

Effective Acceleration of Atom Transfer Carbonylation of Alkyl Iodides by Metal Complexes. Application to the Synthesis of the Hinokinin Precursor and Dihydrocapsaicin

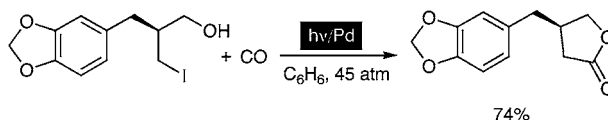
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Received January 16, 2006

ABSTRACT

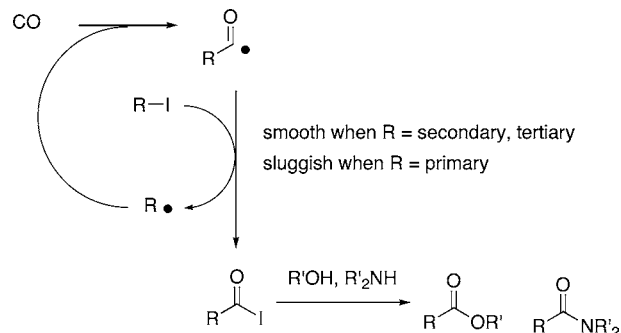


Atom transfer carbonylation (ATC) of alkyl iodides leading to carboxylic acid esters is effectively accelerated by $\text{Pd}(\text{PPh}_3)_4$ and $\text{Mn}_2(\text{CO})_{10}$ under photoirradiation conditions. In the presence of amines, $\text{Pd}(0)$ complexes affected double carbonylations leading to α -keto amides, whereas $\text{Mn}_2(\text{CO})_{10}$ accelerated only a single carbonylation reaction leading to the corresponding amides. The $\text{Pd}(0)$ -accelerated ATC system was successfully applied to the synthesis of hinokinin and dihydrocapsaicin.

The design and implementation of atom transfer radical carbonylation (ATC) reactions has led to efficient carbonylation approaches to basic carbonyl compounds, such as aliphatic carboxylic acid esters, amides, and the related heterocyclic compounds, in which readily available alkyl iodides and carbon monoxide can be employed as key substrates (Scheme 1).^{1,2} Recent applications by the Kobayashi group and the Långström group have expanded this system to include the synthesis of carboxylic acids³ and a series of compounds in which radioactive ^{11}C is incorporated.⁴ In terms of the feasibility of the iodine atom transfer step from alkyl iodides to acyl radicals, atom transfer

carbonylation proceeds more efficiently with secondary and tertiary alkyl iodides, whereas the reaction is sluggish with primary alkyl iodides, in which the longer reaction time required leads to undesirable side reactions such as the

Scheme 1. Original Radical/Ion Hybrid Concept of Atom Transfer Carbonylation of Alkyl Iodides and the Reactivity Issue Associated with Primary Alkyl Iodides



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decomposition of alkyl iodides via ionic reactions.⁵ The recent success of the cascade carbonylations of 4-alkenyl iodides,⁶ which are affected by a Pd/irradiation system, led us to reexamine some atom transfer carbonylations of ordinary alkyl iodides leading to esters and amides in the presence of metal complexes under similar metal/light combined conditions.⁷ Herein, we report that the atom transfer carbonylation of primary, secondary, and tertiary alkyl iodides leading to the corresponding esters is successfully accelerated by metal complexes, such as palladium(0) phosphine complexes and dimanganese decacarbonyl.

Using three types of primary alkyl iodides **1a–c**, we examined the atom transfer carbonylation under photoirradiation conditions (Xenon, Pyrex) in the presence of a catalytic amount of Pd(PPh₃)₄. The results are summarized in Table 1. The findings show that ester formation is

Table 1. Acceleration of Atom Transfer Carbonylation of Primary Alkyl Iodides Leading to Esters and Lactone by Pd(0) and Mn(0)^a

entry	RI, 1	conditions	catalyst	product, 2	yield (%) ^b
1		hv (Xe, Pyrex), 50 h	none		54
2		hv (Xe, Pyrex), 16 h	Pd(PPh ₃) ₄		87
3		hv (Xe, Pyrex), 16 h	Mn ₂ (CO) ₁₀		54
4		hv (Xe, Pyrex), 16 h	none		40
5		hv (Xe, Pyrex), 16 h	Pd(PPh ₃) ₄		83
6		hv (Xe, Pyrex), 16 h	none		27
7		hv (Xe, Pyrex), 16 h	Pd(PPh ₃) ₄		91
				cis/trans = 36/64 ^c	
8		hv (Xe, Pyrex), 6.5 h	none		40
9		hv (Xe, Pyrex), 6.5 h	Pd(PPh ₃) ₄		83
10		hv (Xe, Pyrex), 4 h	Mn ₂ (CO) ₁₀		91
11		hv (Xe, Pyrex), 6.5 h	none		38
12		hv (Xe, Pyrex), 6.5 h	Pd(PPh ₃) ₄		80
13		hv (Xe, Pyrex), 4 h	Mn ₂ (CO) ₁₀		80

^a Conditions: **1** (0.5 mmol); catalyst, Pd(PPh₃)₄ (5–5.7 mol %) or Mn₂(CO)₁₀ (3–4 mol %); base, NEt₃ (1.4–1.7 equiv) plus DMAP (10 mol %) or K₂CO₃ (2.0 equiv, entries 1–3); EtOH (5 mL, entries 1–3); benzene (5 mL, entries 6 and 7); benzene/BuOH (5/0.18 mL, entries 4, 5, 8–13); CO (45 atm); light (500 W xenon lamp, Pyrex). ^b Isolated yield by silica gel chromatography. ^c Cis/trans ratio determined by ¹H NMR.

accelerated in the presence of Pd(0) in all the cases examined (entries 2, 5, and 7). Thus, 1-iodooctane (**1a**) was converted to the corresponding ethyl nonanoate (**2a**) in 87% yield with a considerably shortened reaction time (16 h). Cyclopropylcarbinyl iodide (**1b**) gave a ring-opened product, butyl 4-butenolate (**2b**), in 83% yield. The original atom transfer carbonylation of 1-hydroxyalkyl iodide **1c** suffers from

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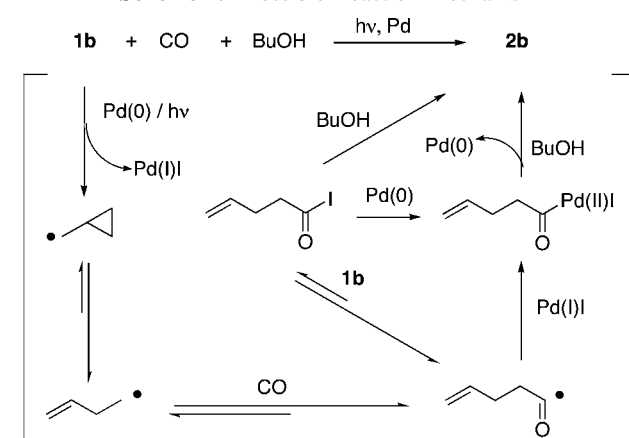
(7) For pioneering efforts on metal-catalyzed carbonylation under photoirradiation conditions, see: (a) Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. *J. Organomet. Chem.* **1994**, *473*, 163. (b) Ishiyama, T.; Murata, M.; Suzuki, A.; Miyaura, N. *J. Chem. Soc., Chem. Commun.* **1995**, 295.

competition by intramolecular S_N2 reactions leading to the corresponding oxetane as a side-reaction product;^{2c} however, the addition of the Pd catalyst resulted in a very effective acceleration to give the desired γ -lactone **2c** in 83% yield with the undesirable ionic reaction being negligible (entry 7). The sole formation of the ring-opening product in the case of **1b** can be rationalized by the intervention of a cyclopropylcarbinyl radical to homoallyl radical ring opening, which is the fastest class of radical reactions.⁸

In contrast to primary alkyl iodides, the atom transfer carbonylation of secondary and tertiary alkyl iodides proceeds smoothly to give good to high yields of esters under the original conditions (Xenon, Pyrex, 16 h). To determine whether Pd(0) exerts an acceleration effect even in secondary and tertiary substrates, we examined the reaction of **1d** and **1e** using a shorter reaction time, such as 6.5 h, in which the reactions are typically incomplete. Again, Pd(0) accelerated the reaction results for both secondary and tertiary iodides (entries 9 and 12). Watanabe and co-workers previously reported that dimanganese decacarbonyl catalyzes the carbonylation of alkyl iodides under a variety of conditions including photoirradiation.^{7a} Consistent with their original findings, we also found that the presence of dimanganese decacarbonyl accelerates the atom transfer carbonylation of secondary and tertiary alkyl iodides in our ATC system (entries 10 and 13), whereas the acceleration for a primary alkyl iodide **1a** was only modest (entry 3).

The proposed mechanism for the Pd-accelerated reaction is outlined in Scheme 2. Thus, at the initial stage, Pd(0) reacts

Scheme 2. Possible Reaction Mechanism



with RI to generate Pd(I)I and R[•] via a one-electron transfer. In the final stage, Pd(I)I couples with acyl radical species to form an acylpalladium,⁹ which undergoes alcoholysis to give the ester and Pd(0). Previous studies reported that Mn₂(CO)₁₀¹⁰ and Pd(PPh₃)₄¹¹ can act as an effective radical initiator, whereas the promotion of the initiation step does

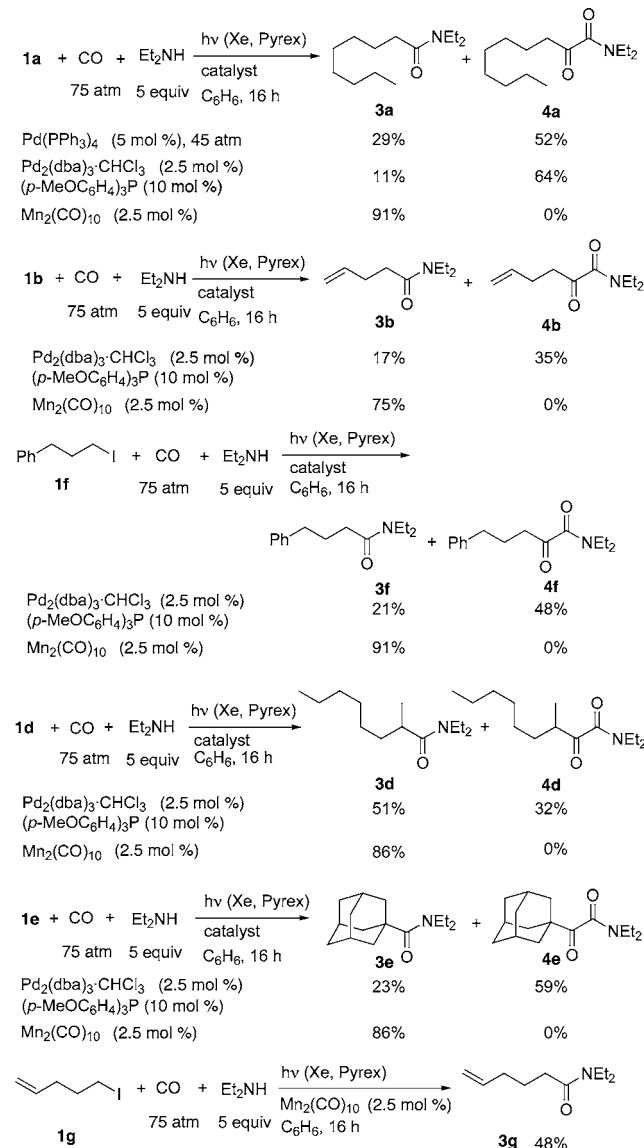
(8) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699.

(9) There are many mechanistic possibilities about the role of Pd, which includes the direct reaction of the acyl radical with the Pd(0) to form RCOPd(I) species, as one referee suggested.

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not appear to be the only function of the Pd(0) catalyst in the present carbonylation system. Indeed, when the reaction was conducted in the presence of amines, the presence of Pd(0) led to the formation of double carbonylated products (Scheme 3). Because the carbonylation of an acyl radical is

Scheme 3. Transition-Metal Accelerated Atom Transfer Carbonylation with Diethylamine



rarely observed in radical carbonylation reactions,¹² the intervention of an acylcarbamoylpalladium complex as the precursor to the keto amide is strongly suggested.¹³ We examined several ligands for the reaction and found that tri-

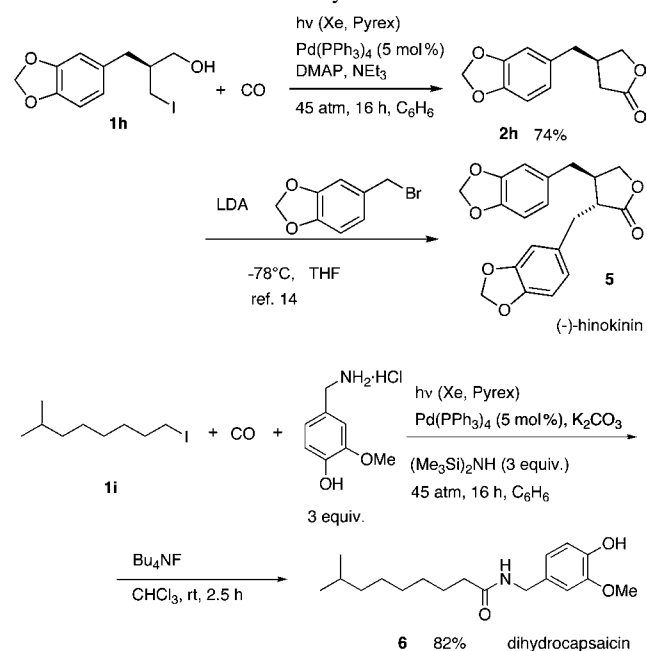
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(*p*-methoxyphenyl)phosphine gave slightly better results for the double carbonylation. Some other transition-metal complexes, such as Ru₃(CO)₁₂ and Re₂(CO)₁₀, were found to promote double carbonylation, but the extent of the reaction was inferior to Pd(0). It is noteworthy that the fact that more single carbonylation products are formed in the cases of secondary and tertiary alkyl iodides is due to the relatively facile background atom transfer reaction for these substrates.² For the purpose of obtaining singly carbonylated amides selectively, the use of Mn₂(CO)₁₀ appears to be promising.

Having an effective method for atom transfer carbonylation of primary alkyl iodides in hand, we then applied the established procedure to the synthesis of the (–)-hinokinin precursor **2h** (Scheme 4).¹⁴ The chiral iodo alcohol **1h**

Scheme 4. Synthesis of the (–)-Hinokinin Precursor and Dihydrocapsaicin Based on Pd–Accelerated Atom Transfer Carbonylation



required for the carbonylation was prepared on the basis of Itoh's method.^{14a} The carbonylation of **1h** under irradiation conditions in the presence of Pd(0) gave the γ -lactone **2h** in 74% yield. Coupled with a subsequent enolate alkylation, the formal synthesis of (–)-hinokinin **5** was achieved.¹⁴ We also successfully carried out the concise synthesis of dihydrocapsaicin (**6**),¹⁵ a hot-tasting compound contained in red pepper. Hexamethyldisilazane (HMDS) was added for the

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purpose of the in situ silyl protection of the phenol portion, to prevent the formation of the phenol ester in a competing reaction. Thus, the carbonylation of 1-iodo-7-methyloctane (**1i**) in the presence of *p*-hydroxy-*m*-methoxybenzylamine and HMDS, followed by treatment with TBAF, gave dihydrocapsaicin (**6**) in 82% yield.

In summary, the findings herein show that the atom transfer carbonylation of a variety of alkyl iodides can be effectively accelerated by the use of Pd(0) phosphine complexes and dimanganese decacarbonyl. The procedure involving Pd(0) is particularly useful for the carbonylation of primary alkyl iodides, the original procedure for which,

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using photoirradiation, was particularly sluggish. The procedure using Pd(0) can be successfully applied to the synthesis of the (–)-hinokinin precursor and dihydrocapsaicin.

Acknowledgment. I.R. acknowledges a Grant-in-Aid for Scientific Research on Priority Areas (A), “Reaction Control of Dynamic Complexes” from MEXT, Japan for financial support.

Supporting Information Available: Experimental procedures and characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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