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Pd/Light-Accelerated Atom-Transfer Carbonylation of Alkyl Iodides; Applications in Multicomponent Coupling Processes Leading to Functionalized Carboxylic Acid Derivatives

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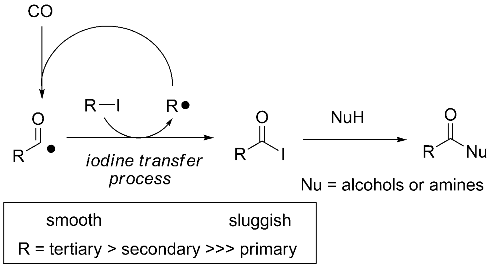
Abstract: The atom-transfer carbonylation reaction of various alkyl iodides thereby leading to carboxylic acid esters was effectively accelerated by the addition of transition-metal catalysts under photoirradiation conditions. By using a combined Pd/*hν* reaction system, vicinal C-functionalization of alkenes was attained in which α-substituted iodoalkanes, alkenes, carbon monoxide, and alcohols were coupled to give functionalized esters. When alkenyl alcohols were used as acceptor alkenes, three-component coupling reactions, which were accompanied by intramolecular esterification, proceeded to give lactones. Pd-dimer complex $[Pd_2(CNMe)_6][PF_6]_2$, which is known to undergo homolysis under photoirradiation conditions, worked quite well as a catalyst in these three- or four-component coupling reactions. In this metal/radical hybrid system, both Pd radicals and acyl radicals are key players and a stereochemical study confirmed the carbonylation step proceeded through a radical carbonylation mechanism.

Keywords: carbon monoxide · carbonylation · multicomponent reactions · palladium · radical reactions

Introduction

Carbonylation reactions by using carbon monoxide have found widespread applications in organic synthesis.[1] Whereas the transition-metal-catalyzed carbonylation of vinyl, allyl, and benzyl halides to give carboxylic acid derivatives has been established as a reliable process, the corresponding carbonylation of alkyl halides has remained a challenge[2–4] because the relatively slow oxidative addition onto the metal center and β-hydride elimination hamper the realization of an efficient carbonylation process.[5] The synthesis of acetic acid by transition-metal-catalyzed carbonylation from MeOH and carbon monoxide represents one of the most successful examples of an industrial carbonylation process for which the transition-metal-catalyzed carbonylation of iodomethane is key.[6,7] However, the extension of Monsanto acetic acid synthesis to C3 and larger alcohols is known to give isomeric mixtures of carboxylic acids owing to the isomerization of rhodium–alkyl intermediates through β-hydride elimination.[7a]

To circumvent a longstanding problem surrounding the carbonylation of alkyl halides thereby leading to aliphatic carboxylic-acid derivatives, we have developed a conceptually different approach involving radical carbonylation and iodine-atom transfer, which we call atom-transfer carbonylation (ATC). Either light initiation or thermal initiation by using a radical initiator begins the ATC process, with which aliphatic carboxylic acid esters, amides, and their related compounds were prepared without isomerization (Scheme 1).[8,9] Recent work by Istchenko, Långström, and co-workers demonstrated the successful application of the ATC method in the synthesis of the positron emission tomography of active carboxylic acids[10] by incorporating ^{11}CO as a carbonyl carbon moiety.[11]



Scheme 1. Atom-transfer carbonylation of alkyl iodides.

To increase the usefulness of the ATC reactions of alkyl iodides, acceleration of the reaction, in particular the acceleration of the reactions of primary alkyl iodides, is crucial because slow reactions that are inherent to the lower ability

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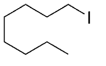
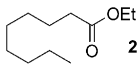
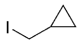
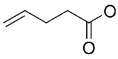
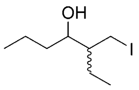
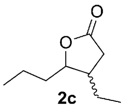
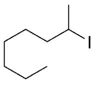
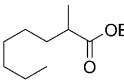
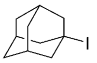
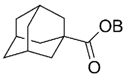
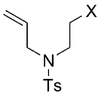
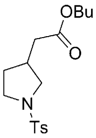
of an iodine-atom transfer compared with secondary and tertiary iodides[12] allows undesirable side reactions, such as the E2-type elimination of HI, to be avoided.[13] Acceleration of the ATC is also desirable in performing effective multicomponent reactions with the incorporation of CO.

In the 1980s, Watanabe and co-workers and Suzuki, Miyaura, and co-workers independently reported that the transition-metal-catalyzed carbonylation of iodoalkanes to give esters[14a,b] and ketones[14c] is facilitated by photoirradiation. In particular, the presence of radical intermediates is proposed in both of these metal-catalyzed carbonylation reactions to lead to alkylmetal species. Stimulated by these precedent-setting studies, we investigated a metal/radical hybrid system by adding transition-metal catalysts to our ATC system under photoirradiation and found that a Pd/*hν* irradiation system significantly accelerated ATC cyclization reactions to form cyclopentanones with ester and amide substituents.[15] This result highly motivated us to explore more general multicomponent coupling processes by using Pd/*hν*-induced ATC reactions. Consequently, we reported a series of three- or four-component coupling reactions to afford a wide range of carboxylic acid derivatives.[16]

Herein, we report the full scope of the Pd/*hν*-induced ATC reaction for primary, secondary, and tertiary alkyl iodides, which can provide useful synthetic methods to prepare a variety of carboxylic acid derivatives. Interestingly, more than two decades ago, Kubiak and co-workers reported that $[Pd_2(CNMe)_6][PF_6]_2$ is an isolable Pd dimer that, under photoirradiation, is likely to produce a pair of Pd radicals.[17] With great interest in this basic phenomena, we tested this dimeric Pd^I complex in our three-component coupling reactions and found that it also worked well. Some mechanistic studies were undertaken to assess how radicals and organopalladium species are associated with the accelerated ATC reactions. The stereochemical outcome of these reactions strongly suggested that radical formation and subsequent carbonylation operated first, followed by the formation of acylpalladium complexes, which we suggested involved a coupling reaction between acyl radicals and Pd^I radicals. We extended our mechanistic probe based on the diastereoselectivity of the above-mentioned studies on the metal-catalyzed carbonylation of haloalkanes under photoirradiation and thermal conditions[14] and found that these carbonylation reactions were also subjected to the same radical-carbonylation mechanism.

Table 1. Acceleration of the atom-transfer carbonylation reactions of alkyl iodides to afford esters and lactones by the addition of Pd catalysts.[a]

Entry	Alkyl iodides	*t* [h]	Catalyst	Ester	Yield [%][b]
1	 **1a**	50	none	 **2a**	54
2		16	$[Pd(PPh_3)_4]$		87
3		14	$[Pd_2(CNMe)_6][PF_6]_2$		87
4	 **1b**	16	none	 **2b**	40
5		16	$[Pd(PPh_3)_4]$		83
6	 **1c**	16	none	 **2c**	27 (*cis*/*trans* = 36:64)[c]
7		16	$[Pd(PPh_3)_4]$		91 (*cis*/*trans* = 36:64)[c]
8	 **1d**	6.5	none	 **2d**	40
9		6.5	$[Pd(PPh_3)_4]$		83
10		6.5	$[Pd_2(CNMe)_6][PF_6]_2$		96
11	 **1e**	6.5	none	 **2e**	38
12		6.5	$[Pd(PPh_3)_4]$		80
13		6.5	$[Pd_2(CNMe)_6][PF_6]_2$		92
14	 **1f**: X = I **1g**: X = Br	16	$[Pd(PPh_3)_4]$	 **2f**	73 (X=I)
15		16	$[Pd(PPh_3)_4]$		58 (X=Br)

[a] Conditions: compound **1** (0.5 mmol); $[Pd(PPh_3)_4]$ (5-5.7 mol%) or $[Pd_2(CNMe)_6][PF_6]_2$ (2 mol%); base, Et_3N (1.4–1.7 equiv) plus DMAP (10 mol%), K_2CO_3 alone (entries 1 and 2; 1.2–2.0 equiv), or K_2CO_3 (1.2–2.0 equiv) plus DMAP (entry 3; 10 mol%); solvent, EtOH (entries 1 and 2; 5 mL), toluene/EtOH (5 mL/40 equiv; entry 3), benzene (entries 6 and 7; 5 mL), benzene/BuOH (entries 4, 5, 8, 9, 11, 12, and 14; 5 mL/0.18 mL), or toluene/BuOH (5 mL/0.18 mL; entries 10, 13, and 15); CO (45 atm); light (500 W xenon lamp, Pyrex). [b] Yield of isolated product after column chromatography on silica gel. [c] *Cis*/*trans* ratio determined by ^1H NMR spectroscopy.

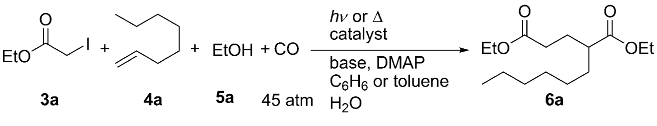
Results and Discussion

To determine the scope of the acceleration of the photoirradiation-promoted atom-transfer carbonylation reaction by Pd salts, various 1-iodoalkanes (**1a**–**1e**) were exposed to both original and Pd-incorporated conditions (Table 1). After optimization of the reaction conditions, we determined the optimal base, amount of alcohol, light source, and CO pressure for each alkyl iodide substrate. When the reaction of 1-iodooctane (**1a**), CO, and EtOH was carried out under photoirradiation conditions (500 W xenon lamp through Pyrex) and 45 atm of CO pressure, the formation of the corresponding ethyl nonanoate (**2a**) was dramatically accelerated in the presence of a $[Pd(PPh_3)_4]$ catalyst (Table 1, entries 1 and 2). We also tested a dimeric Pd complex. When the reaction of 1-iodooctane (**1a**), CO, and EtOH was carried out in the presence of a catalytic amount of $[Pd_2(CNMe)_6][PF_6]_2$ under photoirradiation conditions, the corresponding carboxylic acid ester (**2a**) was obtained in 87% yield (Table 1, entry 3). Pd/light-induced acceleration was also observed when cyclopropylcarbinyl iodide (**1b**) was used as a substrate (Table 1, entries 4 and 5), which gave butyl 4-butenoate (**2b**) through the ring-opening of a cyclopropylcarbinyl radical.[18] Whereas the ATC reaction of hydroxyalkyl iodide **1c** suffered from a competitive ionic cyclization reaction that led to an oxetane ring,[9c] the addition of a Pd catalyst greatly improved the yield of the corresponding lactone (**2c**, Table 1, entries 6 and 7). In the case of secondary and tertiary alkyl iodides, the ATC reactions proceeded more smoothly in the presence of either $[Pd(PPh_3)_4]$

or $[Pd_2(CNMe)_6][PF_6]_2$ as a catalyst (Table 1, entries 8–13). We also examined a cyclization/carbonylation sequence (Table 1, entries 14 and 15). Thus, when alkyl iodide **1f** was exposed to Pd/light-induced carbonylation conditions, the anticipated pyrrolidine derivative (**2f**), which contained a carboxylic acid ester group, was obtained in 73% yield. The reaction of alkyl bromide **1g** also proceeded well to afford the same product in 58% yield. Recently, Alexanian and co-workers reported that, under thermal conditions (110 or 130 °C), intramolecular Heck-type or carbonylative Heck reactions of alkenyl iodides proceeded to afford five- or six-membered rings in the presence of $[Pd(PPh_3)_4]$.[19]

Having confirmed the acceleration of the ATC reaction by using a combined Pd/light system, we embarked on the development of multicomponent coupling processes through the vicinal carbon-functionalization of alkenes. In a related study, we had previously reported the photoinduced addition of α-phenylseleno-substituted esters to alkenes and CO to afford acyl selenides;[20] however, this system was not applicable to the synthesis of ordinary esters. We attempted a four-component coupling reaction that comprised ethyl iodoacetate (**3a**), 1-octene (**4a**), EtOH (**5a**), and CO (Table 2). First, we used thermal conditions in the presence of $[PdCl_2(PPh_3)_2]$, DMAP, base, and small amount of water under CO pressure (45 atm; Table 2, entries 1 and 2). Despite the fact that the anticipated coupling reaction proceeded, the yields of diester **6a** were poor. The reaction under photoirradiation without Pd catalyst was reluctant (Table 2, entry 3) but the combination of the Pd catalyst and photoirradiation conditions was quite effective and compound **6a** was obtained in good yield (Table 2, entry 4). The use of K_2CO_3 as a base in the place of triethylamine was also effective, thus giving compound **6a** in 77% yield (Table 2, entry 5). We assumed that the added water may contribute to the smooth generation of Pd^0 from Pd^{II} because diester **6a** was not obtained without the addition of water.[21] Toluene was a good solvent for this reaction (Table 2, entry 6). The use of a dimeric Pd catalyst under light irradiation also worked well to give diester **6a** in 86% yield (Table 2, entry 7).

Table 2. Four-component coupling reaction of ethyl iodoacetate (**3a**) with 1-octene (**4a**), EtOH (**5a**), and carbon monoxide.[a]



Entry	Catalyst [mol %]	Base	Conditions	t [h]	Yield [%][b]
1	$[PdCl_2(PPh_3)_2]$ (5 mol %)	Et_3N	80 °C	16	21
2	$[PdCl_2(PPh_3)_2]$ (5 mol %)	K_2CO_3	120 °C	16	23
3	none	Et_3N	hν	14	25
4	$[PdCl_2(PPh_3)_2]$ (5 mol %)	Et_3N	hν	8	72
5	$[PdCl_2(PPh_3)_2]$ (5 mol %)	K_2CO_3	hν	8	77
6	$[PdCl_2(PPh_3)_2]$ (5 mol %)	K_2CO_3	hν	14	82
7[c]	$[Pd_2(CNMe)_6][PF_6]_2$ (2 mol %)	K_2CO_3	hν	12	86

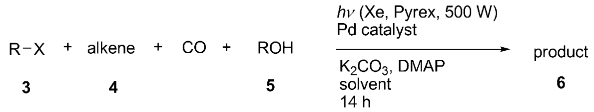
[a] Conditions: compound **3a** (0.5 mmol), compound **4a** (10 equiv), EtOH (**5a**, 40 equiv), CO (45 atm), catalyst (5 or 2 mol %), base (1.1 equiv), DMAP (10 mol %), benzene (entries 1 and 3–5; 5 mL) or toluene (entries 2, 6 and 7; 5 mL), H_2O (10 μL). [b] Yield of isolated compound **6a** after column chromatography on silica gel. [c] Compound **4a** (5.0 equiv) was used without the addition of H_2O.

By using a combination of light irradiation with either a monomeric Pd^{II} catalyst plus water (conditions A) or a dimeric Pd^{I} catalyst (conditions B), we examined a variety of α-substituted iodoalkanes, alkenes, and alcohols in these four-component coupling reactions (Table 3). In general, the dimeric Pd catalyst worked equally as well as the monomeric catalyst to give the anticipated four-component-coupled products. The reaction of benzyl alcohol (**5b**) gave the anticipated diester (**6b**) in 67% yield (conditions A) and 71% yield (conditions B; Table 3, entry 2). The use of MeOH (**5c**) caused transesterification of an ethyl ester and, as a result, dimethyl ester **6c** was obtained as the product in 70% yield (Table 3, entry 3). Cl- and Ph-substituted alkenes **4b** and **4c** were converted into their corresponding diesters (**6d** and **6e**, respectively) in good yields (Table 3, entries 4 and 5). The reaction of perfluorohexyl iodide (**3b**) with compounds **4a** and **4c** also proceeded effectively to furnish esters **6f** and **6g** in good yields (Table 3, entries 6 and 7). Iodoacetonitrile (**3c**) and iodomethyl phenyl sulfone (**3d**) also worked well in these coupling reactions (Table 3, entries 8 and 9). We also examined a radical cascade sequence to accompany the intramolecular 5-*exo*-cyclization process (Table 3, entry 10). When the reaction of compound **3a** with 1,5-hexadiene (**4d**) was carried out in the presence of $[PdCl_2(PPh_3)_2]$ or $[Pd_2(CNMe)_6][PF_6]_2$, the anticipated five-component coupling reaction through the incorporation of two molecules of CO proceeded to give diester **6j** with a cyclopentanone scaffold. In these cases, uncyclized product **6k** was formed as a by-product.

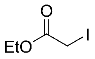
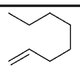
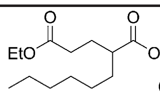
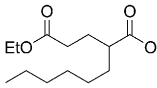
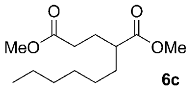
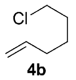
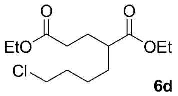
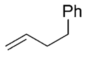
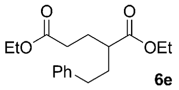
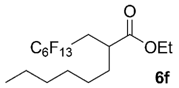
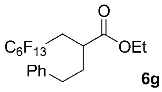
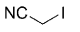
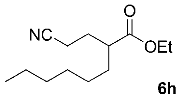
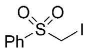
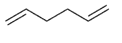
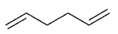
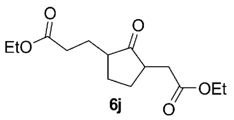
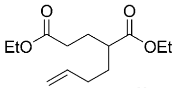
Ester-functionalized lactones **8a**–**8c** were prepared from three-component cyclization reactions of alkenyl alcohols **7a**–**7c** (Scheme 2). The yield of seven-membered-ring lactone **8c** was rather modest, owing to the competitive ionic cyclization reaction to give a tetrahydropyran ring. When the three-component cyclization reaction was carried out with alkenylamine **9**, the anticipated lactam (**10**) was only obtained in 14% yield.[22]

Mechanistic insight: To determine the precise role of the Pd catalyst, we performed experiments by using Pd/photoirradiation and Et_3B-initiated radical conditions (Scheme 3). When the iodine-atom-transfer reaction of 6-iodo-1-octene (**11**) was carried out in the presence of $[Pd(PPh_3)_4]$ under photoirradiation conditions, the anticipated cyclized product (**12**) was obtained as a *cis*/*trans* mixture (73:27). Interestingly, the reaction of compound **11** by using Et_3B as a radical initiator resulted in the formation of compound **12** in the same 73:27 isomeric ratio. We also examined a Pd/hν-induced carbonylation reaction, which also gave ethyl ester **13** in a nearly identical isomeric ratio (74:26). The calculated *cis*/*trans* ratio of the 5-exo cyclization of a 1-methyl-5-hexenyl radical by known rate constants reported by Beckwith

Table 3. Four-component coupling reactions leading to esters.[a]



$$\underset{\mathbf{3}}{R{-}X} + \underset{\mathbf{4}}{\text{alkene}} + CO + \underset{\mathbf{5}}{ROH} \xrightarrow[\text{K}_2\text{CO}_3\text{, DMAP, solvent, 14 h}]{h\nu\text{ (Xe, Pyrex, 500 W), Pd catalyst}} \underset{\mathbf{6}}{\text{product}}$$

Entry	R-I	Alkene	ROH	Product	Conditions	Yield [%][b]
1	 **3a**	 **4a**	EtOH **5a**	 **6a**	A B	82 86
2[c]	**3a**	**4a**	BnOH **5b**	 **6b**	A B	67 71
3	**3a**	**4a**	MeOH **5c**	 **6c**	A	70
4	**3a**	 **4b**	**5a**	 **6d**	A B	72 75
5	**3a**	 **4c**	**5a**	 **6e**	A	74
6	$C_6F_{13}I$ **3b**	**4a**	**5a**	 **6f**	A B	84 79
7	**3b**	**4c**	**5a**	 **6g**	A	76
8	 **3c**	**4a**	**5a**	 **6h**	A B	64 69
9	 **3d**	**4a**	**5a**	 **4d**	A B	56 53
10	**3a**	 **4d**	**5a**	 **6j**	A[d] B[e]	47 (*cis*/*trans* = 38:62) 40 (*cis*/*trans* = 37:63)
				 **6k**	A[d] B[e]	27 30

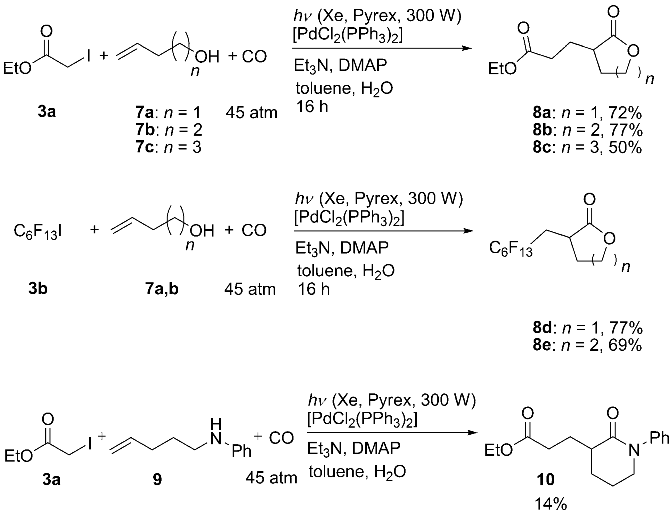
[a] Conditions A: compound **3** (0.5 mmol), compound **4** (10 equiv), compound **5** (40 equiv), CO (45 atm), $[PdCl_2(PPh_3)_2]$ (5 mol%), K_2CO_3 (1.1–1.4 equiv), DMAP (10 mol%), toluene (5 mL), H_2O (10 μL). Conditions B: compound **3** (0.5 mmol), compound **4** (5 equiv), compound **5** (40 equiv), CO (45 atm), $[Pd_2(CNMe)_6][PF_6]_2$ (2 mol%), K_2CO_3 (1.2–1.3 equiv), DMAP (10 mol%), toluene (5 mL). [b] Yield of isolated product after column chromatography on silica gel. [c] BnOH (5.0 equiv). [d] CO (95 atm). [e] CO (85 atm).

and Schiesser[23] was 73:27, which is identical to our observed diastereomeric ratios. Thus, it seems reasonable to say that our Pd/*hν*-induced cyclization ATC reactions proceeded through a mechanism that involved radical formation and subsequent radical cyclization steps. As a precedent, Curran and Chang previously reported that $[Pd(dppe)_2]$ (dppe = 1,2-bis(diphenylphosphino)ethane) acted as radical initiator in the cyclization reaction of α-iodo carbonyl compounds by atom-transfer methods.[24]

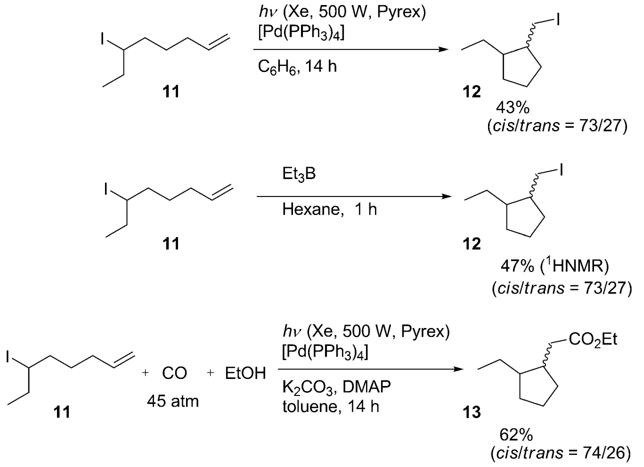
Next, our attention was directed to the carbonylation step; in principle, two mechanistic pathways are conceivable: 1) radical addition of an alkyl radical to CO to form an acyl radical and 2) migratory insertion of CO into an alkyl–palladium bond. We decided to compare the stereochemical outcomes of the carbonylation step by using 2-iodo-3-methylheptane (**14**) as the substrate in both cases, with and without a Pd catalyst (Scheme 4). The three-component coupling reaction of 2-iodo-3-methylheptane (**14**), CO, and MeOH under photoirradiation conditions without a Pd catalyst for 6.5 h gave the corresponding methyl ester (**15**) in 29% yield with a diastereomeric ratio of 42:58 (*anti*/*syn*).[25] A similar reaction in the presence of $[Pd(PPh_3)_4]$ gave the same methyl ester (**15**) in a quite similar diastereomeric ratio (43:57) in 61% yield. This similarity between the diastereoselectivities strongly suggests that the C–C bond-forming step proceeds through a radical CO-addition mechanism in both cases.

The $[PtCl_2(PPh_3)_2]$-catalyzed carbonylation reaction of alkyl iodides in the presence of alcohols under irradiation by a high-pressure Hg lamp (200 W) was previously reported by Watanabe and co-workers, which gave their corresponding carboxylic acid esters.[14a,b] They proposed a non-chain-radical mechanism in which the migratory insertion of carbon monoxide into an alkyl–metal bond, thereby leading to an acyl–metal complex, was negated. We became curious as to whether or not their carbonylation step involved a radical C–C bond-forming process and decided to re-examine the reaction by using alkyl iodide **14** as a stereochemical probe. Thus, the reaction of compound **14**, CO, and MeOH was carried out in the presence of $[PtCl_2(PPh_3)_2]$ under irradiation from a Xe lamp (300 W, Scheme 5). The anticipated methyl ester (**15**) was obtained in 42% yield with a 43:57 diastereomer ratio, which was the same ratio as in our Pd/light reaction. Watanabe and co-workers also reported the Pt-catalyzed carbonylation of iodoalkanes under heat treatment (120 °C).[26] Again, we tested alkyl iodide **14** and found that ester **15** was obtained in 47% yield with a diastereomeric ratio of 42:58. Thus, we can conclude that, even in the Pt/light- or Pt/thermal-carbonylation system reported by Watanabe and co-workers, a radical-carbonylation mechanism operates, as well as in our case.

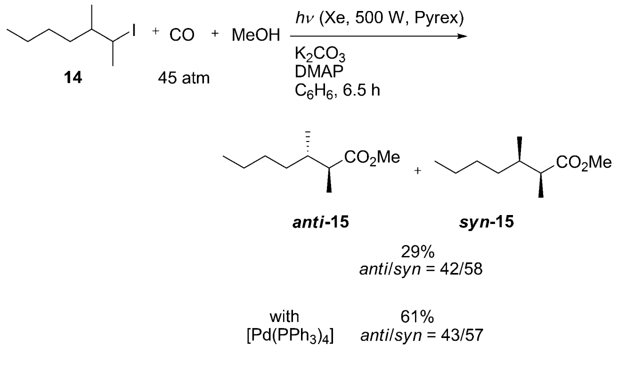
Taking these results into consideration, we proposed a reaction mechanism for this Pd/*hν*-assisted three-component coupling reaction (Scheme 6), by using the transformation from compound **1a** into compound **2a** in the presence of a Pd^0 catalyst as an example. Alkyl radicals are formed by the cleavage of the I–C bond of compound **1a**, which may be triggered by a single electron transfer from the photoexcited Pd^0 species. The precedence for a single electron transfer from low-valent palladium complexes to iodoalkanes is well-established.[27] In addition, the intervention of a radical mechanism has been strongly suggested by radical-cascade experiments and electron spin resonance (ESR) spectroscopy in the iodine-atom-transfer reaction of perfluoroalkyl iodides and alkenes.[28] In the case of a dimeric Pd^I complex, the Pd radical that was generated under photoinduced homolysis of the dimeric Pd complex may undergo iodine-atom abstraction from alkyl iodides. Then, the coupling of the alkyl radical and Pd^I to give an alkylpalladium species might take place, but this process scarcely contributes to this reaction mechanism because we employed highly concentrated CO conditions. The resultant alkyl radical is quickly



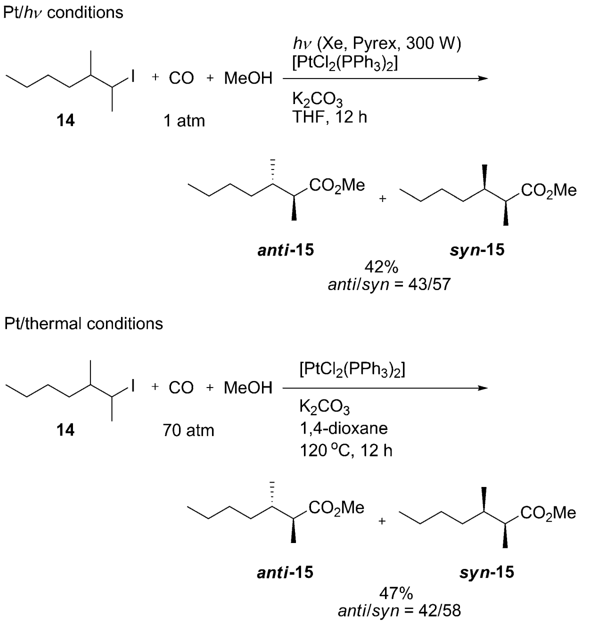
Scheme 2. Three-component coupling reactions to afford lactones and lactams.



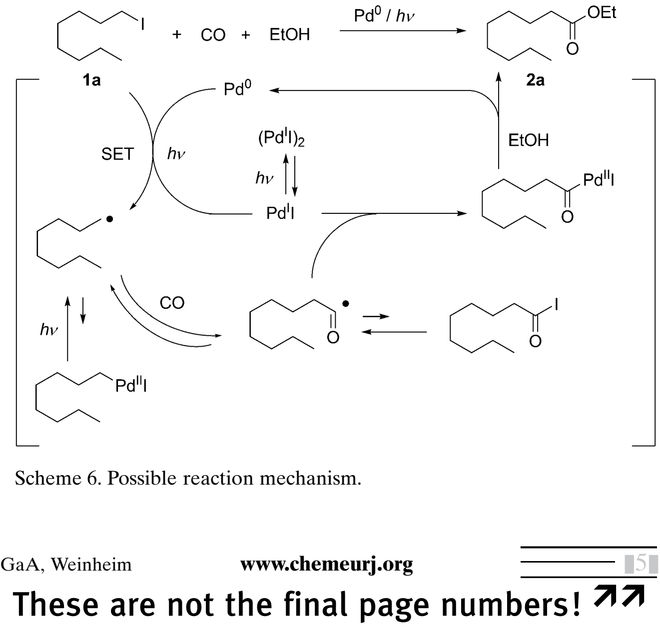
Scheme 3. Comparison of the isomeric ratios of the atom-transfer 5-*exo* cyclization and carbonylation reactions.



Scheme 4. Comparison of the isomeric ratios of the atom-transfer carbonylation reactions with and without a Pd catalyst.

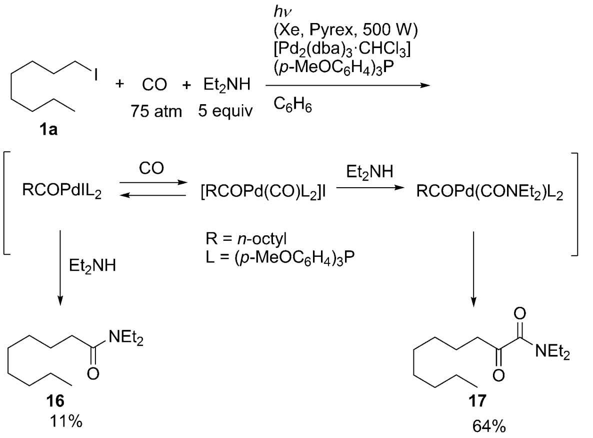


Scheme 5. Comparison of the isomeric ratios of the previously reported Pt-catalyzed carbonylation reactions.[14a,b]



Scheme 6. Possible reaction mechanism.

consumed by adding to CO to afford an acyl radical that is eventually trapped by Pd^{I}I to form an acylpalladium complex, which is a precursor for the ethyl ester (**2a**). When we investigated the three-component reaction of an alkyl iodide, CO, and amines, keto amide **17** was formed as the principal product from the incorporation of two molecules of CO (Scheme 7).[16a] In contrast, in the absence of a Pd catalyst, amide **16** was obtained as the sole carbonylated product.[9b] Because the carbonylation of an acyl radical is rarely observed in radical-carbonylation reactions,[29] the intervention of an acylcarbamoylpalladium complex, which has been well-established by Yamamoto and co-workers for a Pd-catalyzed double-carbonylation reaction,[30] is strongly suggested to account for the formation of compound **17**. We believe that the Pd^{I}I species may be a persistent radical[31] that may exist in equilibrium with a PdI dimer under the photoirradiation conditions.[19] Interestingly, when we measured the MS (FAB) of the reaction mixture with [Pd(PPh$_3$)$_4$] as the catalyst, the observed fragment-ion peaks of the Pd species corresponded well with the simulated isotope pattern for dinuclear Pd complexes.[32]



Scheme 7. Three-component coupling reaction to afford amide **16** and α-keto amide **17.**

Conclusion

In summary, we have demonstrated that the photoinduced atom-transfer carbonylation reactions of a variety of alkyl iodides can be effectively accelerated by the addition of Pd complexes. This procedure provides a general synthetic approach for the synthesis of various carboxylic-acid derivatives through useful cascade sequences that are tolerant of a variety of alkyl iodides as starting materials. In many cases, Pd dimer [Pd$_2$(CNMe)$_6$][PF$_6$]$_2$ worked equally as well as Pd^0 catalysts for these photoinduced carbonylation reactions. To affect the somewhat-inefficient oxidative addition of sp^3-carbon–halogen bonds to Pd^0 complexes, electron-rich ligands are used[33,34] that can suppress the β-hydride elimination of the rather labile alkylpalladium intermediates. However, these Pd/hν-mediated radical processes can avoid these issues by proceeding through a free-radical pathway: 1) the formation of an alkyl-radical/Pd-radical pair, 2) subsequent C–C bond-forming reaction by the radicals (carbonylation), and 3) radical/Pd-radical coupling to form an organopalladium intermediate (acylpalladium complexes). We believe that, as seen in the mechanistic considerations in related work, a radical-carbonylation mechanism may operate in other metal-catalyzed carbonylation reactions that involve alkyl halides.

Experimental Section

General procedure for the synthesis of esters through a three-component coupling reaction: A magnetic stirrer bar, compound **1b** (0.051 g, 0.28 mmol), BuOH (0.095 g, 1.3 mmol), Et$_3$N (0.048 g, 0.47 mmol), 4-dimethylaminopyridine (0.002 g, 0.016 mmol), [Pd(PPh$_3$)$_4$] (0.018 g, 0.016 mmol), and benzene (3.0 mL) were placed in a stainless steel autoclave that was equipped with a Pyrex glass liner. The autoclave was closed, purged three times with carbon monoxide, pressurized with CO (45 atm), and then irradiated by a Xenon arc lamp (500 W) with stirring for 16 h. Excess CO was discharged after the reaction at RT. The reaction mixture was added to water (20 mL) and extracted with Et$_2$O (3× 20 mL). The Et$_2$O layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo to give a residue that was purified by column chromatography on silica gel (n-hexane/EtOAc) to afford compound **2b** (0.036 g, 83 %).

General procedure for the synthesis of esters through a four-component coupling reaction: A magnetic stirrer bar, ethyl iodoacetate (**3a**, 0.13 g, 0.61 mmol), 1-octene (**4a**, 0.69 g, 6.2 mmol), EtOH (**5a**, 1.2 g, 26 mmol), K$_2$CO$_3$ (0.10 g, 0.72 mmol), [PdCl$_2$(PPh$_3$)$_2$] (0.025 g, 0.036 mmol), 4-dimethylaminopyridine (DMAP, 0.0084 g, 0.069 mmol), toluene (5.0 mL), and H$_2$O (10 μL) were placed in a stainless steel autoclave that was equipped with a Pyrex glass liner. The autoclave was closed, purged three times with carbon monoxide, pressurized with CO (45 atm), and then irradiated by a Xenon arc lamp (500 W) with stirring for 14 h. Excess CO was discharged after the reaction at RT. The reaction mixture was added to water (20 mL) and extracted with Et$_2$O (3×20 mL). The combined Et$_2$O layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (n-hexane/Et$_2$O) to afford compound **6a** (0.14 g, 82 %).

General procedure for the synthesis of lactones: A magnetic stirrer bar, ethyl iodoacetate (**3a**, 55 mg, 0.25 mmol), 4-penten-1-ol (**7b**, 105 mg, 1.3 mmol), Et$_3$N (30 mg, 0.30 mmol), [PdCl$_2$(PPh$_3$)$_2$] (9.1 mg, 0.013 mmol), DMAP (4.1 mg, 0.033 mmol), toluene (5.0 mL), and H$_2$O (50 μL) were placed in a stainless steel autoclave that was equipped with a Pyrex glass liner. The autoclave was closed, purged three times with CO (10 atm), pressurized with CO (45 atm), and then irradiated by a Xenon arc lamp (300 W) with stirring for 16 h. Excess CO was discharged after the reaction at RT. The reaction mixture was added to water (20 mL) and extracted with Et$_2$O (3×20 mL). The combined Et$_2$O layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (n-hexane/Et$_2$O) to afford compound **8b** (39 mg, 77 %).

Procedure for the synthesis of lactam: A magnetic stirrer bar, ethyl iodoacetate (**3a**, 50 mg, 0.24 mmol), N-(pent-4-enyl)aniline (**9**, 205 mg, 1.3 mmol), Et$_3$N (29 mg, 0.29 mmol), [PdCl$_2$(PPh$_3$)$_2$] (9.3 mg, 0.013 mmol), DMAP (4.3 mg, 0.035 mmol), toluene (5.0 mL), and H$_2$O (50 μL) were placed in a stainless steel autoclave that was equipped with a Pyrex glass liner. The autoclave was closed, purged three times with CO (10 atm), pressurized with CO (45 atm), and then irradiated by a Xenon arc lamp (300 W) with stirring for 16 h. Excess CO was discharged after the reaction. The reaction mixture was added to water

(20 mL) and extracted with Et_2O (3×20 mL). The combined Et_2O layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (*n*-hexane/Et_2O) to afford compound **10** (9.0 mg. 14 %).

Palladium accelerated atom transfer carbonylation with diethylamine: A magnetic stirrer bar, compound **1a** (0.122 g, 0.51 mmol), Et_2NH (0.187 g, 2.6 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (dba = dibenzylideneacetone, 0.015 g, 0.014 mmol), (p-$MeOC_6H_4)_3P$ (0.019 g, 0.054 mmol), and benzene (5.1 mL) were placed in a stainless steel autoclave that was equipped with a Pyrex glass liner. The autoclave was closed, purged three times with carbon monoxide, pressurized with CO (75 atm), and then irradiated by a Xenon arc lamp (500 W) with stirring for 16 h. Excess CO was discharged after the reaction at RT. The reaction mixture was added to water (20 mL) and extracted with Et_2O (3×20 mL). The Et_2O layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue that was purified by column chromatography on silica gel (*n*-hexane/EtOAc) to afford compounds **16** (0.013 g, 11 %) and **17** (0.082 g, 64 %).

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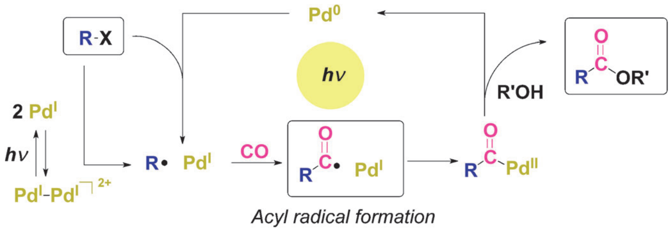

Light, camera, ATCion: Atom-transfer carbonylation of alkyl iodides to afford carboxylic acid esters was accelerated by the addition of transition-metal catalysts under photoirradiation. The carbonylation step proceeded through a radical mechanism.

Carbonylation

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Pd/Light-Accelerated Atom-Transfer Carbonylation of Alkyl Iodides; Applications in Multicomponent Coupling Processes Leading to Functionalized Carboxylic Acid Derivatives