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Vicinal C-Functionalization of Alkenes. Pd/Light-Induced Multicomponent Coupling Reactions Leading to Functionalized Esters and Lactones

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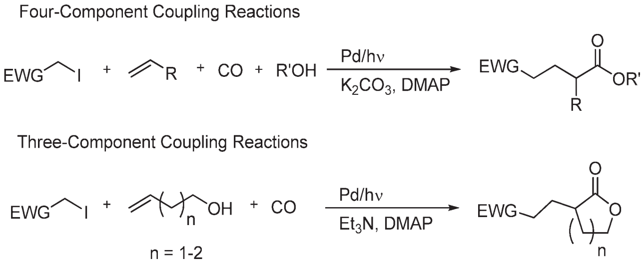
ABSTRACT


Four-Component Coupling Reactions

Three-Component Coupling Reactions

Under photoirradiation conditions using a xenon light, and in the presence of $PdCl_2(PPh_3)_2$ as a catalyst, four-component coupling reactions comprising of α-substituted iodoalkanes, alkenes, carbon monoxide, and alcohols proceeded smoothly to give functionalized esters in good yields. When alkenyl alcohols were used as acceptor alkenes, three-component coupling reactions accompanied by intramolecular esterification proceeded to give lactones in good yields. The present reaction system represents the vicinal C-functionalization of alkenes.

In terms of the high throughput and efficiency required to construct organic compounds with structural diversity in one pot, multicomponent reactions (MCRs) have attracted more and more interest in recent years.[1,2] MCRs involving CO as one of the components allow for direct incorporation of CO as a carbonyl function into carbonyl-containing products, and we are particularly interested in strategies involving radical reactions.[3,4] We previously found that metal/$h\nu$-induced systems[5] caused acceleration

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(1) (a) Bienayme, H.; Hulme, C.; Oddon, G; Schmitt, P. *Chem.—Eur. J.* **2000**, *6*, 3321. (b) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005.

(2) For radical multicomponent reactions, see: (a) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 169–198. Also see reviews: (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (c) Godineau, E.; Landais, Y. *Chem.—Eur. J.* **2009**, *15*, 3044.

(3) For reviews on radical carbonylation reactions using carbon monoxide, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. For a review on acyl radial chemistry, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(4) For atom-transfer carbonylations, see: (a) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465. (b) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun* **1998**, 1953. (c) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389. (d) Ryu, I.; Niguma, T.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1997**, *38*, 7883. (e) Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 1548. Also see a review: Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.

(5) For previous 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.

(6) (a) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, S.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812. (b) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383. (c) Fukuyama, T.; Inouye, T.; Ryu, I. *J. Organomet. Chem.* **2007**, *692*, 685. (d) Fusano, A.; Fukuyama, T.; Nishitani, T.; Inouye, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 2410. (e) Ryu, I. *Chem. Rec.* **2002**, *2*, 249.

(7) (a) Liang, Bo.; Liu, J.; Gao, Y. X.; Wongkhan, K.; Shu, D. X.; Lan, Y.; Li, A.; Batsanov, A. S.; Howard, J. A. H.; Marder, T. B.; Chen, J. H.; Yang, Z. *Organometallics* **2007**, *26*, 4756. (b) Dai, M.; Wang, C.; Dong, G.; Xiang, J.; Luo, T.; Liang, B.; Chen, J.; Yang, Z. *Eur. J. Org. Chem.* **2003**, 4346. (c) Yamamoto, Y.; Maekawa, H.; Goda, S.; Nishiguchi, I. *Org. Lett.* **2003**, *5*, 2755. (d) Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5005. (e) Brechot, P.; Chauvin, Y.; Commereuc, D.; Saussine, L. *Organometallics* **1990**, *9*, 26. (f) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994.

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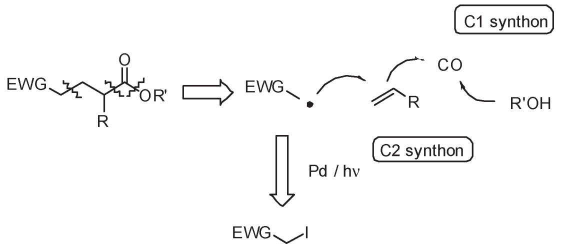
of the atom-transfer carbonylation of alkyl iodides leading to carboxylic acid esters, amides, and alkynyl ketones.[6]

Vicinal carbon functionalization of alkenes is an important challenge in multicomponent reactions. Whereas typical processes with incorporation of CO involve double alkoxycarbonylation of alkenes,[7] reactions attaining the introduction of an alkyl unit and CO into vicinal carbons of alkenes are scarce.[8] In a related study, we previously reported on the photoinduced addition of α-phenylseleno-substituted esters to alkenes and CO to give 4-keto acyl selenides as products.[9] However, a simple ester synthesis has yet to be attained. In this paper, we report that Pd/light-induced radical carbonylation of various α-substituted iodoalkanes allows for vicinal carbon-functionalization of alkenes leading to esters (Scheme 1).

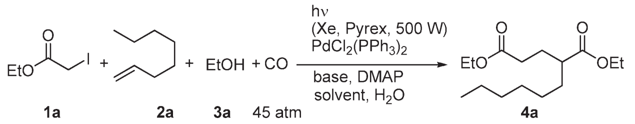
Scheme 1. Strategies for Four-Component Coupling Reactions of α-Iodoalkanes, Alkenes, CO, and Alcohols Leading to Esters



When a benzene solution of ethyl iodoacetate (**1a**), 1-octene (**2a**), and ethanol (**3a**) was exposed to photoirradiation conditions (irradiation with a 500 W xenon lamp through Pyrex) under 45 atm of CO pressure in the presence of $PdCl_2(PPh_3)_2$ (5 mol %), a base (1.1 equiv of NEt_3 and 10 mol % of DMAP), and a small amount of water (ca. 1 equiv), the desired diester **4a** was obtained in 72% yield after chromatographic purification (Table 1, entry 1). In the absence of Pd catalyst, the reaction was sluggish (entry 2). The combination of photoirradiation conditions and Pd catalyst was essential to obtain **4a** in a good yield (entry 3). The reaction using K_2CO_3 as a base was also effective, which gave 77% of **4a** (entry 4).[10] The use of toluene as a solvent also gave a good yield of **4a** (entry 5). NHC Pd complex also worked to give diester **4a**, but was less effective (entry 6).

A variety of α-substituted iodoalkanes, alkenes, and alcohols participate in the present four-component coupling reactions (Table 2). In contrast to **1a**, the reaction of ethyl bromoacetate (**1b**) was sluggish, giving a 26% yield of **4a** (entry 2). Benzyl alcohol (**3b**) gave the anticipated diester **4b** in a 67% yield (entry 3). In the reaction with methanol, dimethyl ester **4c**, arising from the further transesterification of an ethyl ester, was formed in 70% yield (entry 4). Terminal olefins having a chlorine atom or a phenyl group also worked well to give the corresponding diesters **4d** and **4e** in good yields (entries 5 and 6). Cycloheptene (**2d**) also gave the corresponding diester **4f** in a 51% yield as a single trans diastereomer (entry 7). The reaction of perfluorohexyl iodide (**1c**) with **2a** or **2c** afforded the corresponding esters **4g** or **4h** in 84 and 76% yields, respectively (entries 8 and 9). Iodoacetonitrile (**1d**) and iodomethyl phenyl sulfone (**1e**) gave the anticipated cyano ester **4i** and sulfone ester **4j** in 64 and 56% yields, respectively (entries 10 and 11). In a radical cascade sequence involving the incorporation of two molecules of CO, the reaction of **1a** with 1,5-hexadiene (**2e**) was carried out, which gave the desired diester (**4k**) bearing a cyclopentanone scaffold via a five-component coupling reaction (entry 12). The relatively low yield of **4k** was the result of the competitive formation of singly carbonylated product **4l** (24% yield).

Table 1. Pd/Light Induced, Four-Component Coupling Reaction of Ethyl Iodoaceate (**1a**) with 1-Octene (**2a**), Ethanol (**3a**), and Carbon Monoxide[a]



entry	base	solvent	time (h)	yield[b] (%)
1	Et_3N	C_6H_6	8	72
2[c]	Et_3N	C_6H_6	14	25
3[d]	Et_3N	C_6H_6	16	21
4	K_2CO_3	C_6H_6	8	77
5	K_2CO_3	toluene	14	82
6[e]	K_2CO_3	toluene	14	57

[a] Conditions: **1a** (0.5 mmol), **2a** (10 equiv), **3a** (40 equiv), CO (45 atm), $PdCl_2(PPh_3)_2$ (5 mol %), base (1.1 equiv), DMAP (10 mol %), solvent (5 mL), H_2O (10 μL). [b] Isolated yield of **4a** after silica gel chromatography. [c] The reaction was carried out without $PdCl_2(PPh_3)_2$. [d] The reaction was performed under 80 °C without photoirradiation conditions. [e] Dichloro[1,3-bis(diisopropylphenyl)imidazolylidene](3-chloropyridyl)palladium(II) was used as a Pd catalyst. Iodoalkane **5** was formed as byproduct (16%).

We next examined cyclizative three-component coupling reactions, using alkenyl alcohols **6**, which also worked well to give the desired ester-functionalized lactones (Table 3). Thus, when ethyl iodoacetate (**1a**) was treated with 4-penten-1-ol (**6a**) and carbon monoxide in the presence of $PdCl_2(PPh_3)_2$ and triethylamine under standard conditions, the reaction proceeded smoothly to give δ-lactone **7a** in a 77% yield (entry 1). The reaction of 4-buten-1-ol (**6b**) also worked to give γ-lactone **7b** in a good yield (entry 2). Perfluorohexyl iodide (**1c**) also worked well to give the corresponding lactones **7c** and **7d** in good yields (entries 3 and 4). We also examined the synthesis of seven-membered ring lactone **7e**

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(8) (a) Urata, H.; Kinoshita, Y.; Asanuma, T.; Kosukegawa, O.; Fuchikami, T. *J. Org. Chem.* **1991**, *56*, 4996. (b) Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron Lett.* **1982**, *23*, 893. (c) Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* **1985**, *41*, 5003.

(9) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396.

(10) When the reaction was performed without DMAP, the yield of diester **4a** dropped to 53%. In this case, the iodoalkane **5** arising from the addition of **1a** to **2a** was also obtained in 24% yield.

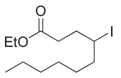

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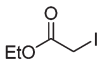
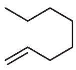
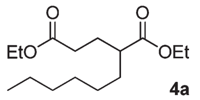
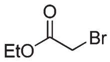
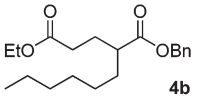
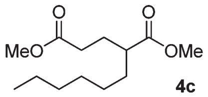
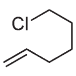
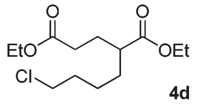
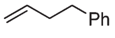
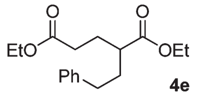
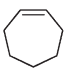
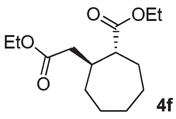
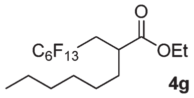
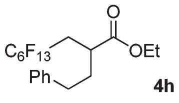
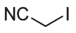
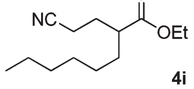
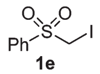
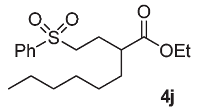
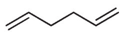
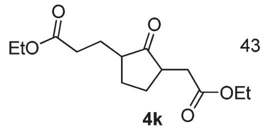
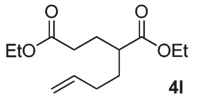
Table 2. Four-Component Coupling Reactions Leading to Esters[a]

$$\underset{\mathbf{1}}{\text{R–X}} + \underset{\mathbf{2}}{\text{alkene}} + \text{CO} + \underset{\mathbf{3}}{\text{ROH}} \xrightarrow[\text{K}_2\text{CO}_3\text{, DMAP, toluene, H}_2\text{O}]{h\nu\text{ (Xe, Pyrex, 500W), PdCl}_2(\text{PPh}_3)_2} \underset{\mathbf{4}}{\text{product}}$$

entry	R–I	alkene	ROH	product	yield (%)[b]
1	 **1a**	 **2a**	EtOH **3a**	 **4a**	82
2[c]	 **1b**	**2a**	**3a**	**4a**	26
3[d]	**1a**	**2a**	BnOH **3b**	 **4b**	67
4	**1a**	**2a**	MeOH **3c**	 **4c**	70
5	**1a**	 **2b**	**3a**	 **4d**	72
6	**1a**	 **2c**	**3a**	 **4e**	74
7	**1a**	 **2d**	**3a**	 **4f**	51
8	$C_6F_{13}I$ **1c**	**2a**	**3a**	 **4g**	84
9	**1c**	**2c**	**3a**	 **4h**	76
10	 **1d**	**2a**	**3a**	 **4i**	64
11	 **1e**	**2a**	**3a**	 **4j**	56
12[e]	**1a**	 **2e**	**3a**	 **4k** (cis/trans = 18/82)	43
				 **4l**	24

[a] Conditions: **1** (0.5 mmol), **2** (10 equiv), **3** (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). [b] Isolated yield after silica gel chromatography. [c] C_6H_6 and Et_3N were used. [d] BnOH (5.0 equiv) was used. [e] CO (65 atm) and $PdCl_2(PPh_3)_2$ (20 mol %) were used.

using **6c**. In this case, due to the competition of ionic cyclization giving a tetrahydropyran ring, the yield of ε-lactone **7e** was moderate (entry 5).

A possible reaction mechanism for the present multicomponent coupling reaction is shown in Scheme 2. Alkyl radicals are formed via cleavage of the I–C bond of **1a**, which may be triggered by single electron transfer from the photoirradiated Pd(0) complex.[11,12]Addition of the radicals to alkene then takes place to give alkyl radicals. The subsequent iodine atom transfer form **1a** affords iodoalkane **5**. The reaction between alkyl radical and Pd(I) to give alkyl palladium might take place but scarcely contributes in this reaction mechanism, judging from the fact that β-hydrogen elimination product was not observed. Probably pressurized CO drives these equilibriums to afford the acylradical intermediate, which would be trapped by Pd(I)I to form acylpalladium species, precursors for the diester **4a**. Persistent radical character of Pd(I) species may be supported by the dimerization behavior.[13,14]

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(11) For examples of an electron transfer from low-valent palladium or platinum complexes to iodoalkanes, see: (a) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832. (b) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145. (c) Knochel, P.; Manolikakes, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 205. Also see ref 6b.

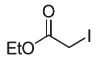
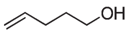
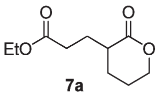
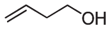
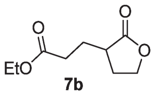
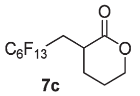
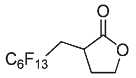
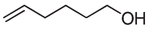
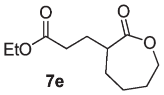
(12) For SET-induced radical reactions of perfluoroalkyl iodides, see: (a) Chen, Q. Y.; Yang, Z. Y.; Zhao, C. X.; Qiu, Z. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 563. (b) Qiu, Z. M.; Burton, D. J. *J. Org. Chem.* **1995**, *60*, 5570. (c) Yoshida, M.; Iizuka, M. *J. Fluorine Chem.* **2009**, *130*, 926.

(13) For reviews on persistent radical effect, see: (a) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. (b) Studer, A. *Chem.—Eur. J.* **2001**, *7*, 1159. (c) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267. (d) Studer, A.; Schulte, T. *Chem. Rec.* **2005**, *5*, 27. Also see:(e) Focsaneanu, K. S.; Aliaga, C.; Scaiano, J. C. *Org. Lett.* **2005**, *7*, 4979.

(14) For photogeneration of Pd radical from Pd dimer complex, see: Lemke, F. R.; Kubiak, C. P. *J. Organomet. Chem.* **1989**, *373*, 391.

Table 3. Three-Component Coupling Reactions Leading to Lactones[a]

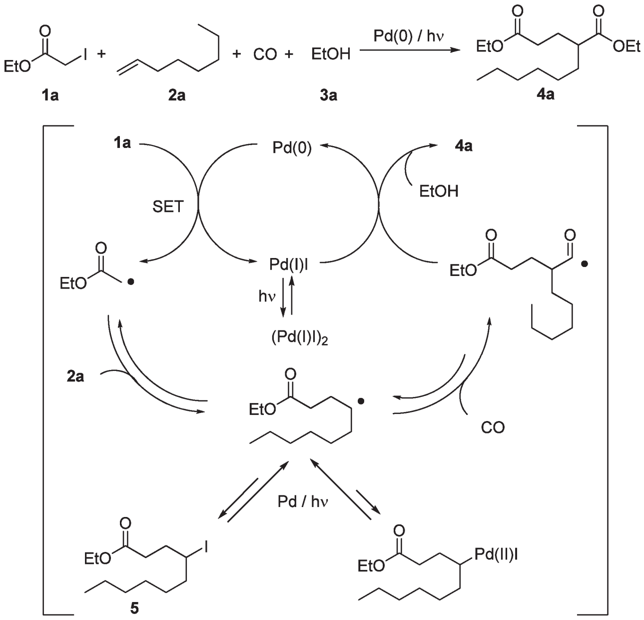
$$\underset{\mathbf{1}}{\text{R–X}} + \underset{\mathbf{6}}{\text{alkenyl alcohol}} + \underset{\text{45 atm}}{\text{CO}} \xrightarrow[\text{Et}_3\text{N, DMAP; toluene, H}_2\text{O}]{h\nu\text{ (Xe, Pyrex, 300 W)}; \text{PdCl}_2(\text{PPh}_3)_2} \underset{\mathbf{7}}{\text{product}}$$

entry	R–I	alkenyl alcohol	product	yield (%)[b]
1	 **1a**	 **6a**	 **7a**	77
2	**1a**	 **6b**	 **7b**	72
3	$C_6F_{13}I$ **1b**	**6a**	 **7c**	77
4	**1b**	**6b**	 **7d**	69
5[c]	**1a**	 **6c**	 **7e**	50

[a] Conditions: **1** (0.25 mmol), **6** (5 equiv), CO (45 atm), $PdCl_2(PPh_3)_2$ (5 mol %), Et_3N (1.1–1.4 equiv), DMAP (10 mol %), toluene (5 mL), H_2O (50 μL). [b] Isolated yield after silica gel chromatography. [c] DMAP (20 mol %) and CO (80 atm) were used.

In summary, we have demonstrated novel four-component coupling reactions leading to functionalized esters, which use α-substituted iodoalkanes, alkenes, CO, and alcohols under Pd/light combined conditions. A three-component reaction using iodoalkanes, alkenyl alcohols, and CO also worked well to give the corresponding functionalized lactones. These reactions represent the vicinal carbon-functionalization of alkenes.

Scheme 2. Possible Reaction Mechanism



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Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org