituted furans from alkynoates and 2-yn-1-ols in the presence of Pd catalyst and air with high regioselectivity.[25] Interestingly, it was found that the regioselectivity leading to the three kinds of furans was dependent on both the reaction behavior of the substrates and the reaction conditions (Scheme 10).

The mechanism of Pd-catalyzed domino reactions for different furans was proposed (Scheme 11). Propargyl vinyl ether **15**, in-situ-formed via DABCO-catalyzed nucleophilic addition of propargyl alcohol **13** to alkynoate **14**, underwent propargyl Claisen rearrangement to furnish allene **19**. Pd-mediated oxypalladation and 5-*exo* cyclization converted **20** into intermediate **21**. Subsequently, protonolysis of **21** at ambient temperature efficiently generated the polysubstituted furan **18** and the active catalyst species Pd^{II} when R^3 are aryls; otherwise, a β-hydride elimination of **21** would occur to give 5-vinyl-substituted furan **16** at elevated temperatures and more importantly with a suitable base in the reaction system. On the other hand, $Bu_4N^+F^-$ as an additive might promote the isomerization of allene **19** to 1,3-diene **22**. Pd-mediated cyclization of **22** and β-hydride elimination of **23** readily provided 4-vinyl-substituted furan **17**. Both procedures led to vinyl-substituted furans and released Pd^0 in the end. Cu^{II} and O_2 functioned as the oxidant oxidizing Pd^0 to Pd^{II} and finished the catalytic cycle.

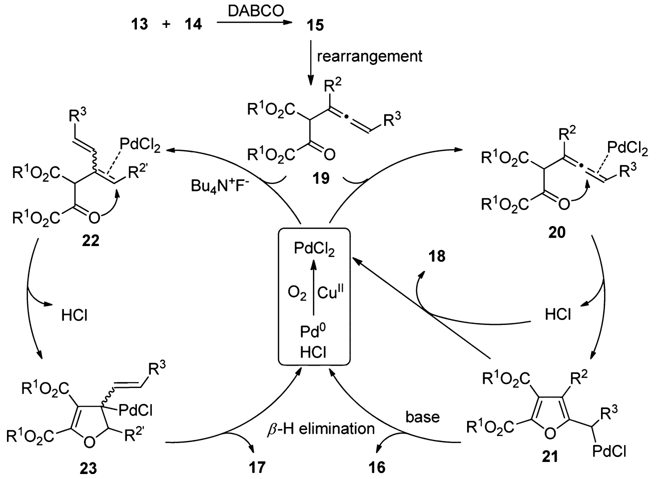
IV. Pd-Catalyzed Oxidative Coupling Reactions of Alkenes or/and Alkynes

Pd-catalyzed oxidative coupling reactions are attractive since they enable the use of more readily available

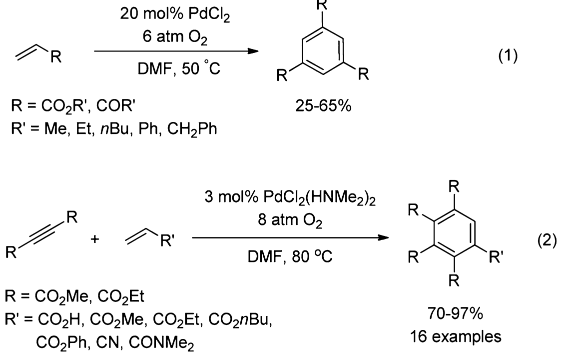
SCHEME 10. Pd-Catalyzed Synthesis of Polysubstituted Furans



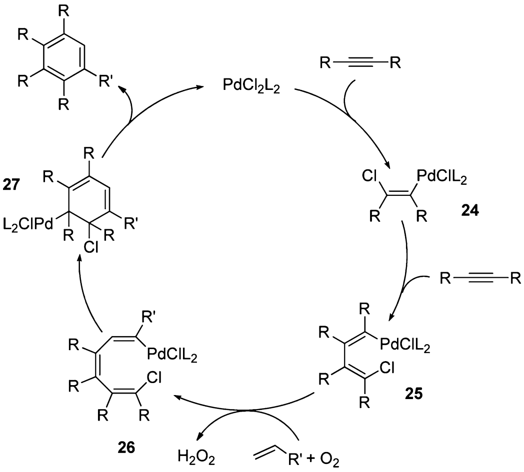
SCHEME 11. Proposed Mechanism for Pd-Catalyzed Furan Synthesis



SCHEME 12. Pd-Catalyzed Synthesis of Substituted Benzenes



SCHEME 13. Reasonable Mechanism for Pd-Catalyzed Cross [2+2+2] Cyclization

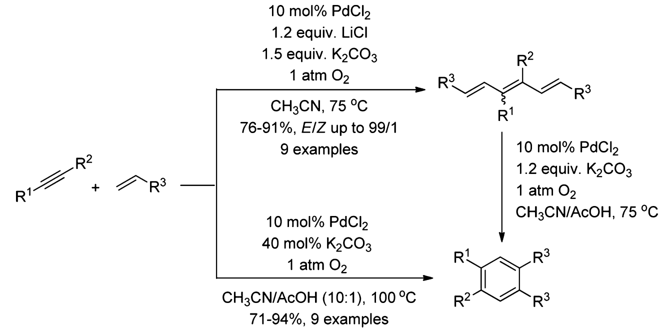


substrates and increase net atom efficiency. Nucleopalladation, especially halopalladation, of π-compounds is well-recognized to be one of the most important and convenient methods for the construction of both the carbon–carbon and carbon–heteroatom bonds. How to capture the active palladium intermediate and quench the resultant carbon–palladium bond efficiently still remain challenging. This section presents our recent studies on nucleopalladation chemistry while incorporating the use of O_2 in oxidative coupling reactions of alkenes or/and alkynes.

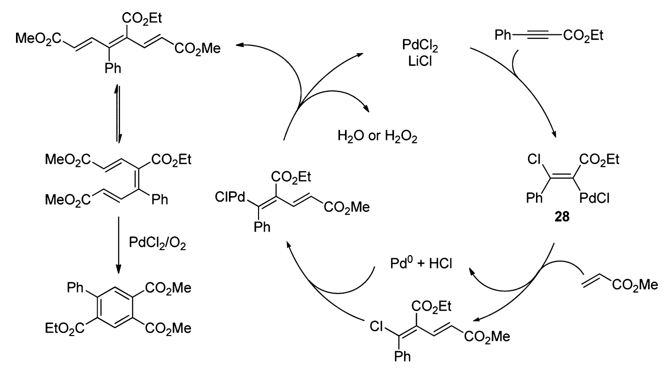
A. Halopalladation-Initiated Linear/Cyclic Cross-Trimerization of Alkenes or/and Alkynes. Both polysubstituted aromatic compounds and 1,3,5-trienes are of great importance in the field of pharmaceutical and materials chemistry.[26] In the course of our study on Pd-catalyzed aerobic oxidation synthesis, we found that $PdCl_2/O_2$/DMF was an efficient catalyst system for [2+2+2] cyclotrimerization of electron-deficient alkenes to selectively afford 1,3,5-trisubstituted benzene derivatives (Scheme 12, eq 1).[27] Later, we expanded this palladium chemistry to a highly selective cross [2+2+2] cyclization with alkynoates and activated alkenes under O_2 and disclosed for the first time that $PdCl_2(HNMe_2)_2$ produced in situ by DMF hydrolysis was the key to this oxidative reaction (Scheme 12, eq 2).[28]

We proposed that the cyclization started with the *cis*-chloropalladation of C–C triple bond by $PdCl_2(HNMe_2)_2$ giving vinylpalladium intermediate **24**, and the succeeding

SCHEME 14. Pd-Catalyzed Cross-Trimerization between Alkynes and Alkenes



SCHEME 15. Catalytic Cycle for the Pd-Catalyzed Cross-Trimerization

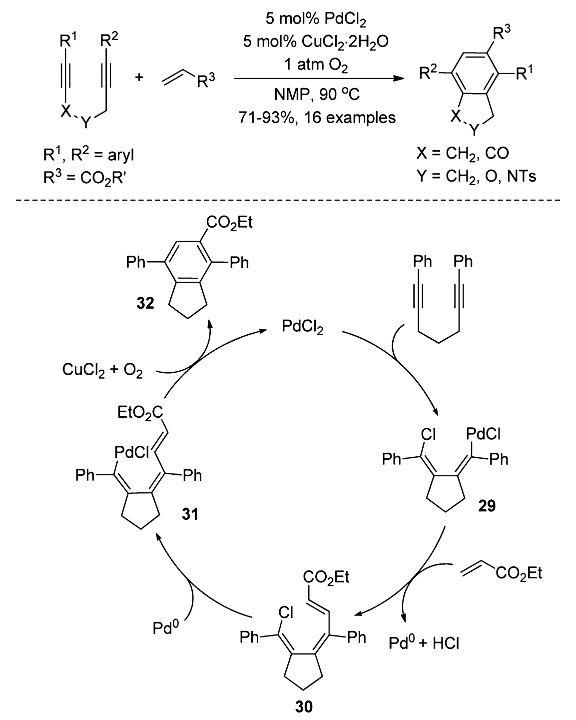


insertion into the Pd-vinyl bond afforded intermediate **25** (Scheme 13). Coordination of alkene to **25**, followed by insertion and β-hydride elimination-oxidation with O_2, led to the new chloropalladation intermediate **26**, where Pd–Cl bond made a further insertion into C–C double bond generating intermediate **27**. The presence of O_2 converted $H{-}PdL_2{-}Cl$ to $Cl{-}PdL_2{-}OOH$, which released H_2O_2 and kept the Pd^{II} oxidative state. Finally, β-chloride elimination of **27** yielded the desired product and the catalyst was regenerated. We believed that the thermal stability and less geometrical rigidity around the metal center of $PdCl_2(HNMe_2)_2$ made it an excellent catalyst for this transformation.[29]

Further investigation revealed that a highly chemoselective Pd-catalyzed oxidative cross-trimerization of one alkyne with two alkenes could occur to provide 1,3,5-trienes or 1,2,4,5-tetrasubstituted benzenes controlled by different reaction conditions (Scheme 14).[30]

Based on the experiment results, we proposed that the mechanism of these processes should come by the combination of three steps (Scheme 15): (1) *trans*-chloropalladation of alkyne and a Heck cross-coupling with alkene to chloro-substituted 1,3-diene, (2) another Heck cross-coupling with alkene through a β-hydride elimination to 1,3,5-trienes, and (3) isomerization of (1*E*,3*E*,5*E*)-trienes to (1*E*,3*Z*,5*E*)-trienes under higher temperature and then Pd-catalyzed cyclization of trienes to afford benzenes. O_2 was needed in the first and the third steps, which could oxidize Pd^0 to Pd^{II}.

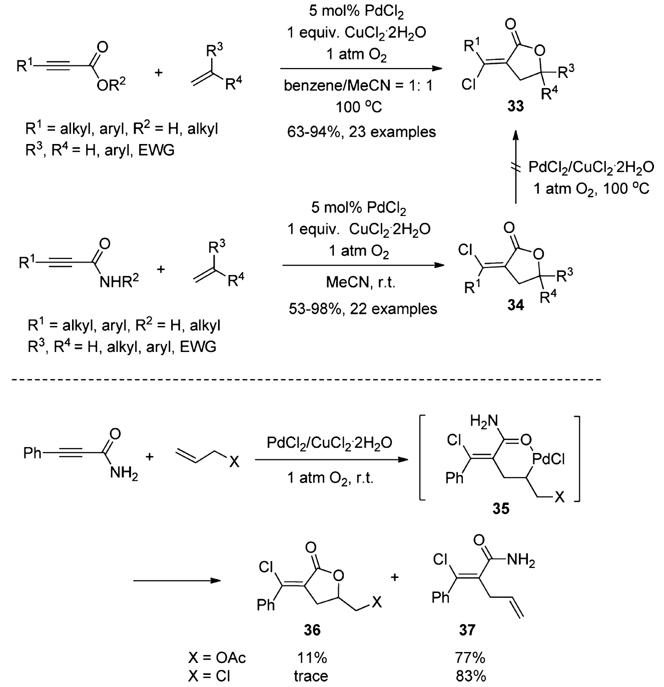
SCHEME 16. Pd-Catalyzed $[2+2+2]$ Cyclization of 1,6-Diynes with Alkenes and Proposed Pathway



However, our efforts to detect and isolate the key intermediate **28** were not fruitful. Considering that the cyclization of 1,6-diynes via a vinylpalladium intermediate might provide important mechanistic information about this novel process, we turned our attention to exploring a tandem cycloaddition-cyclization reaction of 1,6-diynes and acrylates.[31] Detailed studies showed that the best conditions for this transformation were: 5 mol % $PdCl_2$, 5 mol % $CuCl_2 \cdot 2H_2O$ and 1 atm O_2 in NMP at 90 °C. This chemistry could provide a series of polysubstituted aromatic carbo- and heterocyclic compounds in good to excellent yields (Scheme 16).

Thus, a plausible pathway for this Pd-catalyzed aerobic $[2+2+2]$ cycloaddition was proposed. Intermediate **29** was first generated by the chloropalladation of diyne with Pd^{II} catalyst. Subsequent intermolecular Heck reaction with acrylate would be expected to afford triene **30**. Vinylpalladium intermediate **31** was then generated by the oxidative addition of triene **30** with Pd^0 species, and the succeeding intramolecular Heck reaction would lead to the desired cyclization product **32**. Finally, O_2 and Cu^{II} oxidized Pd^0 to Pd^{II} and completed the catalytic cycle. Indeed, the vinyl chloride **30** had been isolated from the reaction and it could be transferred into the final product under the standard conditions, but in the absence of O_2, which suggested the involvement of intermediate **30** in the catalytic cycle. Additionally, only trace cyclization product **31** was obtained when **30** was treated with the optimal conditions without $PdCl_2$, indicating that the transformation of **30** to **32** should be a Heck cross-coupling instead of an electrocyclic reaction. The isolation and characterization of intermediate **30** provided the first mechanistic evidence in [2+2+2] cyclization reactions via chloropalladation process.

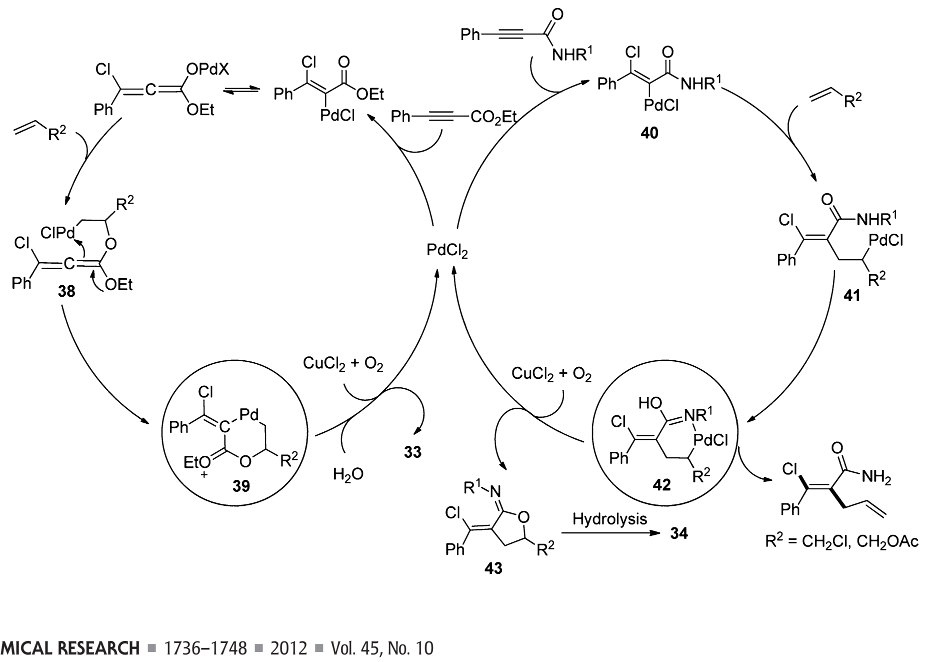
SCHEME 17. Stereoselectivity Switch in Pd-Catalyzed Carboesterification



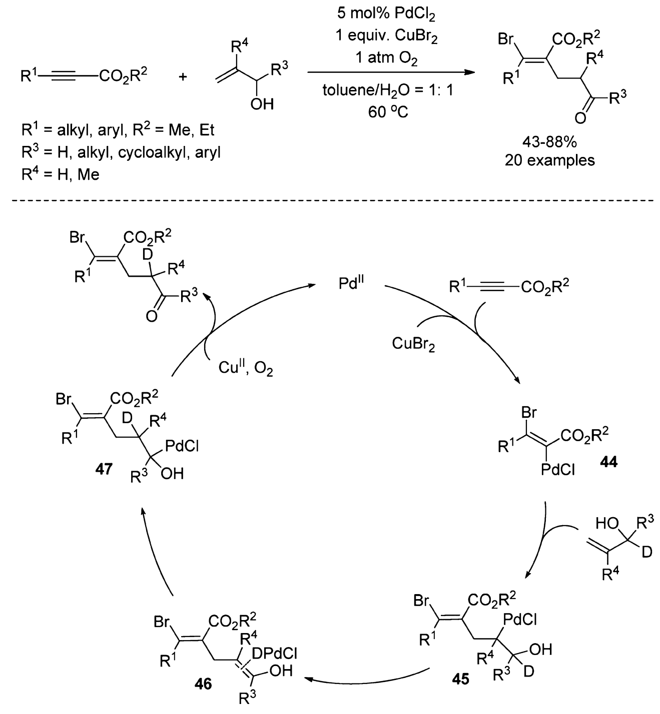
B. Halopalladation-Initiated Carboesterification of Alkenes and Alkynes. Very recently, we have developed a new and convenient carboesterification method for constructing naturally occurring, biologically active α-methylene-γ-lactone skeletons.[32] The *E*/*Z* selectivity can be switched by using alkynoates or alkynamides as the substrates under different temperatures (Scheme 17). However, the (*Z*)-product obtained at room temperature could not convert to the corresponding (*E*)-isomer even heated to 100 °C, which implied that the two configurations might be formed via two different pathways. Several control experiments were carried out for more insightful mechanistic information. The isotopic labeling study elucidated that the carbonyl oxygen atom in the final product came from water. In addition, when allyl chloride or allyl acetate was used as the terminating coupling reagent, a competitive reaction occurred. A tentative explanation for this phenomenon was that the C−Pd bond of intermediate **35** could be quenched by C(sp^3)−O bond formation to get **36** or β-halide elimination to afford **37**.

On the basis of the above results, a reasonable mechanism was proposed (Scheme 18). The left pathway was initiated by *trans*-halopalladation of alkynoate. The subsequent keto−enol equilibrium and *cis*-oxypalladation provided intermediate **38**, followed by the nucleophilic attack

SCHEME 18. Tentative Mechanism for Pd-Catalyzed Carboesterification



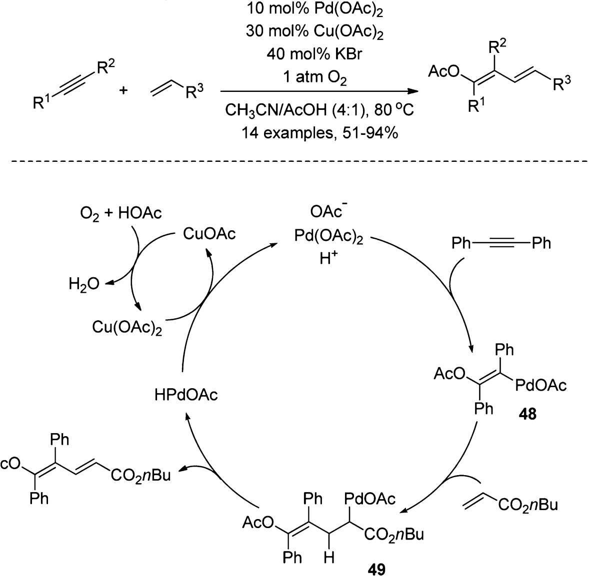
SCHEME 19. Pd-Catalyzed Alkylation of Alkynoates and Mechanistic Hypothesis



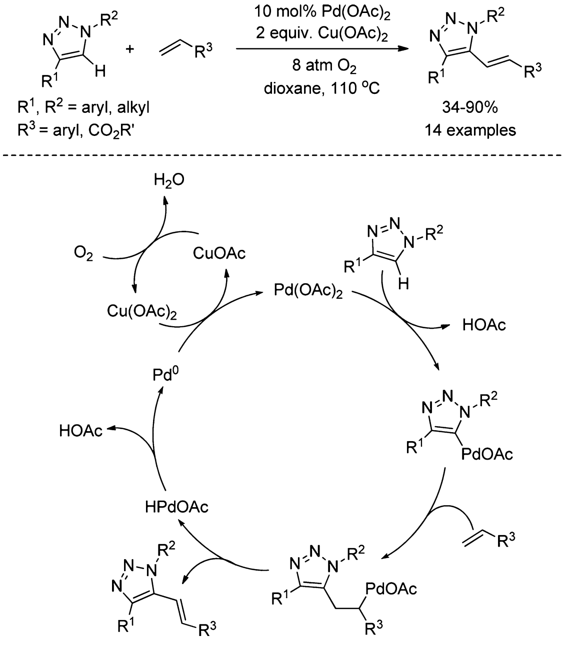
to afford **39**. And then reductive elimination of C(sp^2)–C(sp^3) bond and hydrolysis afforded the (*E*)-product. For the right pathway, the reaction was also initiated by the halopalladation of alkynamide, which gave the vinylpalladium intermediate **40**. Subsequently, **40** was captured by the alkene via a Heck addition to produce **41**, followed by isomerization to form the intermediate **42**, which would undergo a β-halide elimination if the alkenes were allyl choride and allyl acetate, or C(sp^3)–O bond formation. The hydrolysis of intermediate **43** offered the (*Z*)-lactones. Finally, Pd^{II} active species was regenerated with Cu^{II} and O$_2$.

C. Halopalladation-Initiated Alkylation of Alkynoates. Except for the active alkenes, we also attempt to utilize allylic alcohols to capture the active σ-vinylpalladium intermediate generated from the nucleopalladation reaction of alkynes. Thus, a regio- and stereoselective approach for δ-bromo-γ,δ-unsaturated carbonyls was developed (Scheme 19).[33] Mechanistic studies showed remarkable intra- and intermolecular ($k_H/k_D = 4.52$) kinetic isotopic effects, indicating that the allylic hydrogen shift might be the rate-limiting step. The transformation presumably involved a few key steps described as below: *trans*-selective Kaneda reaction[34] of alkynoate afforded (*E*)-vinylpalladium intermediate **44**, followed by Mizoroki-Heck reaction of allylic alcohol inserting into the C–Pd bond of vinylpalladium species to form species **45**. The β-deuterium elimination of **45** gave intermediate **46** and the subsequent reinsertion of palladium deuterium species into enol generated intermediate **47**, which underwent reductive elimination to yield the carbonyl product, similar to a Wacker process, and Pd^{II} species was regenerated in the presence of oxidizing reagents CuBr$_2$ and O$_2$.

SCHEME 20. Pd-Catalyzed Synthesis of 1-Acetoxy-1,3-Dienes and Plausible Reaction Pathway



SCHEME 21. Pd-Catalyzed Alkenylation of Triazoles and Proposed Mechanism



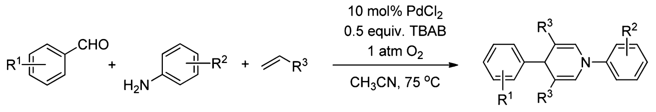
D. Acetoxypalladation-Initiated Cross-Coupling of Alkenes and Alkynes. Acetoxypalladation of alkynes has been proven to be another convenient method for the construction of both carbon−carbon and carbon−oxygen bonds in a single step. We recently have exposed an intermolecular acetoxypalladation of unactivated alkynes which was captured by alkenes and quenched by β-hydride elimination to afford 1-acetoxy-1,3-dienes taking O_2 as the oxidant (Scheme 20).[35] Detailed examinations revealed that the additive as well as the pressure of O_2 played an important role in this process. Moreover, the methodology could apply to a variety of alkynes and alkenes with good yields and selectivity. We proposed that the transformation should come by the unique combination of several steps below: (1) *trans*-acetoxypalladation and (*E*)-vinylpalladium intermediate **48** was formed, followed by (2) a Heck cross-coupling with alkenes and intermediate **49** was produced, and (3) a final β-hydride elimination gave the target product. Pd^{II} was regenerated in the presence of $Cu(OAc)_2$ for the next cycle and the resulting Cu^{I} was oxidized to Cu^{II} by O_2. According to Lu's research, halide ions serve as a ligand.[36]

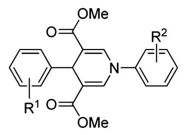
E. Other Oxidative Cross-Coupling of Alkenes. Pd-catalyzed vinylation of arenes via C−H bond activation has become a hotspot in recent years.[37] In 2009, we discovered a new method to synthesize highly substituted 1,2,3-triazoles via direct oxidative vinylation in the $Pd(OAc)_2/O_2$ catalytic system (Scheme 21).[38] A reaction pathway similar to that of Fujiwara et al.[37b] was proposed.

On the other hand, as part of our continuing research into the discovery and development of new multicomponent reactions to synthesize heterocyclic compound library with high diversity, we developed a highly efficient protocol for the synthesis of 2,6-unsubstituted 1,4-dihydropyridines (1,4-DHPs) via Pd-catalyzed one-pot three-component reactions of aromatic aldehydes, arylamines, and terminal olefins under O_2 atmosphere (Table 6).[39]

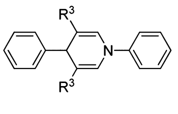
With regard to the mechanism, we proposed **50** as a key intermediate, which could be isolated from the reaction of aniline and methyl acrylate under the optimized conditions. Therefore, a plausible pathway was shown in Scheme 22. First, a Pd^{II} catalyst coordinated to the olefin which would undergo a nucleophilic attack by the amine to generate the σ-alkylpalladium complex **51**, followed by β-hydride elimination to afford an unstable Pd hydride complex and

TABLE 6. Pd-Catalyed Synthesis of 1,4-DHPs with O_2

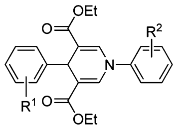




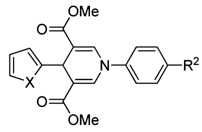
R^1 = 3-H, R^2 = H, 80%
R^1 = 3-Cl, R^2 = H, 87%
R^1 = 3-OMe, R^2 = H, 65%
R^1 = 3-NO$_2$, R^2 = H, 83%
R^1 = H, R^2 = 2-Me, 70%
R^1 = H, R^2 = 3-Cl, 82%
R^1 = H, R^2 = 4-Br, 81%
R^1 = H, R^2 = 3,4-2Me, 87%
R^1 = 4-OMe, R^2 = 4-OPh, 72%
R^1 = 4-Br, R^2 = 3-Cl, 85%



R^3 = CO$_2$Me, 80%
R^3 = CO$_2$Et, 45%
R^3 = CO$_2$*n*Bu, 85%
R^3 = CO$_2$CH$_2$CF$_3$, 83%
R^3 = CO$_2$CH(Et)(C$_5$H$_{11}$), 75%
R^3 = CN, 87%

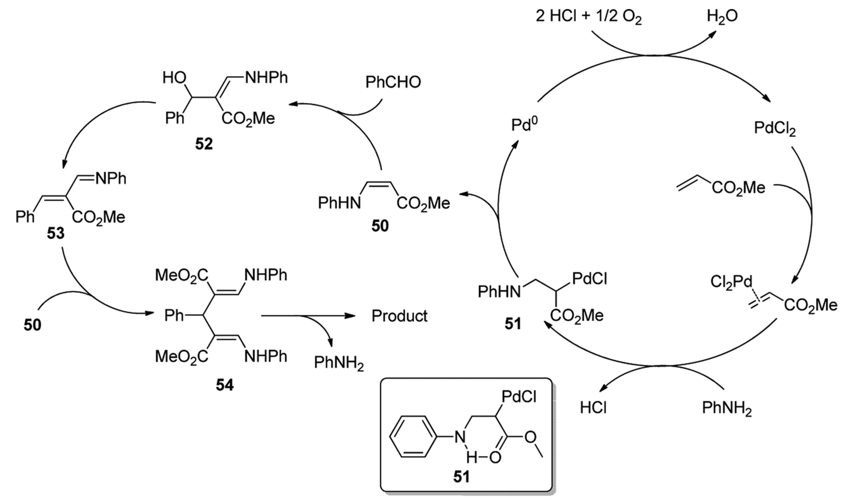


R^1 = H, R^2 = H, 45%
R^1 = H, R^2 = 2-Me, 52%
R^1 = OMe, R^2 = H, 40%



X = O, R^2 = H, 62%
X = S, R^2 = H, 15%
X = S, R^2 = OPh, 45%

SCHEME 22. Plausible Pathway for Pd-Catalyzed 1,4-DHP Synthesis



anti-Markovnikov oxidative amination product **50**. The Pd hydride complex ultimately formed Pd^0, which was oxidized by O_2 to regenerate the Pd^{II} catalyst. Next, nucleophilic addition of the previously formed enamine **50** to the aldehyde occurred to give **52**, which possibly underwent dehydration to yield imine **53**. Reaction with **53** and a second molecule of enamine **50** gave bisenamine **54**, which liberated the final product by nucleophilic attack of the amino group to the enone moiety.

V. Conclusions and Outlook

In summary, we have detailed our recent studies on the development of Pd-catalyzed oxidation of unsaturated hydrocarbons using O_2. As an effort to develop green chemistry in the field of chemical synthesis, a variety of simple and efficient methods for carbon−carbon and carbon−hetero bond formations were established. These new methodologies may find synthetic applecications in a broad spectrum of settings, including natural-product synthesis, materials science, and bioorganic chemistry. Moreover, we also have made efforts in elucidating the mechanism of palladium oxidation catalysis of alkenes and alkynes. We expect that the mechanistic understanding garnered in the development of these processes will provide us with valuable insight to design more green and atom-economical oxidative transformations. Further progress in the field of aerobic oxidation will be most likely related to the clarifying the O_2 activation principles and broadening its synthetic utilities and scope.

We are grateful for financial support from the National Natural Science Foundation of China (21172076 and 20932002), National Basic Research Program of China (973 Program) (2011CB808600), Guangdong Natural Science Foundation (10351064101000000), and the Fundamental Research Funds for the Central Universities (2010ZP0003). We would also like to thank all the co-workers, whose names are cited in the references, for their invaluable contributions.

BIOGRAPHICAL INFORMATION

Wanqing Wu received her B.S. in chemistry from Hunan University in 2005 before obtaining her Ph.D. at Peking University in organic chemistry with Professor Zhen Yang and Chi-Sing Lee in 2010. She then joined the South China University of Technology (SCUT) and is currently a postdoctoral fellow with Professor Huanfeng Jiang. Her research work is focused on the development and applications of new oxidation methods.

Huanfeng Jiang received a B.S. in chemistry from Hubei University (1983), M.S at Wuhan University (1990), and Ph.D. from Shanghai Institute of Organic Chemistry (SIOC) with Professor Xiyan Lu (1993). And then he became a research fellow at Guangzhou Institute of Chemistry, Chinese Academy of Sciences. In 2003, he moved to the South China University of Technology (SCUT), where he is currently the leading professor of Chemistry. He received Chinese Chemical Society-BASF Young Investigator's Award (2002) and National Natural Science Funds for Distinguished Young Scholar (2006). His research interests include synthetic methodology, green and sustainable chemistry.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: jianghf@scut.edu.cn.
The authors declare no competing financial interest.

REFERENCES

1 Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev.* **2005**, *105*, 2329–2364.

2 *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

3 *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, 2002.

4 For reviews, see: (a) Stahl, S. S. Palladium Oxidase Catalysis: Selective Oxidation of Organic Chemicals by Direct Dioxygen-Coupled Turnover. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Stahl, S. S. Palladium-Catalyzed Oxidation of Organic Chemicals with O_2. *Science* **2005**, *309*, 1824–1826. (c) Gligorich, K. M.; Sigman, M. S. Mechanistic Questions about the Reaction of Molecular Oxygen with Palladium in Oxidase Catalysis. *Angew. Chem., Int. Ed.* **2006**, *45*, 6612–6615.

5 For selected examples: (a) Xu, Y.-H.; Lu, J.; Loh, T.-P. Direct Cross-Coupling Reaction of Simple Alkenes with Acrylates Catalyzed by Palladium Catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 1372–1373. (b) Feng, C.; Loh, T.-P. Palladium-Catalyzed Bisolefination of C−C Triple Bonds: A Facile Method for the Synthesis of Naphthalene Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 17710–17712. (c) Xu, Y.-H.; Cho, Y. K.; Loh, T.-P. Synthesis and Characterization of a Cyclic Vinylpalladium(II) Complex: Vinylpalladium Species as the Possible Intermediate in the Catalytic Direct Olefination Reaction of Enamide. *Chem. Sci.* **2011**, *2*, 1822–1825. (d) Powers, D. C.; Ritter, T. Bimetallic Redox Synergy in Oxidative Palladium Catalysis. *Acc. Res. Chem.* **2012**, *45*, 840–850. (e) Campbell, A. N.; Stahl, S. S. Overcoming the “Oxidant Problem”: Strategies to Use O_2 as the Oxidant in Organometallic C−H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Res. Chem.* **2012**, *45*, 851–863.

6 For selected examples, see: (a) Qi, C.-R.; Jiang, H.-F. Efficient Synthesis of β-Oxopropylcarbamates in Compressed CO_2 without Any Additional Catalyst and Solvent. *Green Chem.* **2007**, *9*, 1284–1286. (b) Jiang, H.-F.; Wang., A.-Z.; Liu, H.-L.; Qi, C.-R. Reusable Polymer-Supported Amine-Copper Catalyst for the Formation of α-Alkylidene Cyclic Carbonates in Supercritical Carbon Dioxide. *Eur. J. Org. Chem.* **2008**, 2309–2312. (c) Jiang, H.-F.; Zhao, J.-W. Silver-Catalyzed Activation of Internal Propargylic Alcohols in Supercritical Carbon Dioxide: Efficient and Eco-Friendly Synthesis of 4-Alkylidene-1,3-Oxazolidin-2-Ones. *Tetrahedron Lett.* **2009**, *50*, 60–62.

7 (a) Yang, S.-R.; Jiang, H.-F.; Chen, H.-J.; Xu, Y.-B.; Luo, W. Palladium-Catalyzed Enyne Cyclization of 2′-Alkenyl 2-Alkynoates in Imidazolium-Type Ionic Liquids. *Synth. Commun.* **2007**, *37*, 2121–2129. (b) Yang, S.-R.; Jiang, H.-F.; Li, Y.-Q.; Chen, H.-J.; Luo, W.; Xu, Y.-B. Protonolysis of the Carbonepalladium Bond in Palladium(II)-Catalyzed Enyne Cyclization in Imidazoliumtype Ionic Liquids. *Tetrahedron* **2008**, *64*, 2930–2937.

8 Jia, L.-Q.; Jiang, H.-F.; Li, J.-H. Palladium(II)-Catalyzed Oxidation of Acrylate Esters to Acetals in Supercritical Carbon Dioxide. *Chem. Commun.* **1999**, 985–986.

9 Wang, Z.-Y.; Jiang, H.-F.; Qi, C.-R.; Wang, Y.-G.; Dong, Y.-S.; Liu, H.-L. PS-BQ: An Efficient Polymer-Supported Cocatalyst for the Wacker Reaction in Supercritical Carbon Dioxide. *Green Chem.* **2005**, *7*, 582–585.

10 For reviews, see: (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547. For selected examples, see: (b) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. Palladium(II)-Catalyzed Intramolecular Diamination of Unfunctionalized Alkenes. *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587. (c) Alexanian, E. J.; Lee, C.; Sorensen, E. J. Palladium-Catalyzed Ring-Forming Aminoacetoxylation of Alkenes. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (d) Liu, G.; Stahl, S. S. Highly Regioselective Pd-Catalyzed Intermolecular Aminoacetoxylation of Alkenes and Evidence for cis-Aminopalladation and S_N2 C−O Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 7179–7181. (e) Li, Y.; Song, D.; Dong, V. M. Palladium-Catalyzed Olefin Dioxygenation. *J. Am. Chem. Soc.* **2008**, *130*, 2962–2964. (f) Zhu, M.-K.; Zhao, J.-F.; Loh, T.-P. Palladium-Catalyzed Oxime Assisted Intramolecular Dioxygenation of Alkenes with 1 atm of Air as the Sole Oxidant. *J. Am. Chem. Soc.* **2010**, *132*, 6284–6285.

11 Bäckvall, J.-E. Palladium in Some Selective Oxidation Reactions. *Acc. Chem. Res.* **1983**, *16*, 335–342.

12 Wang, A.-Z.; Jiang, H.-F.; Chen, H.-J. Palladium-Catalyzed Diacetoxylation of Alkenes with Molecular Oxygen as Sole Oxidant. *J. Am. Chem. Soc.* **2009**, *131*, 3846–6847.

13 Wang, A.-Z.; Jiang, H.-F. Palladium-Catalyzed Direct Oxidation of Alkenes with Molecular Oxygen: General and Practical Methods for the Preparation of 1,2-Diols, Aldehydes, and Ketones. *J. Org. Chem.* **2010**, *75*, 2321–2326.

14 (a) Muñiz, K. High-Oxidation-State Palladium Catalysis: New Reactivity for Organic Synthesis. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412–9423. (b) Vedernikov, A. N. Direct Functionalization of M−C (M = $\mathrm{Pt^{II}}$, $\mathrm{Pd^{II}}$) Bonds Using Environmentally Benign Oxidants, O_2 and H_2O_2. *Acc. Chem. Res.* **2012**, *45*, 803–813.

15 Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Synthesis of Key Intermediates for Triazole Antifungal Agents. *Org. Lett.* **2005**, *7*, 2527–2530.

16 (a) Anbarasan, P.; Neumann, H.; Beller, M. A General Rhodium-Catalyzed Cyanation of Aryl and Alkenyl Boronic Acids. *Angew. Chem., Int. Ed.* **2011**, *50*, 519–522. (b) Liu, C.-R.; Yang, F.-L.; Jin, Y. Z.; Ma, X.-T.; Cheng, D.-J.; Li, N.; Tian, S.-K. Catalytic Regioselective Synthesis of Structurally Diverse Indene Derivatives from N-Benzylic Sulfonamides and Disubstituted Alkynes. *Org. Lett.* **2010**, *12*, 3832–3835. (c) Golisz, S. R.; Hazari, N.; Labinger, J. A.; Bercaw, J. E. Activation of the C−N Bond in Nitromethane by Palladium α-Diimine Complexes. *J. Org. Chem.* **2009**, *74*, 8441–8443. (d) Liu, Z.; Larock, R. C. Intermolecular C−N Addition of Amides and S−N Addition of Sulfinamides to Arynes. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113.

17 Wang, A.-Z.; Jiang, H.-F.; Li, X.-W. Palladium-Catalyzed Carbonation-Diketonization of Terminal Aromatic Alkenes via Carbon−Nitrogen Bond Cleavage for the Synthesis of 1,2-Diketones. *J. Org. Chem.* **2011**, *76*, 6958–6961.

18 (a) Miyamoto, S.; Martinez, G. R.; Medeiros, M. H. G.; Mascio, P. D. Singlet Molecular Oxygen Generated from Lipid Hydroperoxides by the Russell Mechanism: Studies Using ^{18}O-Labeled Linoleic Acid Hydroperoxide and Monomol Light Emission Measurements. *J. Am. Chem. Soc.* **2003**, *125*, 6172–6179. (b) *Metal-Catalyzed Oxidations of Organic Compounds*; Sheldon, R. A., Kochi, J. K., Eds.; Academic Press: New York, 1981.

19 Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; pp 97−129.

20 (a) For reviews, see: Bunz, U. H. F.; Kloppenburg, L. Alkyne Metathesis as a New Synthetic Tool: Ring-Closing, Ring-Opening, and Acyclic. *Angew. Chem., Int. Ed.* **1999**, *38*, 478–481. (b) For selected examples, see: Liu, Y.; Song, F.; Guo, S. Cleavage of a Carbon−Carbon Triple Bond via Gold-Catalyzed Cascade Cyclization/Oxidative Cleavage Reactions of (Z)-Enynols with Molecular Oxygen. *J. Am. Chem. Soc.* **2006**, *128*, 11332–11333.

21 Wang, A.-Z.; Jiang, H.-F. Palladium-Catalyzed Cleavage Reaction of Carbon-Carbon Triple Bond with Molecular Oxygen Promoted by Lewis Acid. *J. Am. Chem. Soc.* **2008**, *130*, 5030–5031.

22 Hou, X. L.; Yang, Z.; Wong, H. N. C. In *Progress in Hetereocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Oxford, 2003; Vol. 15, pp 167−205.

23 Wang, A.-Z.; Jiang, H.-F.; Xu, Q.-X. Synthesis of Tetrasubstituted Furans via Sequential $Pd(OAc)_2$/$Zn(OTf)_2$-Catalyzed Oxidation and Cyclization of Aromatic Alkynes with Molecular Oxygen. *Synlett* **2009**, 929–932.

24 Wen, Y.-M.; Zhu, S.-F.; Jiang, H.-F.; Wang, A.-Z.; Chen, Z.-W. Palladium-Catalyzed Oxidation and Cyclization of Carbon-Carbon Triple Bonds under Fluorous Media Using Molecular Oxygen. *Synlett* **2011**, 1023–1027.

25 Huang, H.-W.; Jiang, H.-F.; Cao, H.; Zhao, J.-W.; Shi, D.-B. Palladium-Catalyzed One-Pot Synthesis of Polysubstituted Furans from Alkynoates and 2-Yn-1-ols. *Tetrahedron* **2012**, *68*, 3135–3144.

26 Thirsk, C.; Whiting, A. Polyene Natural Products. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999–1023.

27 Jiang, H.-F.; Shen, Y.-X.; Wang, Z.-Y. Palladium-Catalyzed Aerobic Oxidation of Terminal Olefins with Electron-Withdrawing Groups in $scCO_2$. *Tetrahedron* **2008**, *64*, 508–514.

28 (a) Li, J.-H.; Jiang, H.-F.; Chen, M.-C. $CuCl_2$-Induced Regiospecifical Synthesis of Benzene Derivatives in the Palladium-Catalyzed Cyclotrimerization of Alkynes. *J. Org. Chem.* **2001**, *66*, 3627–3629. (b) Shen, Y.-X.; Jiang, H.-F.; Chen, Z.-W. $PdCl_2(HNMe_2)_2$-Catalyzed Highly Selective Cross [2+2+2] Cyclization of Alkynoates and Alkenes Under Molecular Oxygen. *J. Org. Chem.* **2010**, *75*, 1321–1324.

29 Zhang, L.; Zetterberg, K. The Concept of Geometrical Rigidity Around A Transition-Metal Center, A Significant Factor in Improving Thermal Stability for .Sigma.-Alkyl Transition-Metal Complexes. *Organometallics* **1991**, *10*, 3806–3813.

30 Zhou, P.; Huang, L.-B.; Jiang, H.-F.; Wang, A.-Z.; Li, X.-W. Highly Chemoselective Palladium-Catalyzed Cross-Trimerization between Alkyne and Alkenes Leading to 1,3,5-Trienes or 1,2,4,5-Tetrasubstituted Benzenes with dioxygen. *J. Org. Chem.* **2010**, *75*, 8279–8282.

31 Zhou, P.; Zheng, M.-F.; Jiang, H.-F. An Aerobic [2+2+2] Cyclization via Chloropalladation: From 1,6-Diynes and Acrylates to Substituted Aromatic Carbocycles. *J. Org. Chem.* **2011**, *76*, 4759–4763.

32 Huang, L.-B.; Wang, Q.; Liu, X.-H.; Jiang, H.-F. Switch of Selectivity in the Synthesis of α-Methylene-γ-Lactones: Palladium-Catalyzed Intermolecular Carboesterification of Alkenes with Alkynes. *Angew. Chem., Int. Ed.* **2012**, *51*, 5696–5700.

33 Wen, Y.-M.; Huang, L.-B.; Jiang, H.-F.; Chen, H.-J. Synthesis of δ-Bromo γ,δ-Unsaturated Carbonyl Compounds via Palladium-Catalyzed Bromoalkylation of Alkynoates. *J. Org. Chem.* **2012**, *77*, 2029–2034.

34 Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55–62.

35 Zhou, P.; Jiang, H.-F.; Huang, L.-B.; Li, X.-W. Acetoxypalladation of Unactivated Alkynes and Capture with Alkenes to Give 1-Acetoxy-1,3-dienes Taking Dioxygen as Terminal Oxidant. *Chem. Commun.* **2011**, *47*, 1003–1005.

36 (a) Wang, Z.; Zhang, Z.; Lu, X. Effect of Halide Ligands on the Reactivity of Carbon-Palladium Bonds: Implications for Designing Catalytic Reactions. *Organometallics* **2000**, *19*, 775–780. (b) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. Role of Halide Ions in Divalent Palladium−Mediated Reactions: Competition between β-Heteroatom Elimination and β-Hydride Elimination of a Carbon-Palladium Bond. *Organometallics* **2001**, *20*, 3724–3728.

37 (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. Aromatic Substitution of Olefins. VI. Arylation of Olefins with Palladium(II) Acetate. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169. (b) Jia, C. G.; Kitamura, T.; Fujiwara, Y. Catalytic Functionalization of Arenes and Alkanes via C−H Bond Activation. *Acc. Chem. Res.* **2001**, *34*, 633–639.

38 Jiang, H.-F.; Feng, Z.-N.; Wang, A.-Z.; Liu, X.-H.; Chen, Z.-W. Palladium-Catalyzed Alkenylation of 1,2,3-Trizoles with Terminal Conjugated Alkenes by Direct C−H Bond Functionalization. *Eur. J. Org. Chem.* **2010**, 1227–1230.

39 Jiang, H.-F.; Ji, X.-C.; Li, Y.-B. Palladium-Assisted Multicomponent Cyclization of Aromatic Aldehydes, Arylamines and Terminal Olefins under Molecular Oxygen: an Assembly of 1,4-Dihydropyridines. *Org. Biomol. Chem.* **2011**, *9*, 5358–5361.