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Carbonylation Reactions of Alkyl Iodides through the Interplay of Carbon Radicals and Pd Catalysts

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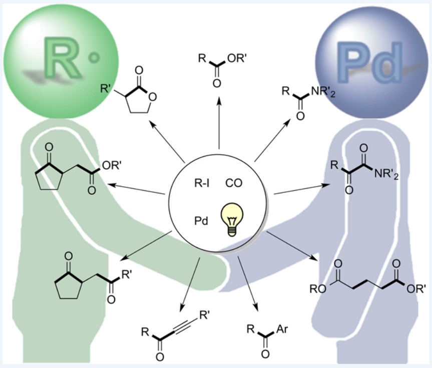
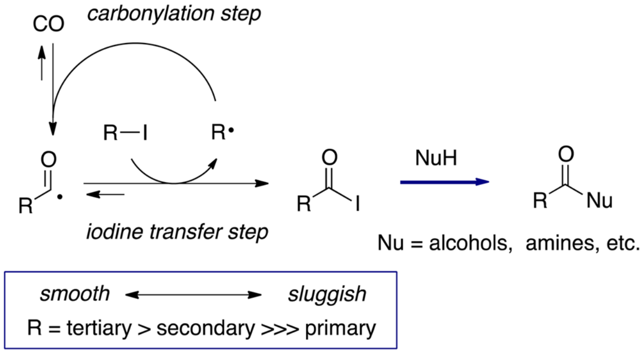


CONSPECTUS: Numerous methods for transition metal catalyzed carbonylation reactions have been established. Examples that start from aryl, vinyl, allyl, and benzyl halides to give the corresponding carboxylic acid derivatives have all been well documented. In contrast, the corresponding *alkyl* halides often encounter difficulty. This is inherent to the relatively slow oxidative addition step onto the metal center and subsequent β-hydride elimination which causes isomerization of the alkyl metal species. Radical carbonylation reactions can override such problems of reactivity; however, carbonylation coupled to iodine atom transfer (atom transfer carbonylation), though useful, often suffers from a slow iodine atom transfer step that affects the outcome of the reaction. We found that atom transfer carbonylation of primary, secondary, and tertiary alkyl iodides was efficiently accelerated by the addition of a palladium catalyst under light irradiation. Stereochemical studies support a mechanistic pathway based on the synergic interplay of radical and Pd-catalyzed reaction steps which ultimately lead to an acylpalladium species. The radical/Pd-combined reaction system has a wide range of applications, including the synthesis of carboxylic acid esters, lactones, amides, lactams, and unsymmetrical ketones such as alkyl alkynyl and alkyl aryl ketones. The design of unique multicomponent carbonylation reactions involving vicinal C-functionalization of alkenes, double and triple carbonylation reactions, in tandem with radical cyclization reactions, has also been achieved. Thus, the radical/Pd-combined strategy provides a solution to a longstanding problem of reactivity involving the carbonylation of *alkyl* halides. This novel methodology expands the breadth and utility of carbonylation chemistry over either the original radical carbonylation reactions or metal-catalyzed carbonylation reactions.

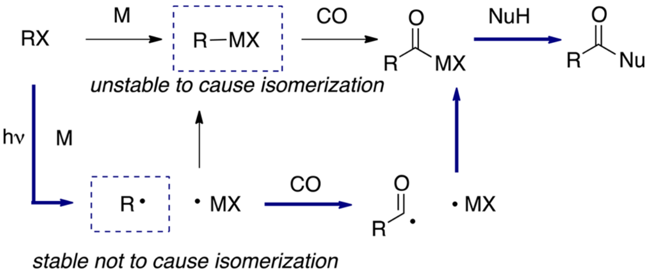
1. INTRODUCTION

Carbonylation reactions using carbon monoxide have found tremendous applications for the synthesis of a wide range of organic carbonyl compounds.[1] Whereas numerous examples of transition metal catalyzed carbonylation of aryl, vinyl, allyl, and benzyl halides to give carboxylic acid derivatives have been established,[2] the corresponding alkyl halides often encounter difficulty inherent to the relatively slow oxidative addition onto the metal center and β-hydride elimination causing isomerization of alkyl metal species. Acetic acid synthesis from methanol and carbon monoxide by Rh catalysis (the Monsanto process)[3] or Ir catalysis (the Cativa process)[4] represents the most successful example of industrial carbonylation processes. However, extension of the Monsanto's acetic acid synthesis to C3 and higher alcohols has proved difficult, since isomeric mixtures of carboxylic acids are formed due to the isomerization of alkyl-Rh intermediates via β-hydride elimination.[3] In the past decade, notable progress has been made in efficient transition metal catalyzed cross-coupling reactions of alkyl halides.[5] Examples include Fu's Pd catalysts with electron-rich and bulky trialkylphosphine ligands, such as PCy$_3$ and P(tBu)$_2$Me,[6]

Scheme 1. Concept of ATC (Atom Transfer Carbonylation) Reactions of Alkyl Iodides



Scheme 2. General Concept for Carbonylation of Alkyl Halides by Interplay of Metal Catalyst and Carbon Radicals



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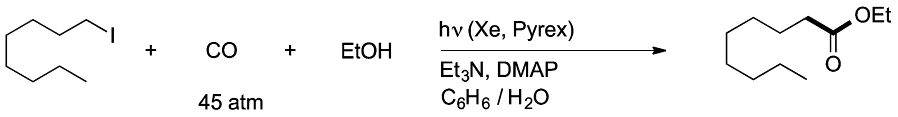
Scheme 3. Acceleration of Photoinduced ATC Reaction of 1-Iodooctane by Pd Catalysts



none, 50 h	54%
$Pd(PPh_3)_4$ (5 mol %),16 h	87%
$[Pd_2(CNMe)_6][PF_6]_2$ (2.5 mol %), 14 h	87%

Ni catalysts with bidentate nitrogen ligands,[7] Organ's Pd catalysts with bulky NHC ligands, such as PEPPSI-IPr,[8] Kambe's Grignard type coupling catalyzed by transition metals, such as Ni, Pd, Cu, and Co with *π*-carbon ligands,[9] and Oshima's Co catalysts with bidentate phosphine ligands,[10] just to name a few.

There is a conceptually different way to carbonylate alkyl halides, which is based on radical reactions.[11] Alkyl radicals, irrespective of whether they are primary, secondary, or tertiary, do not suffer from isomerization like the corresponding alkyl-metal species. To achieve effective carbonylation of alkyl halides, we have been involved in the development of carbonylation methods using the addition reaction of alkyl radicals to CO to form acyl radicals as the key step.[12] Now, many useful examples of radical carbonylations to give aldehydes, ketones, esters, amides, lactams, lactones, and so forth exist.[13] To synthesize carboxylic acid derivatives from alkyl iodides and CO, the approach consists of radical carbonylation and iodine atom transfer, which we call atom transfer carbonylation (ATC) (Scheme 1).[14] This system does not require any radical mediators, like tributyltin hydride, rather it requires either photoirradiation or a thermal radical initiator. To shift the equilibrium of the thermodynamically unfavorable iodine atom transfer step, the acyl iodide formed is quenched by a nucleophile in the final step of the reaction. The system works well for the synthesis of aliphatic carboxylic acid esters,[15] amides[16] and related heterocyclic compounds.[17] The Uppsala group successfully applied the ATC reaction to include the synthesis of positron emission tomography (PET) active carboxylic acids by incorporating ^{11}CO.[18]

For ATC reactions to be more synthetically useful, it is important to be able to accelerate the reaction when faced with a slow iodine atom transfer step. This is particularly important for primary alkyl iodides, due to their reduced ability to form primary alkyl radical and acyl iodide (ΔG = 15.0 kJ/mol: BHandHLYP/DZP) compared with secondary and tertiary iodides (ΔG = 6.7 and −4.1 kJ/mol: BHandHLYP/DZP).[19] Acceleration of ATC is also desirable in achieving effective cascade reactions employing CO, alkenes, and alkynes, since depending on simple equilibrium shift by polar reactions over multiple steps results in competing side reactions.

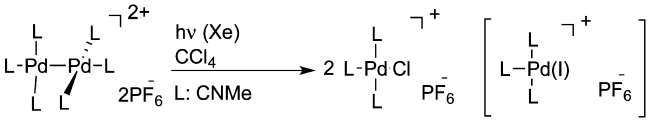
In the 1980s, Watanabe and co-workers[20] and Suzuki, Miyaura, and co-workers,[21] independently reported that transition metal catalyzed carbonylation of alkyl iodides can be improved by photoirradiation. Both groups reasoned that photoirradiation would smoothly generate an alkyl-metal species via a radical mechanism, which would then undergo CO insertion to lead to a key acylmetal species. Inspired by these reports and intrigued by the mechanistic possibilities of the interplay of radical species with transition metal species, we decided to introduce Pd catalysts into our photoirradiative ATC system and observed excellent acceleration of carbonylation for all types of alkyl iodides. We assumed that in the photoirradiative system, a carbon radical/metal radical pair would be formed, which would be then converted to the corresponding acyl radical/metal radical pair in the presence of CO. This would ultimately form an acylmetal species serving as a source of carbonylated products (Scheme 2).

In this Account, we will discuss how Pd/light-induced carbonylation reactions of alkyl iodides have been used in basic to complex cascade carbonylation chemistry through numerous examples. It is also our intention to discuss the interplay of Pd catalysts and radical species, and how this chemistry has improved our original radical reaction system and other previously reported carbonylation systems.

2. SYNTHESIS OF CARBOXYLIC ACID ESTERS AND AMIDES BY Pd/LIGHT ACCELERATED CARBONYLATION OF ALKYL IODIDES

The acceleration of light-induced ATC by Pd complexes was observed for primary, secondary, and tertiary alkyl iodides. For example, when the reaction of 1-iodooctane, CO, and ethanol was carried out under photoirradiation conditions (500 W xenon lamp through Pyrex) and 45 atm of CO pressure, ethyl

Scheme 4. Photoreaction Behavior of Dimeric Pd(I) Complex toward CCl_4[24a]



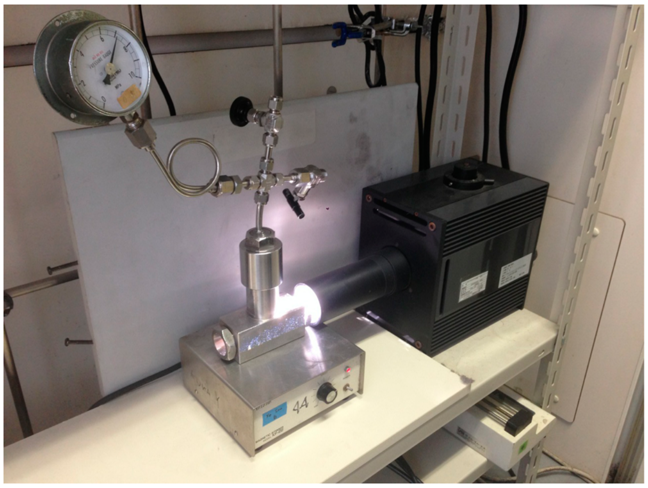
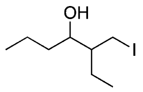
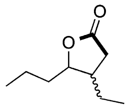
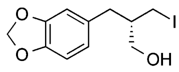
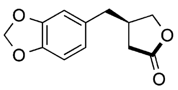
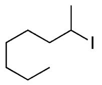
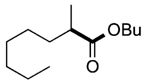
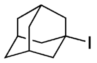
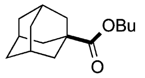
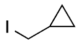
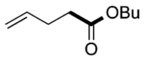
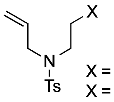
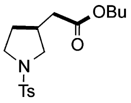


Figure 1. Typical photocarbonylation equipment: xenon lamp (500 W) irradiation through glass windows of a stainless steel autoclave (inner volume: 100 mL).

Table 1. Pd/light Accelerated Atom Transfer Carbonylation of Alkyl Iodides Leading to Esters and Lactones[a]

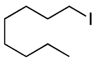
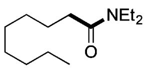
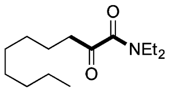
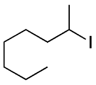
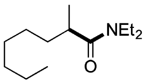
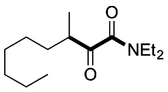
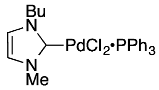
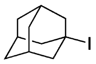
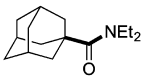
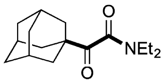
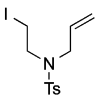
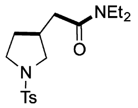
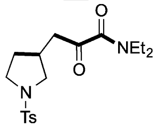
entry	RI	catalyst	RCO_2R'	yield (%)
1		none		27 *cis*/*trans* = 36/64
2		$Pd(PPh_3)_4$		91 *cis*/*trans* = 36/64
3		$Pd(PPh_3)_4$		73
4		none		40
5		$Pd(PPh_3)_4$		83
6		none		38
7		$Pd(PPh_3)_4$		80
8		$[Pd_2(CNMe)_6][PF_6]_2$		92
9		none		40
10		$Pd(PPh_3)_4$		83
11	 X = I X = Br	$Pd(PPh_3)_4$		73 (X = I)
12		$Pd(PPh_3)_4$		58 (X = Br)

[a]Reaction conditions: *hν* (Xe, Pyrex), 16 or 6.5 h (entries 4–8), Pd catalyst, 5 mol % or 2.5 mol % (entry 8).

nonanoate was formed but in modest yield of 54% even with prolonged irradiation over 50 h (Scheme 3). However, an identical reaction except in the presence of a catalytic amount of $Pd(PPh_3)_4$ gave the ester in 86% yield after 16 h.[22] Kubiak and co-workers previously reported that photoirradiation of $[Pd_2(CNMe)_6][PF_6]_2$,[23] an isolable Pd dimer complex, in the presence of carbon tetrachloride (Scheme 4) or allyl chloride gave the corresponding Pd mononuclear complexes.[24] It is suggested that Pd radicals are formed by homolysis which undergoes chlorine abstraction. The same complex was tested in our system and proved to be an effective catalyst (Scheme 3). In this reaction, a base, typically triethylamine or potassium carbonate, is used to trap HI and the couse of catalytic DMAP further accelerates the reaction. The reaction requires light irradiation with a xenon lamp through a Pyrex tube and a stainless steel made autoclave with quartz windows, a photo is shown in Figure 1.

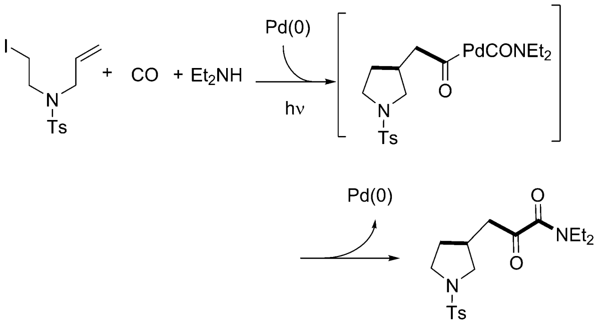
Table 1 summarizes selected results of the synthesis of carboxylic acid esters and related compounds from alkyl iodides using either the original metal free or Pd-accelerated conditions.[22] The ATC reaction of *γ*-hydroxy primary alkyl iodide was sluggish, as ionic cyclization leading to an oxetane ring competed with the desired reaction (entry 1). However, acceleration by a Pd catalyst improved the yield of the lactone up to 91% yield (entry 2). Acceleration of carbonylation by the Pd catalyst was also observed with secondary and tertiary alkyl iodides (entries 5 and 7). Fast radical reactions[25] such as radical ring-opening and 5-*exo* cyclization are effectively sequenced with carbonylation to give good yields of butyl 4-pentenoate (entry 10) and pyrrolidine bearing an ester tether (entry 11), respectively. For the cyclization-carbonylation reaction, bromoalkene also worked, albeit in lower yield (entry 12).

Table 2. Pd/Light Accelerated Single and Double Carbonylation Reactions of RI Leading to Amides and Keto Amides[a]

entry	RI, catalyst	$RCONR_2$	$RCOCONR_2$
			
1	$Pd(PPh_3)_4$	23%	50%
2	$Pd_2(dba)_3{\cdot}CHCl_3/P(p\text{-}MeOPh)_3$	11%	64%
3	$Mn_2(CO)_{10}$	91%	—
			
4	$Pd_2(dba)_3{\cdot}CHCl_3/P(p\text{-}MeOPh)_3$	11%	64%
5		87%	4%
6	$Mn_2(CO)_{10}$	91%	—
			
7	$Pd_2(dba)_3{\cdot}CHCl_3/P(p\text{-}MeOPh)_3$	23%	59%
8	$Mn_2(CO)_{10}$	81%	—
			
9	$Pd(PPh_3)_4$	14%	51%

[a]Reaction conditions: R-I (0.5 mmol), Et_2NH (2.5 mmol), catalyst (2.5 mol %, 5 mol % for entries 1, 5, and 9), C_6H_6 ([bmim]NTf_2 for entry 5), CO (70–80 atm), *hν* (Xe, Pyrex), 16 h.

Scheme 5. Intermediacy of Acyl Carbamoyl Pd Complex in Double Carbonylation Reactions



The ATC reaction comprising of alkyl iodide, CO, and amines without a Pd catalyst, gave the corresponding amides as the carbonylation product,[16] whereas a similar reaction in the presence of Pd catalyst gave the corresponding keto amide as the major product via the incorporation of two molecules of CO (Table 2).[22] This is in contrast with results observed in the presence of $Mn_2(CO)_{10}$,[26] where the carbonylation of alkyl iodides gave singly carbonylated amides selectively. The single/double ratio is dependent on the ligand of the Pd catalyst. Thus, the use of $P(p\text{-}MeOPh)_3$ ligand gave more double carbonylated product, and more singly carbonylated product was formed when Pd-NHC carbene complex was used with [bmim]NTf_2 as the solvent.[27] The formation of keto amides in

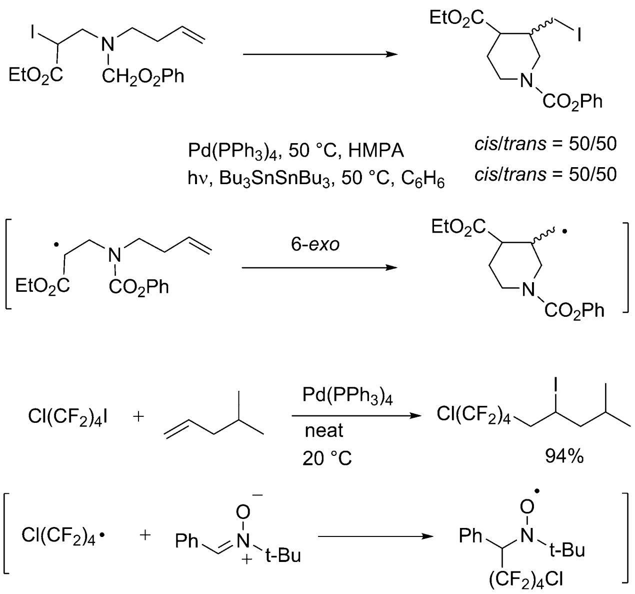
Pd/light systems lends support to the generation of acylpalladium complexes, since such double carbonylation is well-known for palladium catalyzed carbonylation of iodobenzene,[28] iodomethane,[28] and β-perfluoroalkyl iodides,[29] whereas amines and acyl radicals are rarely carbonylated. Yamamoto and Ozawa, the pioneers of double carbonylation chemistry, established the mechanism for the formation of keto amides, which includes nucleophilic attack at the coordinated CO of acylpalladium complex by an amine to form acyl(carbamoyl) palladium complex, followed by reductive elimination of the complex to give the product and Pd(0).[30] This strongly suggests that the Pd/light system would ultimately lead to a CO-coordinated acylpalladium species via radical reactions (Scheme 5). In the next section we discuss how acylpalladium species would form from the Pd/photoirradiation system with RI and CO.

3. MECHANISTIC INSIGHTS INTO THE INTERPLAY OF RADICAL SPECIES AND PALLADIUM CATALYST

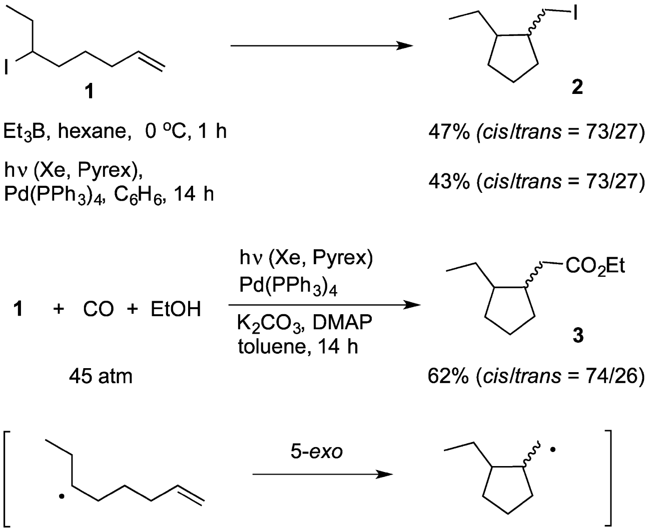
3.1. Radical Initiation

In 1985, Mori and co-workers reported on Pd catalyzed 6-*exo* atom transfer cyclization of an α-iodo ester.[31] Curran and Chang proved that the $Pd(PPh_3)_4$ complex acts as radical initiator in the cyclization (Scheme 6).[32] Later, Chen and co-workers reported that Kharasch type carboiodation of alkenes by perfluoroalkyl iodides is effectively initiated by $Pd(PPh_3)_4$ (Scheme 6).[33] A single electron transfer (SET) induced radical generation mechanism has been supported by ESR detection of perfluoroalkyl radical trapped by phenyl t-butyl nitrone.[33,34]

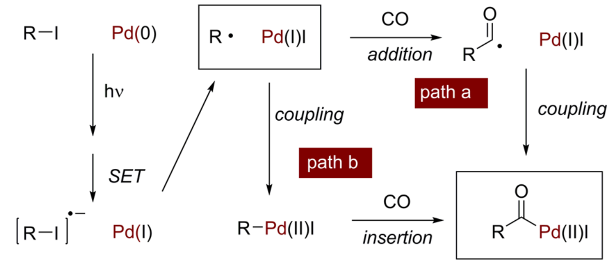
Scheme 6. Examples of Initiation of Atom Transfer Reaction by $Pd(PPh_3)_4$



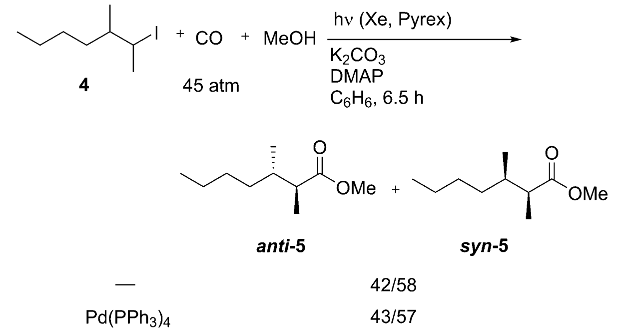
Scheme 7. Comparison of Diastereomeric Isomer Ratios for Atom Transfer 5-*exo* Cyclizations and Carbonylation Reaction



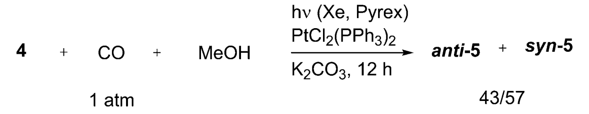
Scheme 8. Two Possible Pathways for Acylpalladium Formation



Scheme 9. Comparison of Diastereomer Ratios of ATC Reactions with or without Pd Catalyst

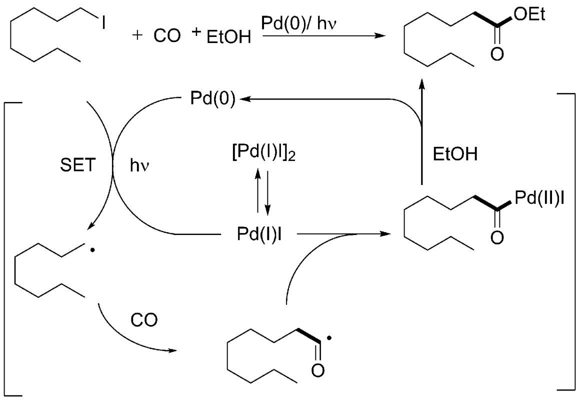


Scheme 10. Comparison of Diastereomer Ratios of Watanabe's Pt-Catalyzed Carbonylation Reactions



Encouraged by these studies, we examined the diastereoselectivity of the 5-*exo*-cyclization reaction of 6-iodo-1-octene (**1**) as a test substrate using the Pd/photoirradiation, since rate constants of *cis* and *trans* 5-*exo* cyclization of the corresponding 1-methyl-5-hexenyl radical have been reported by Beckwith and Schiesser.[35] We confirmed that the atom transfer cyclization of **1** was initiated by the addition of $Pd(PPh_3)_4$ when the reaction was photoirradiated or via thermal heating (Scheme 7).[36] The cyclized product **2** was obtained as a 73/27 mixture of *cis* and *trans* isomers in the presence of $Pd(PPh_3)_4$, identical with the ratio obtained using Et_3B/air as the radical initiator. The Pd/light-induced cyclization-carbonylation of **1** was also carried out, which gave the cyclized ethyl ester **3** again in a nearly

Scheme 11. Proposed Reaction Mechanism



identical isomer ratio of 74/26. These values are in good accordance with the calculated value of 73/27 from the kinetic data.[35] To summarize, the Pd/light-induced cyclizative ATC reaction of **1** proceeds through a mechanism involving generation of a radical and subsequent cyclization. As previous studies proposed, SET from Pd(0) to RI would take place to generate both alkyl radical and PdI radical (or expressed as Pd(I)I), serving as the radical initiation step.

3.2. Carbonylation Step

The second step is the carbonylative C–C bond-forming reaction, where in principle two mechanistic pathways are conceivable: (i) addition of the alkyl radical to CO to form the corresponding acyl radical (path a) and (ii) coupling of the alkyl radical and PdI radical to form alkyl-Pd(II)I, which undergoes migratory insertion of CO into the alkyl palladium bond forming acyl-Pd(II)I (path b) (Scheme 8). The reaction of 2-iodo-3-methylheptane (**4**), CO, and methanol was carried out under photoirradiation conditions in the absence of a Pd catalyst, giving the corresponding methyl ester **5** in a 42/58 ratio of *anti*/*syn* diastereomers (Scheme 9). When a similar reaction was carried out in the presence of $Pd(PPh_3)_4$, the product **5** was formed in quite a similar *anti*/*syn* ratio of 43/57. The coincidence of the diastereoselectivities strongly suggests that the C–C bond-forming step via carbonylation does proceed via addition of an alkyl radical to CO, which ultimately leads to an acylpalladium complex (path a).

The $PtCl_2(PPh_3)_2$-catalyzed carbonylation reaction of alkyl iodides in the presence of alcohols under irradiation was previously reported by Watanabe and co-workers.[20] To determine whether the carbonylation step involved a radical C–C bond-forming process, we re-examined the reaction using alkyl iodide **4** as a stereochemical probe. When the reaction of **4**, CO, and methanol was carried out in the presence of $PtCl_2(PPh_3)_2$ under Xe lamp (300 W) irradiation, methyl ester **5** was obtained with a 43/57 *anti*/*syn* ratio (Scheme 10). Exactly the same diastereomer ratio was observed in our Pd/light reaction from Scheme 9. Thus, we conclude that Watanabe's Pt/light carbonylation system operates via a radical carbonylation mechanism.

Taking these stereochemical outcomes into consideration, we propose a reaction mechanism involving a radical carbonylation step followed by the subsequent formation of an acyl palladium species (Scheme 11). Alkyl radicals are formed via cleavage of RI, triggered by single electron transfer from photoexcited Pd(0) to RI. When the Pd dimeric complex is used, the Pd(I) radical, formed via bond homolysis, abstracts iodide from RI to generate the corresponding alkyl radical. The resultant alkyl radical is quickly consumed by addition to CO affording the acyl radical that is eventually trapped by Pd(I)I to form an acylpalladium complex, which is the precursor for the carbonylated products. The mechanism illustrated in Scheme 11 also suggests that Pd(I)I may behave as a persistent radical,[37] since a potential side reaction could occur, when the alkyl radical couples with the Pd(I) radical to give alkylpalladium.

Table 3. Synthesis of Alkyl Alkynyl Ketones by Three-Component Coupling Reaction

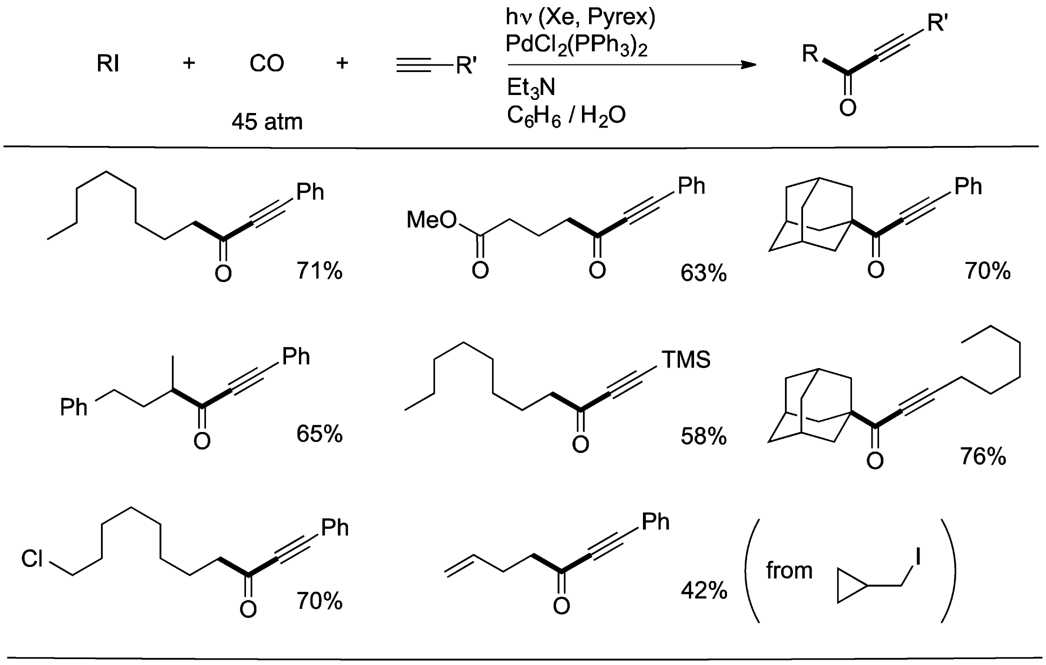


Table 4. Synthesis of Alkyl Aryl Ketones by Three-Component Coupling Reaction

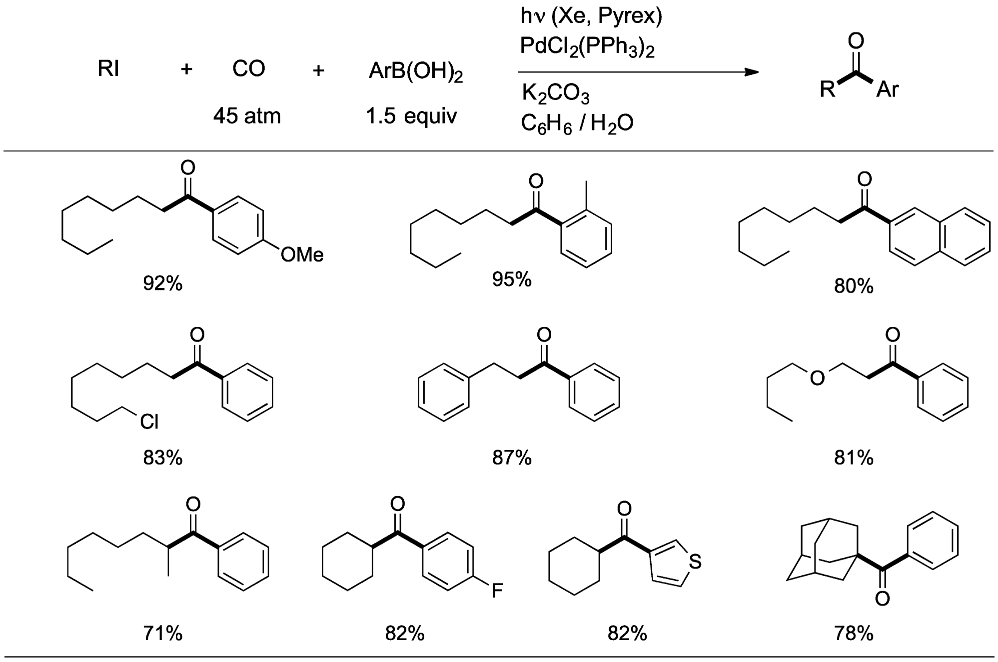
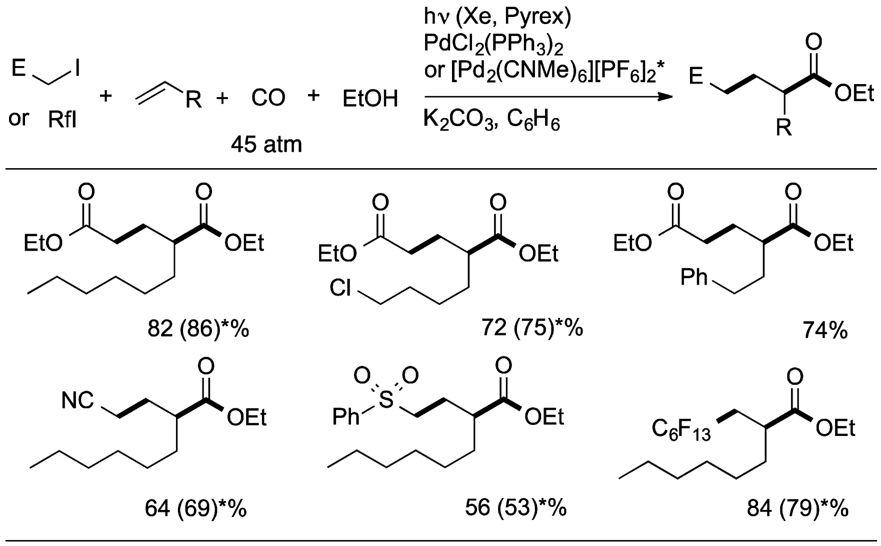


Table 5. Four-Component Coupling Reactions Leading to Functionalized Esters



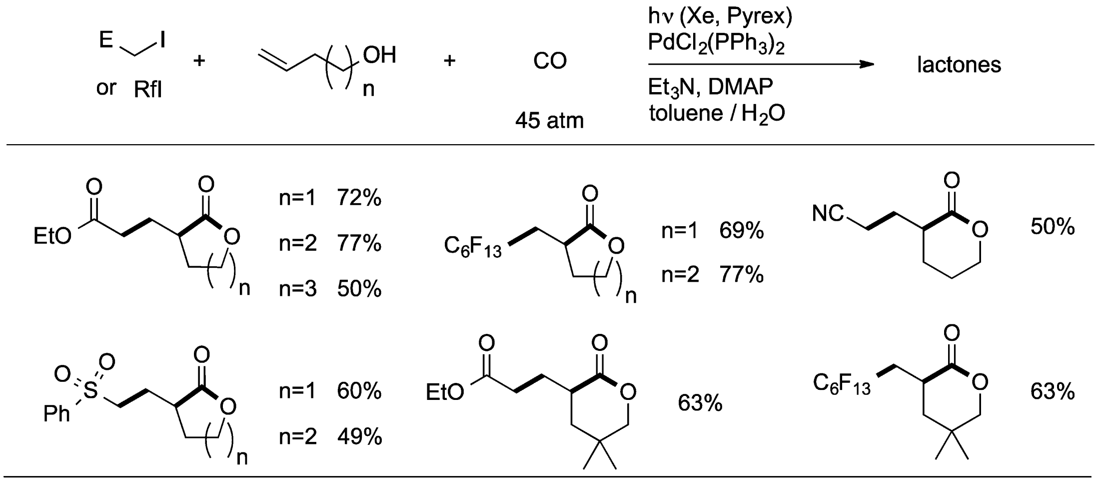
4. SYNTHESIS OF UNSYMMETRICAL KETONES

In this Pd/photoirradiation carbonylation reaction, alkyl iodides react with 1-alkynes to give alkyl alkynyl ketones (Table 3).[38] For example, when a benzene solution of 1-iodooctane and phenylacetylene was exposed to photocarbonylation conditions in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, the alkynyl ketone product was obtained in 71% yield. Similarly, alkyl iodides, possessing a chlorine or methyl ester functionality, also gave the desired ketones in good yields. Secondary and tertiary alkyl iodides were reactive substrates, and aliphatic acetylenes, such as 1-octyne and trimethylsilylacetylene, where effective coupling partners. The reaction of cyclopropylmethyl iodide gave an alkenyl alkynyl ketone, possessing a straight-chain olefin which was generated from the ring-opening of a cyclopropylcarbinyl radical.[25]

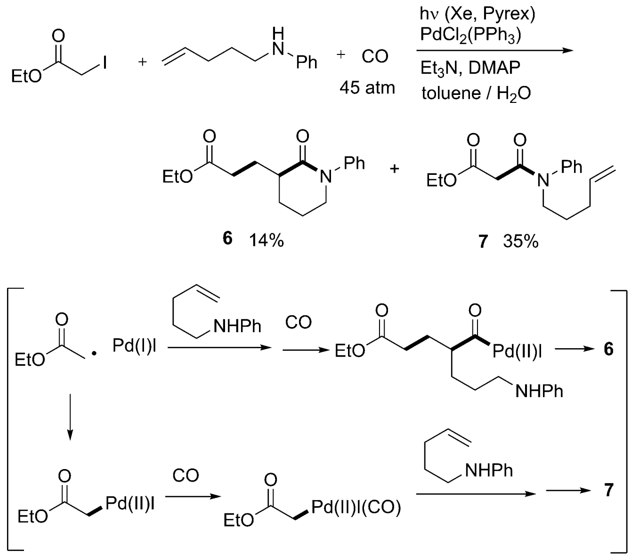
We also examined the Pd-catalyzed synthesis of alkyl aryl ketones via a three-component reaction starting from alkyl iodides, CO, and arylboronic acids.[39] As demonstrated in Table 4, under photoirradiation conditions, primary, secondary, and tertiary alkyl iodides effectively coupled with CO and arylboronic acids in the presence of a Pd catalyst to give the corresponding alkyl aryl ketones in good yields.

It should be noted that Miyaura, Suzuki, and co-workers previously reported examples of carbonylative cross-coupling reactions of alkyl iodides, CO (atmospheric pressure), and alkyl- and aryl-9-BBN under tungsten lamp irradiation,[21a] some examples include 5-*exo* cyclization.[21b] They proposed a radical mechanism leading to alkyl-Pd species, and CO insertion to form the acyl-Pd species (path b in Scheme 8) followed by transmetalation with organyl-9-BBN.

Table 6. Three-Component Coupling Reactions Leading to Lactones



Scheme 12. Two Reaction Courses in Three-Component Reaction of α-Iodo Acetate, 4-Pentenylamine, and CO



5. APPLICATIONS TO CASCADE CARBONYLATION REACTIONS

The utility of the Pd/photoirradiation system can be demonstrated through the design of cascade carbonylation reactions. The four-component reactions comprising α-substituted alkyl iodides, alkenes, CO, and alcohols proceeded well to give substituted esters in good yields (Table 5).[22b,40] The initial carbon radical formed is electrophilic due to α-substitution by an electron-withdrawing substituent, such as ethoxycarbonyl group. This radical adds rapidly to terminal alkenes, such as 1-octene,[41] and the resulting alkyl radical reacts consecutively with CO and the Pd(I)I to form an acylpalladium species. Subsequent alcoholysis gives the substituted ester product in good to high yields. Other α-substituted alkyl iodides also underwent the four-component reaction. The dimeric Pd catalyst worked equally well as the Pd monomer catalyst.

When alkenyl alcohols were employed, α-functionalized lactones could be prepared by cyclization (Table 6).[22b,40]

In contrast, when the coupling reaction was carried out using 4-pentenylamine, the anticipated lactam product **6** was obtained in low yield and carbamoyl acetate **7** was obtained as the predominant product (Scheme 12). This suggested that

Table 7. Three-Component Coupling Reactions Leading to Carbamoyl Acetates

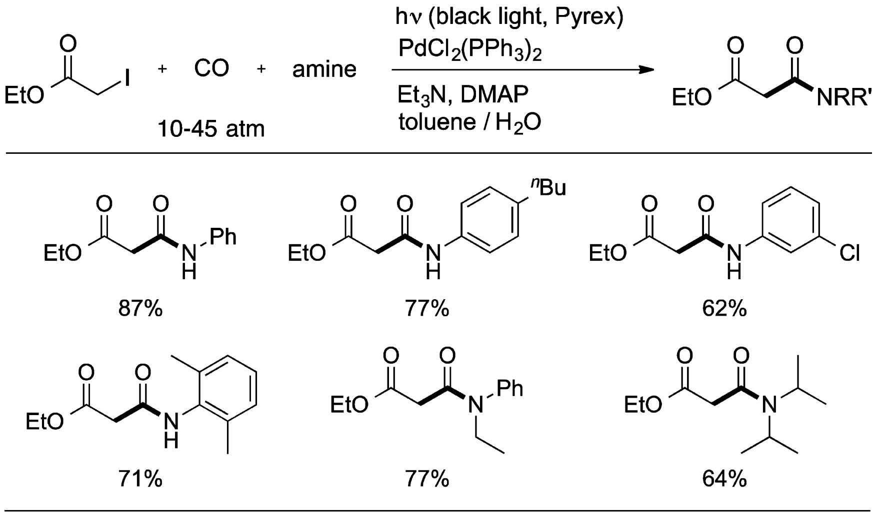
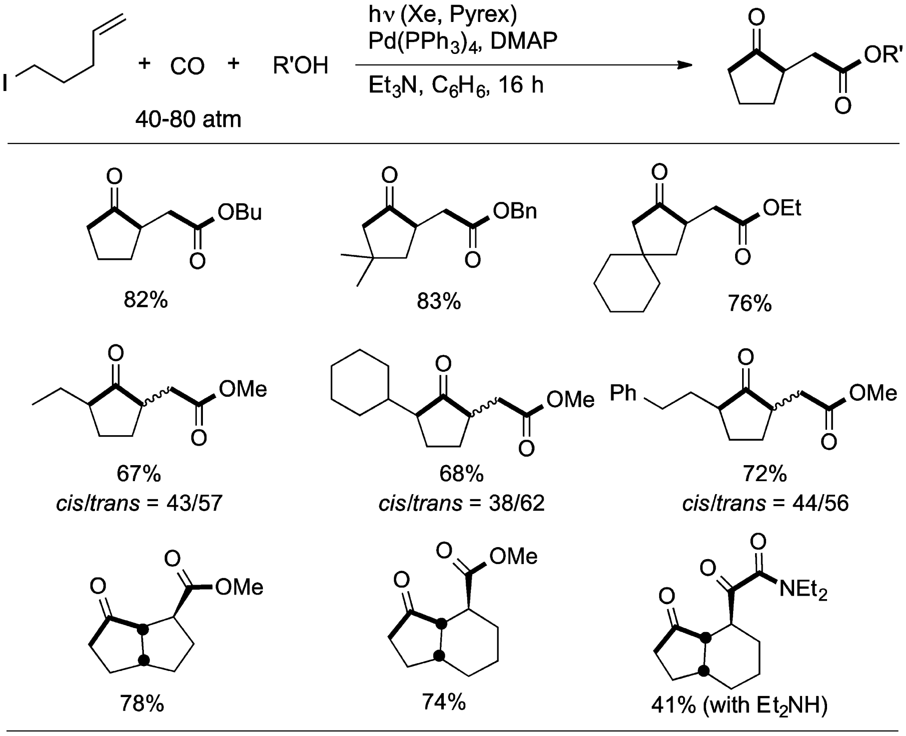
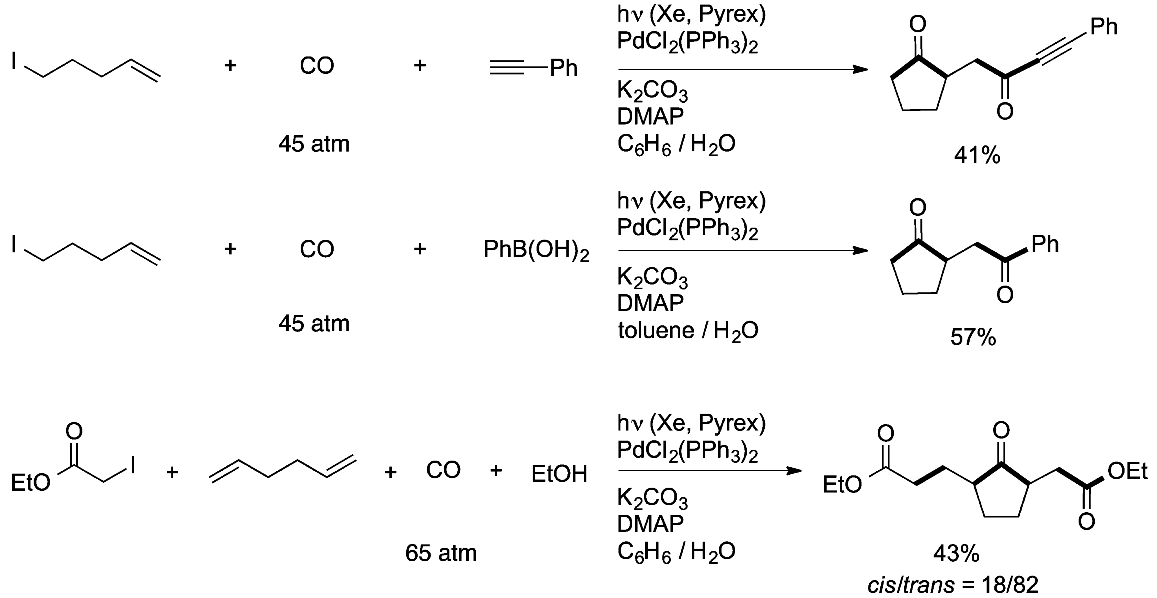


Table 8. Cyclizative Double and Triple Carbonylation Reactions



Scheme 13. Applications of Cyclizative Double Carbonylation Reactions

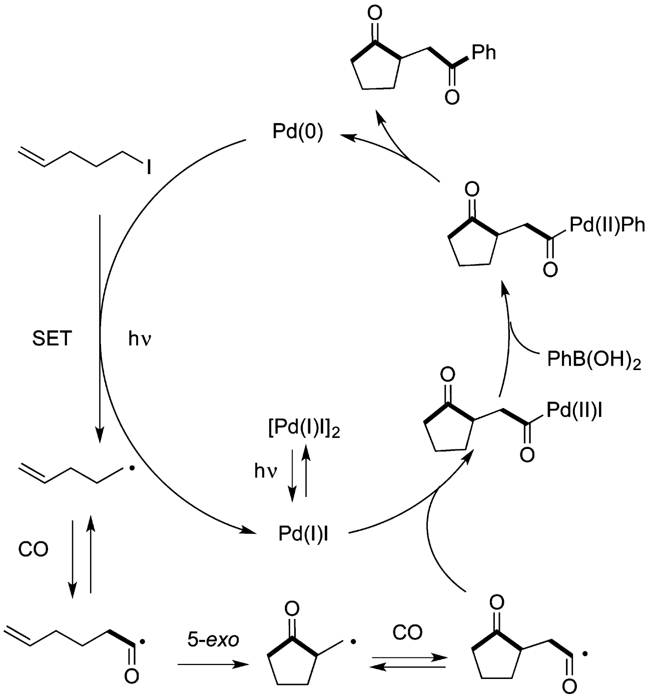


the α-carbonyl radical has two reaction courses: (i) addition to an alkene and (ii) coupling with Pd(I)I to form the α-pallado ester. The reaction in the absence of an alkene, but with the addition of an amine, gave good yields of carbamoyl acetates (Table 7). In these cases, it is likely that the α-pallado ester undergoes traditional CO insertion followed by aminolysis.[42]

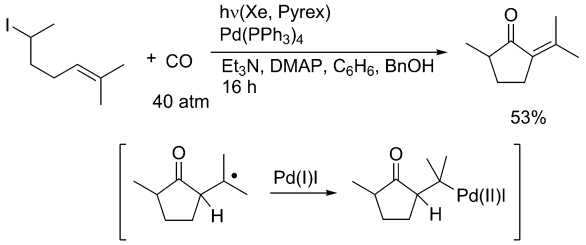
The 4-pentenyl radical is known to add to CO forming 5-hexenoyl radical, which undergoes 5-*exo*-cyclization.[43] Under high CO pressure, cyclizative double carbonylation takes place.[44] We applied the [4 + 1] annulation to form 2-oxo-cyclopentylcarbinyl radicals for further cascade reactions involving the addition of a second molecule of CO. In the presence of alcohols, esters with a cyclopentanone scaffold were synthesized via cyclizative double carbonylation reaction (selected results are given in Table 8).[45] Interestingly, when amine is used as a nucleophile, the reaction gave the keto amide product as major product via incorporation of three molecules of CO.

When the reaction of 5-iodo-1-pentene and CO was carried out in the presence of phenylacetylene or phenylboronic acid, alkynyl[38] or aryl[39] ketone products, bearing a cyclopentanone scaffold, were formed in modest yield through a carbonylation–cyclization–carbonylation–alkynylation or –arylation sequence (Scheme 13). The reaction of ethyl α-iodoacetate with 1,5-

Scheme 14. Proposed Reaction Mechanism of Cyclizative Double Carbonylation



Scheme 15. Heck Type Carbonylation Reaction by Pd/photoirradiation System



hexadiene gave the five-component coupling product with a cyclopentanone scaffold.[22b]

These results show that Pd/photoirradiation carbonylation reactions combine well with cascade radical pathways to form multiple new carbon−carbon bonds in a single reaction. The proposed mechanism for Pd/light-assisted carbonylation is shown in Scheme 14 with the second example. In the first step, alkyl iodide reacts with Pd(0) under irradiation to afford 4-pentenyl radical and Pd(I)I via single electron transfer. 4-Pentenyl radical traps CO to form the acyl radical which undergoes 5-*exo* cyclization to afford the alkyl radical. The alkyl radical adds to a second molecule of CO to form the acyl radical, which couples with Pd(I)I to give the acylpalladium intermediate and the product ketone through an arylated Pd intermediate.

As shown in Scheme 15, the example of the Heck type carbonylation product can be obtained from the tertiary radical formed via radical carbonylation and subsequent 5-*exo* cyclization of a secondary iodide.[46] In this case, β-hydride elimination proceeds due to inefficient carbonylation of the tertiary alkyl radical, as described by the mechanism of path b in Scheme 8. This is a very subtle aspect of the Pd/photoirradiation system. Very recently Alexanian and co-workers developed a Pd-catalyzed carbonylative Heck cyclization reaction using 4-alkenyl iodides and CO under thermal conditions,[47] demonstrating that the Pd/RI system with either light or heat ensures the interplay of radical and Pd species.

6. CONCLUSIONS

Photoinduced atom transfer carbonylation reaction of a variety of alkyl iodides can be effectively accelerated by the addition of Pd complexes. A SET reaction between a Pd complex and RI takes place to generate an alkyl radical and a PdI radical (also expressed as Pd(I)I). Stereochemical studies strongly suggest that the radical carbonylation step to form the acyl radical from alkyl radical and CO is essential in this reaction system. The overall reaction between the radical and Pd species occurs due to three critical steps: (i) formation of alkyl radical/PdI radical pair, (ii) subsequent radical C−C bond-forming reaction (carbonylation), and (iii) radical/PdI radical coupling to form an organopalladium intermediate (acylpalladium complexes). The Pd/photoirradiation strategy for carbonylation allows for a variety of cascade multicomponent reactions with incorporation of CO. In some cases, the formation of alkylpalladium species has also been observed, suggesting that mechanistic analysis should be done carefully on a case-by-case basis. Nevertheless, there is little doubt that metal-mediated radical chemistry will continue to have more and more applications in organic synthesis.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Colquhoun, H. M., Thompson, D. J., Twigg, M. V., Eds.; Plenum Press: New York, 1991. (b) Beller, M. Wu, X.-F. *Transition Metal Catalyzed Carbonylation Reactions Carbonylative Activation of C-X Bonds*; Springer: Berlin, Heidelberg; 2013. (c) Kollár, L. *Modern Carbonylation Methods*; Wiley-VCH: Weinheim, 2008. (d) Fukuyama, T.; Ryu, I. Carbon Monoxide. *e-EROS Encycl. Reagents Org. Synth.* **2006**, DOI: 10.1002/047084289X.rc013.pub2. (e) Fukuyama, T.; Maetani, S.; Ryu, I. Carbonylation and Decarbonylation Reactions. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol 3.

(2) Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114−4133.

(3) Dekleva, T. W.; Forster, D. The Rhodium-Catalyzed Carbonylation of Linear Primary Alcohols. *J. Am. Chem. Soc.* **1985**, *107*, 3565−3567.

(4) Haynes, A.; Maitlis, P. M.; Morris, G. E.; Sunley, G. J.; Adams, H.; Badger, P. W.; Bowers, C. M.; Cook, D. B.; Elliott, P. I. P.; Ghaffar, T.; Green, H.; Griffin, T. R.; Payne, M.; Pearson, J. M.; Taylor, M. J.; Vickers, P. W.; Watt, R. J. Promotion of Iridium-Catalyzed Methanol Carbonylation: Mechanistic Studies of the Cativa Process. *J. Am. Chem. Soc.* **2004**, *126*, 2847−2861.

(5) For reviews on cross-coupling reaction of alkyl halides, see: (a) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. Transition Metal-Catalyzed Activation of Aliphatic C−X Bonds in Carbon−Carbon Bond Formation. *Chem. Rev.* **2000**, *100*, 3187−3204. (b) Frisch, A. C.; Beller, M. Catalysts for Cross-Coupling Reactions with Non-activated Alkyl Halides. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (c) Rudolph, A.; Lautens, M. Secondary Alkyl Halides in Transition-Metal-Catalyzed Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656−2670. (d) Hu, X. Nickel-catalyzed Cross Coupling of Non-activated Alkyl Halides: A Mechanistic Perspective. *Chem. Sci.* **2011**, *2*, 1867−1886.

(6) For a review, see: Netherton, M. R.; Fu, G. C. Palladium-Catalyzed Cross-Coupling Reactions of Unactivated Alkyl Electrophiles with Organometallic Compounds. *Top. Organomet. Chem.* **2005**, *14*, 85−108.

(7) For selected recent reports, see: (a) Binder, J. T.; Cordier, C. J.; Fu, G. C. Catalytic Enantioselective Cross-Couplings of Secondary Alkyl Electrophiles with Secondary Alkylmetal Nucleophiles: Negishi Reactions of Racemic Benzylic Bromides with Achiral Alkylzinc Reagents. *J. Am. Chem. Soc.* **2012**, *134*, 17003−17006. (b) Zultanski, S. L.; Fu, G. C. Nickel-Catalyzed Carbon−Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations. *J. Am. Chem. Soc.* **2013**, *135*, 624−627. (c) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. Nickel/Bis(oxazoline)-Catalyzed Asymmetric Negishi Arylations of Racemic Secondary Benzylic Electrophiles to Generate Enantioenriched 1,1-Diarylalkanes. *J. Am. Chem. Soc.* **2013**, *135*, 16288−16291.

(8) For selected recent reports, see: (a) Nasielski, J.; Hadei, N.; Achonduh, G.; Kantchev, E. A. B.; O'Brien, C. J.; Lough, A.; Organ, M. G. Structure−Activity Relationship Analysis of Pd−PEPPSI Complexes in Cross-Couplings: A Close Inspection of the Catalytic Cycle and the Precatalyst Activation Model. *Chem.—Eur. J.* **2010**, *16*, 10844−10853. (b) Hadei, N.; Achonduh, G. T.; Valente, C.; O'Brien, C. J.; Organ, M. G. Differentiating C-Br and C-Cl Bond Activation by Using Solvent Polarity: Applications to Orthogonal Alkyl−Alkyl Negishi Reactions. *Angew. Chem., Int. Ed.* **2011**, *50*, 3896−3899.

(9) (a) Iwasaki, T.; Takagawa, H.; Singh, S. P.; Kuniyasu, H.; Kambe, N. Co-Catalyzed Cross-Coupling of Alkyl Halides with Tertiary Alkyl Grignard Reagents Using a 1,3-Butadiene Additive. *J. Am. Chem. Soc.* **2013**, *135*, 9604−9607. (b) Terao, J.; Kambe, N. Cross-Coupling Reaction of Alkyl Halides with Grignard Reagents Catalyzed by Ni, Pd, or Cu Complexes with π-Carbon Ligand(s). *Acc. Chem. Res.* **2008**, *41*, 1545−1554.

(10) For reviews, see: (a) Yorimitsu, H.; Oshima, K. New synthetic reactions catalyzed by cobalt complexes. *Pure Appl. Chem.* **2006**, *78*, 441−449. (b) Oshima, K. Highly Selective Synthetic Reactions by the Combined Use of Organometallic Reagents and Radical Species. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1−24.

(11) For earlier reviews, see: (a) Ryu, I.; Sonoda, N. Free-Radical Carbonylations: Then and Now. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050−1066. (b) Ryu, I.; Sonoda, N.; Curran, D. P. Tandem Radical Reactions of Carbon Monoxide, Isonitriles, and Other Reagent Equivalents of the Geminal Radical Acceptor/Radical Precursor Synthon. *Chem. Rev.* **1996**, *96*, 177−194.

(12) For a review on acyl radicals: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. Chemistry of Acyl Radicals. *Chem. Rev.* **1999**, *99*, 1991−2070.

(13) (a) Ryu, I. New Approaches in Radical Carbonylation Chemistry: Fluorous Applications and Designed Tandem Processes by Species-Hybridization with Anions and Transition Metal Species. *Chem. Rec.* **2002**, *2*, 249−258. (b) Schiesser, C. H.; Wille, U.; Matsubara, H.; Ryu, I. Radicals Masquerading as Electrophiles: Dual Orbital Effects in Nitrogen-Philic Acyl Radical Cyclization and Related Addition Reactions. *Acc. Chem. Res.* **2007**, *40*, 303−313. (c) Fusano, A.; Ryu, I. Free-Radical-Mediated Multicomponent Reactions Involving Carbon Monoxide. In *Science of Synthesis: Multicomponent Reactions 2*; Muller, T. J. J., Ed.; Georg Thieme Verlag KG: Germany, 2014.

(14) For a review, see Ryu, I. Radical Carboxylations of Iodoalkanes and Saturated Alcohols Using Carbon Monoxide. *Chem. Soc. Rev.* **2001**, *30*, 16−25.

(15) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. Radical Carboxylation: Ester Synthesis from Alkyl Iodides, Carbon Monoxide, and Alcohols under Irradiation Conditions. *J. Am. Chem. Soc.* **1997**, *119*, 5465−5466.

(16) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. Metal Catalyst-Free by Design. The Synthesis of Amides From Alkyl Iodides, Carbon Monoxide and Amines by a Hybrid Radical/Ionic Reaction. *Chem. Commun.* **1998**, 1953−1954.

(17) (a) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. Lactone Synthesis Based on Atom Transfer Carbonylation. *Org. Lett.* **2000**, *2*, 389−391. (b) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. Synthesis of Nitrogen Heterocycles Based on Atom Transfer Carbonylation of Bifunctional Amines. *C. R. Acad. Sci. Paris Chim.* **2001**, *4*, 497−503.

(18) (a) Itsenko, O.; Kihlberg, T.; Långström, B. Photoinitiated Carbonylation with $[^{11}\text{C}]$Carbon Monoxide Using Amines and Alkyl Iodides. *J. Org. Chem.* **2004**, *69*, 4356−4360. (b) Itsenko, O.; Långström, B. Radical-Mediated Carboxylation of Alkyl Iodides with $[^{11}\text{C}]$Carbon Monoxide in Solvent Mixtures. *J. Org. Chem.* **2005**, *70*, 2244−2249. Also see a review: (e) Långström, B.; Itsenko, O.; Rahman, O. $[^{11}\text{C}]$Carbon Monoxide, a Versatile and Useful Precursor in Labeling Chemistry for PET-Ligand Development. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 794−810.

(19) Matsubara, H.; Ryu, I.; Schiesser, C. H. An *ab initio* and DFT Study of Some Halogen Atom Transfer Reactions from Alkyl Groups to Acyl Radical. *Org. Biomol. Chem.* **2007**, *5*, 3320–3324.

(20) (a) Kondo, T.; Tsuji, Y.; Watanabe, Y. Photochemical Carbonylation of Alkyl Iodides in the Presence of Various Metal Carbonyls. *Tetrahedron Lett.* **1988**, *29*, 3833–3836. (b) Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. Photo-, Electro-, and Thermal Carbonylation of Alkyl Iodides in the Presence of Group 7 and 8–10 Metal Carbonyl Catalysts. *J. Organomet. Chem.* **1994**, *473*, 163–173.

(21) (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. Palladium-Catalyzed Carbonylative Cross-Coupling Reaction of Iodoalkanes with 9-Alkyl-9-BBN Derivatives. A Direct and Selective Synthesis of Ketones. *Tetrahedron Lett.* **1991**, *32*, 6923–6926. (b) Ishiyama, T.; Murata, M.; Suzuki, A.; Miyaura, N. Synthesis of Ketones from Iodoalkenes, Carbon Monoxide and 9-Alkyl-9-borabicyclo[3.3.1]nonane Derivatives *via* a Radical Cyclization and Palladium-Catalyzed Carbonylative Cross-Coupling Sequence. *J. Chem. Soc., Chem. Commun.* **1995**, 295–296.

(22) (a) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. Effective Acceleration of Atom Transfer Carbonylation of Alkyl Iodides by Metal Complexes. Application to the Synthesis of the Hinokinin Precursor and Dihydrocapsaicin. *Org. Lett.* **2006**, *8*, 1383–1386. (b) Fusano, A.; Sumino, S.; Nishitani, S.; Inouye, T.; Morimoto, K.; Fukuyama, T.; Ryu, I. Pd/Light-Accelerated Atom-Transfer Carbonylation of Alkyl Iodides: Applications in Multicomponent Coupling Processes Leading to Functionalized Carboxylic Acid Derivatives. *Chem.—Eur. J.* **2012**, *18*, 9415–9422.

(23) Doonan, D. J.; Balch, A. L.; Goldberg, S. Z.; Eisenberg, R.; Miller, J. S. Hexakis(methyl isocyanide)dipalladium(I). Preparation, Structure, and Fluxional Behavior. *J. Am. Chem. Soc.* **1975**, *97*, 1961–1962.

(24) For photoinduced homolysis of Pd dimer complex, see: (a) Reinking, M. K.; Kullberg, M. L.; Cutler, A. R.; Kubiak, C. P. The Photochemistry of Palladium and Platinum Homo- and Heteronuclear Metal-Metal σ-Bonds: Efficient Photogeneration of 15-Electron Radicals. *J. Am. Chem. Soc.* **1985**, *107*, 3517–3524. (b) Lemke, F. R.; Kubiak, C. P. Activation of Unsaturated Alkyl Chlorides by Photogenerated $[\mathrm{Pd(CNMe)_3}]^{\bullet+}$ Radicals. Transient Absorbance Kinetics Studies of the Formation of η^3-Allyl and "Oxaallyl" Palladium Complexes. *J. Organomet. Chem.* **1989**, *373*, 391–400.

(25) (a) Bowry, V. W.; Ingold, K. U. A Radical Clock Investigation of Microsomal Cytochrome P-450 Hydroxylation of Hydrocarbons. Rate of Oxygen Rebound. *J. Am. Chem. Soc.* **1991**, *113*, 5699–5707. (b) Newcomb, M. Competition Methods and Scales for Alkyl Radical Reaction Kinetics. *Tetrahedron* **1993**, *49*, 1151–1176.

(26) Friestad, G. K.; Qin, J. Intermolecular Alkyl Radical Addition to Chiral N-Acylhydrazones Mediated by Manganese Carbonyl. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923.

(27) Fukuyama, T.; Inouye, T.; Ryu, I. Atom Transfer Carbonylation Using Ionic Liquids as Reaction Media. *J. Organomet. Chem.* **2007**, *692*, 685–690.

(28) Ozawa, F.; Yamamoto, A. Double Carbonylation Reactions of Methyl- and Phenylpalladium(II) Complexes in the Presence of Secondary Amines Affording α-Keto Amides. *Chem. Lett.* **1982**, 865–868.

(29) Urata, H.; Ishii, Y.; Fuchikami, T. Palladium-catalyzed Double Carbonylation of Alkyl Iodides Bearing Perfluoroalkyl Group. *Tetrahedron Lett.* **1989**, *30*, 4407–4410.

(30) (a) Yamamoto, A. Palladium-catalyzed Double and Single Carbonylation of Aryl Halides and Allylic Compounds. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 433–446. (b) Lin, Y.-S.; Yamamoto, A. Studies Relevant to Palladium-Catalyzed Carbonylation Processes. Mechanisms of Formation of Esters and Amides from Benzylpalladium and (Phenylacetyl)palladium Complexes on Reactions with Alcohols and Amines. *Organometallics* **1998**, *17*, 3466–3478. (c) Yamamoto, A. Insertion Chemistry into Metal–Carbon Bond. *J. Chem. Soc., Dalton Trans.* **1999**, 1027–1038.

(31) (a) Mori, M.; Kubo, Y.; Ban, Y. Reaction of α-Haloester having Internal Double Bond with the Low-Valent Metal Complex. *Tetrahedron Lett.* **1985**, *26*, 1519–1522. (b) Mori, M.; Kubo, Y.; Ban, Y. Palladium Catalyzed Ene-Halogenocyclization of α-Haloester having Internal Double Bond with the Low-Valent Metal Complex. *Tetrahedron* **1988**, *44*, 4321–4330.

(32) Curran, D. P.; Chang, C.-T. Evidence that Palladium(0)-Promoted Cyclizations of Unsaturated α-Iodocarbonyls Occur by an Atom Transfer Mechanism. *Tetrahedron Lett.* **1990**, *31*, 933–936.

(33) (a) Chen, Q.-Y.; Yang, Z.-Y.; Zhao, C.-X.; Qiu, Z.-M. Studies on Fluoroalkylation and Fluoroalkoxylation. Part 28. Palladium(0)-Induced Addition of Fluoroalkyl Iodides to Alkenes: an Electron Transfer Process. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563–567. (b) Qiu, Z.-M.; Burton, D. J. Synthesis of α,α-Difluoro-Functionalized Ketones. *J. Org. Chem.* **1995**, *60*, 5570–5578.

(34) For single electron transfer from low valent palladium or platinum complexes to alkyl iodides, see: (a) Kramer, A. V.; Osborn, J. A. Mechanistic Studies of Oxidative Addition to Low Valent Metal Complexes. IV. Observation of CIDNP Effects in Platinum(0) and Palladium(0) Reactions. *J. Am. Chem. Soc.* **1974**, *96*, 7832–7833. (b) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. Mechanistic Studies of Oxidative Addition to Low-Valent Metal Complexes. III. Mechanism of Formation of Platinum to Carbon Bonds. *J. Am. Chem. Soc.* **1974**, *96*, 7145–7147. (c) Manolikakes, G.; Knochel, P. Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 205–209.

(35) Beckwith, A. L. J.; Schiesser, C. H. Regio- and Stereo-Selectivity of Alkenyl Radical Ring Closure: A Theoretical Study. *Tetrahedron* **1985**, *41*, 3925–3941.

(36) For photoredox catalyst and radical initiation, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363. (b) Sebren, L. J.; Devery, J. J., III; Stephenson, C. R. J. Catalytic Radical Domino Reactions in Organic Synthesis. *ACS Catal.* **2014**, *4*, 703–716.

(37) For persistent radical effect, see: (a) Fischer, H. The Persistent Radical Effect: A Principle for Selective Radical Reactions and Living Radical Polymerizations. *Chem. Rev.* **2001**, *101*, 3581–3610. (b) Studer, A. Tin-free Radical Chemistry Using the Persistent Radical Effect: Alkoxyamine Isomerization, Addition Reactions and Polymerizations. *Chem. Soc. Rev.* **2004**, *33*, 267–273.

(38) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. Synthesis of Alkyl Alkynyl Ketones by Pd/Light-Induced Three-Component Coupling Reactions of Iodoalkanes, CO, and 1-Alkynes. *Org. Lett.* **2010**, *12*, 2410–2413.

(39) Sumino, S.; Ui, T.; Ryu, I. Synthesis of Alkyl Aryl Ketones by Pd/Light Induced Carbonylative Cross-Coupling of Alkyl Iodides and Arylboronic Acids. *Org. Lett.* **2013**, *15*, 3142–3145.

(40) Fusano, A.; Sumino, S.; Fukuyama, T.; Ryu, I. Vicinal C-Functionalization of Alkenes. Pd/Light-Induced Multicomponent Coupling Reactions Leading to Functionalized Esters and Lactones. *Org. Lett.* **2011**, *13*, 2114–2117.

(41) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. Group Transfer Carbonylations: Photoinduced Alkylative Carbonylation of Alkenes Accompanied by Phenylselenenyl Transfer. *J. Org. Chem.* **1996**, *61*, 6396–6403.

(42) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. Synthesis of Carbamoylacetates from α-Iodoacetate, CO, and Amines under Pd/Light Combined Conditions. *Synlett* **2012**, *23*, 1331–1334.

(43) (a) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. Free-Radical-Mediated Carbonylative Cyclisation of Alk-4-enyl Halides Leading to Cyclopentanones. *J. Chem. Soc. Chem. Commun.* **1991**, 1018–1019. (b) Curran, D. P.; Liu, H. 4 + 1 Radical Annulations with Isonitriles: A Simple Route to Cyclopenta-fused Quinolines. *J. Am. Chem. Soc.* **1991**, *113*, 2127–2132. (c) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. A. 5-exo-trig Versus 6-endo-trig Cyclization of Alk-5-enoyl Radicals: The Role of One-Carbon Ring Expansion. *Chem.—Eur. J.* **1997**, *3*, 376–387.

(44) Tsunoi, S.; Ryu, I.; Yamasaki, S.; Fukushima, H.; Tanaka, M.; Komatsu, M.; Sonoda, N. Free Radical Mediated Double Carbon-

ylations of Alk-4-enyl Iodides. *J. Am. Chem. Soc.* **1996**, *118*, 10670−10671.

(45) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. Cascade Radical Reactions Catalyzed by a Pd/Light System: Cyclizative Multiple Carbonylation of 4-Alkenyl Iodides. *J. Am. Chem. Soc.* **2002**, *124*, 3812−3813.

(46) Araki, F. Master Thesis, Osaka University, 1999.

(47) (a) Bloome, K. S.; Alexanian, E. J. Palladium-Catalyzed Carbonylative Heck-Type Reactions of Alkyl Iodides. *J. Am. Chem. Soc.* **2010**, *132*, 12823−12825. (b) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. Palladium-Catalyzed Heck-Type Reactions of Alkyl Iodides. *J. Am. Chem. Soc.* **2011**, *133*, 20146−20148.