

Heck-Type Arylation of 2-Cycloalken-1-ones with Arylpalladium Intermediates Formed by Decarboxylative Palladation and by Aryl Iodide Insertion

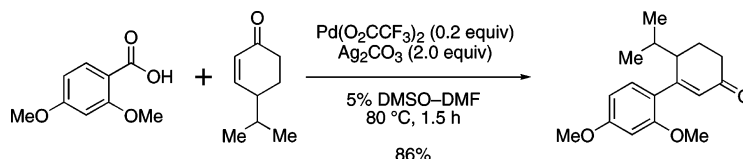
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ABSTRACT



A palladium-catalyzed decarboxylative arylation reaction was shown to produce Heck-type coupling products using a number of different arene carboxylic acid and 2-cycloalken-1-one substrates. The more conventional Heck coupling of an aryl iodide and a 2-cycloalken-1-one reactant was also briefly explored for comparison, where it was found that phosphine-free (Jeffery) conditions afforded the highest yield of product.

The Heck reaction, traditionally defined as the palladium-catalyzed coupling of an aryl halide with an olefinic substrate (forming a conjugated arene and hydrogen halide as products), is among the most useful carbon–carbon bond-forming processes in synthesis.¹ Since its inception, many new developments related to the Heck reaction have been reported, leading to improvements in the catalytic efficiency of the process and to the introduction of enantioselective variants of the Heck reaction.² Although the pool of viable aryl halide coupling partners in the Heck reaction has effectively been expanded as a result of the exploration of new ligand systems,^{1b,3} less has been achieved with respect to broadening the diversity of potential olefinic coupling

partners. The literature of the Heck reaction is dominated by couplings of derivatives of styrene and acrylic acid, substrates that are known to react with particular efficiency. By contrast, successful Heck couplings with α,β -unsaturated ketones as substrates are relatively rare,⁴ and efficient Heck-type couplings of 2-cycloalken-1-ones are almost unknown.^{5–7} With these substrate classes, a conjugative addition process has been reported to occur instead.^{7,8} In the case of small-

(1) Recent reviews: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449–7476.

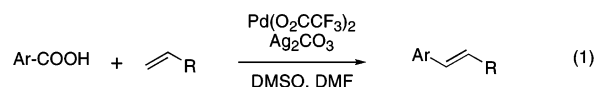
(2) Recent reviews: (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.

(3) Review: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.

(4) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289. (b) Arcadi, A.; Marinelli, F.; Cacchi, S. *J. Organomet. Chem.* **1986**, *312*, C27–C32. (c) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortari, G. *Tetrahedron* **1989**, *45*, 813–828. (d) Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253–6254. (e) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Tetrahedron* **1996**, *52*, 6983–6996. (f) Hagiwara, H.; Eda, Y.; Morohashi, K.; Suzuki, T.; Ando, M.; Ito, N. *Tetrahedron Lett.* **1998**, *39*, 4055–4058. (g) Cacchi, S.; Fabrizi, G.; Gasparrini, F.; Villani, C. *Synlett* **1999**, 345–347. (h) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 8487–8491.

(5) (a) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715–717. (b) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. M. N.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657–6670. (c) Costa, A.; Najera, C.; Sansano, J. M. *J. Org. Chem.* **2002**, *67*, 5216–5225.

to medium-ring 2-cycloalken-1-ones, this is perhaps not unexpected, in light of the fact that such substrates are precluded stereochemically from undergoing the final step in the traditional Heck process, syn β -hydride elimination (following cis arylpalladium addition).¹ Thus, the formation of vinylic substitution products, which we refer to here as a "Heck-type" process, requires some variation in the traditional Heck mechanism, such as the invocation of an anti β -hydride elimination reaction,^{9,10} stereochemical inversion of a C–Pd bond,^{5a,6d,7b,c} or the like. We are aware of selected cases of intramolecular Heck-type carbon–carbon bond formations within 2-cycloalken-1-one-aryl iodide substrates,⁷ but it is fair to say that no efficient procedure for inter- or intramolecular Heck-type coupling reactions of 2-cycloalken-1-ones is in common use today, if at all.¹¹



Our interest in Heck-type coupling reactions of 2-cycloalken-1-ones arose in the context of investigations of a decarboxylative palladation of arene carboxylic acids, a process that typically led to the formation of Heck-type coupling products when an alkene was present in the reaction mixture (eq 1).¹² We were surprised to find that 2-cyclohexen-1-one was a viable olefinic coupling partner in decarboxylative Heck-type couplings, although only two substrates (2,4-dimethoxybenzoic acid and mesitylene carboxylic acid) were investigated in our initial studies.¹² Byproducts arising from conjugative aryl addition were not observed. Recognizing the potential utility that a general process for Heck-type coupling reactions of 2-cycloalken-1-ones might hold, we initiated a study to determine the scope of the decarboxylative palladation coupling process and also briefly explored more traditional Heck-type couplings using aryl halides as coupling partners, to assess the relative merits of the two processes, as detailed below.

We began our study by exploring the scope of the palladium-catalyzed decarboxylative Heck-type coupling,

(6) Examples of intramolecular Heck-type couplings of 4-pyridones: (a) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron* **1994**, 50, 359–370. (b) Comins, D. L.; Joseph, S. P.; Zhang, Y. *Tetrahedron Lett.* **1996**, 37, 793–796. (c) Yoneda, R.; Kimura, T.; Kinomoto, J.; Harusawa, S.; Kurihara, T. *J. Heterocycl. Chem.* **1996**, 33, 1909–1913. (d) Kirschbaum, S.; Waldmann, H. *Tetrahedron Lett.* **1997**, 38, 2829–2832. (e) Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, 63, 4936–4946.

(7) (a) Zhang, Y.; O'Connor, B.; Negishi, E. *J. Org. Chem.* **1988**, 53, 5588–5590. (b) Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, 36, 7047–7050. (c) Ikeda, M.; Hirose, K.; El Bialy, S. A. A.; Sato, T.; Yakura, T.; Bayomi, S. M. M. *Chem. Pharm. Bull.* **1998**, 46, 1084–1089.

(8) Cacchi, S. *Pure Appl. Chem.* **1990**, 62, 713–722.

(9) Lautens, M.; Fang, Y.-Q. *Org. Lett.* **2003**, 5, 3679–3682 and references therein.

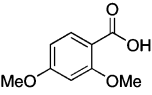
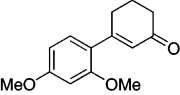
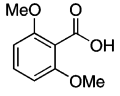
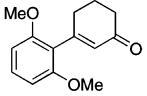
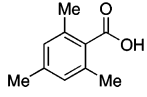
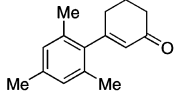
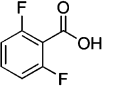
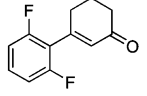
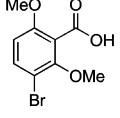
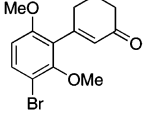
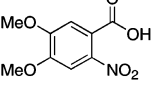
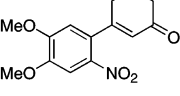
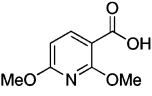
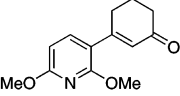
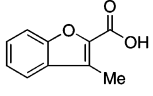
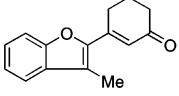
(10) Review: Ikeda, M.; El Bialy, S. A. A.; Yakura, T. *Heterocycles* **1999**, 51, 1957–1970.

(11) Heck-type coupling reactions of aryl halides with 2-cycloalken-1-ones have been reported in the patent literature, without mention of coupling efficiency. We have not obtained more than 30% yield in the coupling of 4-bromobenzonitrile with 2-cyclohexen-1-one by the method reported in the following patent reference (two attempts): Sucrow, W.; Fiedel, D.; Poetsch, E.; Rädcker, G. German Patent DE 3827675, Aug 16, 1988.

(12) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, 124, 11250–11251.

both with respect to the arene carboxylic acid substrate (Table 1) and potential 2-cycloalken-1-one reactants (Table 2).

Table 1. Decarboxylative Heck-Type Couplings of 2-Cyclohexen-1-one with Various Arene Carboxylic Acids^a

entry	carboxylic acid	product	temp (°C)	time (h)	yield(%) ^c
1 ^b			80	0.5	92
2			80	1.0	89
3 ^b			120	0.5	61
4			120	0.5	52
5			120	2.0	58
6			120	0.5	49
7			80	1.0	63
8			120	0.5	66

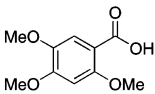

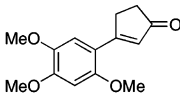
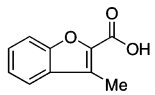

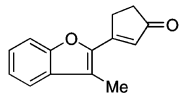
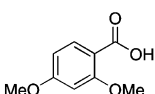

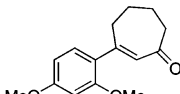
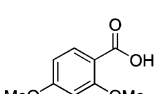
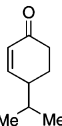
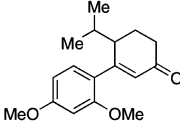
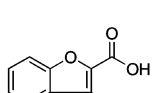
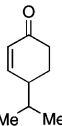
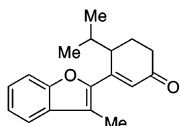
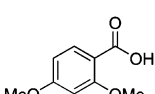

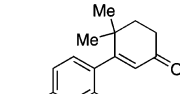
^a Conditions: carboxylic acid (1.0 mmol), 2-cycloalken-1-one (1.5 mmol), Pd(O₂CCF₃)₂ (0.2 mmol), Ag₂CO₃ (2.0 equiv), 5% DMSO–DMF.

^b These coupling reactions were reported in a previous publication (ref 12), but using 3.0 equiv of Ag₂CO₃, not 2.0 equiv, as presented here. ^c All yields refer to isolated, pure products.

Critical reaction parameters previously identified, including the catalyst (palladium(II) trifluoroacetate, 0.2 equiv) and solvent (5% DMSO–DMF) remained the same in this study, but the amount of silver(I) carbonate employed in the reaction was reduced from 3.0 to 2.0 equiv; additional details of the coupling procedures for specific substrates (time, temperature) appear in Table 1.¹³ As summarized in Table 1, carboxylic acids that had been shown to undergo decarboxylative coupling with styrene and butyl acrylate were found to couple efficiently with the much more demanding reactant

2-cyclohexen-1-one as well. Among carboxylic acids we examined were bromo- and nitro-substituted examples (entries 5 and 6, respectively) and many sterically hindered substrates (entries 2, 3, and 5). The tolerance of the decarboxylative palladation reaction to *o,o'*-disubstitution is one of its more interesting features; at least one ortho substituent appears to be required for decarboxylative palladation to occur.¹² Results summarized in Table 2 suggest

Table 2. Decarboxylative Heck-Type Couplings with a Range of 2-Cycloalken-1-one Reactants^a

entry	carboxylic acid	alkene	product	time (h)	yield (%) ^b
1				3.0	81
2 ^c				1.0	65
3				0.7	65
4				1.5	86
5 ^c				2.0	64
6				1.5	30

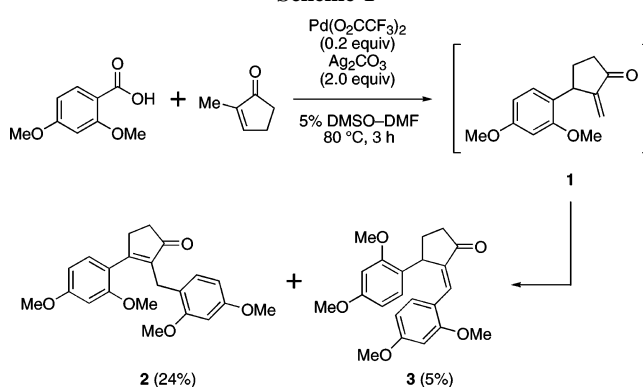
^a Conditions: carboxylic acid (1.0 mmol), 2-cycloalken-1-one (1.5 mmol), Pd(O₂CCF₃)₂ (0.2 mmol), Ag₂CO₃ (2.0 equiv), 5% DMSO–DMF at 80 °C, except as noted. ^b All yields refer to isolated, pure products. ^c Reaction conducted at 120 °C.

that Heck-type coupling is possible with a range of different 2-cycloalken-1-ones. 2-Cycloalken-1-ones of ring sizes 5

(13) **General Reaction Procedure.** A mixture of arene carboxylic acid (1.0 mmol), 2-cycloalken-1-one (1.5 mmol), Pd(O₂CCF₃)₂ (0.2 mmol), and Ag₂CO₃ (2.0 mmol) in 5% DMSO–DMF (4.2 mL) was heated at 80 or 120 °C (as noted, Table 1 or 2) under air. After the time period indicated in Table 1 or 2 (0.5–3.0 h), the reaction mixture was allowed to cool, then was diluted with ethyl acetate (30 mL), and the resulting dark suspension was filtered through a Celite pad. The filtrate was washed sequentially with an aqueous solution of hydrochloric acid (1 M, 10 mL) and water (5 × 10 mL). The product solution was dried over MgSO₄; the dried solution was filtered, and the filtrate was concentrated. Purification of the residue by flash column chromatography afforded the 3-aryl-2-cycloalken-1-one product, typically in 50–90% yield.

(entries 1 and 2), 6 (entries 4–6 and Table 1), and 7 (entry 3) were all effective substrates. Furthermore, the reaction appears to be tolerant of at least moderate steric encumbrance within the 2-cycloalken-1-one reactants, for 4-isopropyl-2-cyclohexen-1-one was found to couple as effectively as 2-cyclohexen-1-one (cf. entry 1, Table 1, with entry 4, Table 2, and entry 8, Table 1, with entry 5, Table 2), although 4,4-dimethyl-2-cyclohexen-1-one was less effective as a substrate (entry 6, Table 2). We explored only one reactant with substitution in the 2-position (2-methyl-2-cyclopenten-1-one), in which case none of the expected coupling product was obtained. Rather, the double addition products **2** and **3** were isolated (24 and 5% yield, respectively).¹⁴ These products are believed to arise by β -hydride elimination (toward the methyl group) after initial *cis* arylpalladium addition— β -hydride elimination sequence then gives rise to **2** and **3** (Scheme 1).¹⁵

Scheme 1

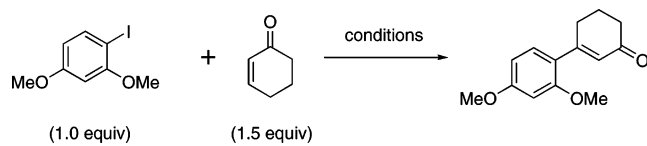


To better assess the significance of the present findings, we conducted a brief survey of conditions to achieve a similar bond construction by using the more traditional Heck reaction, initially investigating the coupling of 2,4-dimethoxy-1-iodobenzene with 2-cyclohexen-1-one, which, if successful, would form the same product that we had prepared by decarboxylative coupling (entry 1, Table 1, 92% yield). This was a demanding test case, for electron-rich aryl halides are known to be poor substrates in conventional Heck reactions.^{1b} As summarized in Table 3, the coupling of 2,4-dimethoxy-1-iodobenzene and 2-cyclohexen-1-one was indeed a sluggish and poorly efficient reaction under a range of typically conditions employed for Heck couplings.^{4a,c,f,7} Significantly, the so-called “Jeffery” conditions (entries 6 and 7, Table 3)^{4a} emerged as superior for the reaction under study; however, 10-fold higher levels of palladium than are typically recommended were required to achieve a reasonably efficient coupling (we used 0.1–0.2 equiv), and a higher reaction temperature than is typical was also necessary (80 °C). Preliminary evidence suggests that the Jeffery conditions may

(14) Structure **3** is believed to be the (*E*)-stereoisomer, as shown. This assignment is based upon one-dimensional NOESY experiments.

(15) Arcadi, A.; Chiarini, M.; Marinelli, F.; Berente, Z.; Kollar, L. *Org. Lett.* **2000**, *2*, 69–72.

Table 3. Investigation of Different Protocols in a More Conventional Heck-type Coupling Process^a

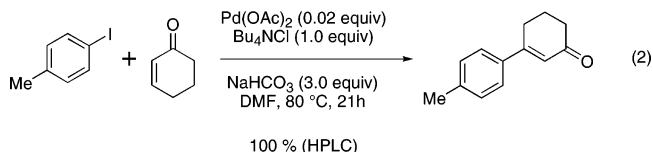
			
entry	conditions (equiv)	yield (%) ^b	ref
1	Pd(OAc) ₂ (0.1), PPh ₃ (0.2), TEA (2.0), AgNO ₃ (1.3), CH ₃ CN, 80 °C, 19 h	3	7b
2	Pd(OAc) ₂ (0.2), P(<i>o</i> -tolyl) ₃ (0.5), Ag ₂ CO ₃ (2.5), DMF, 150 °C, 3 h	12	7c
3	Pd(PPh ₃) ₄ (0.1), TEA (1.7), CH ₃ CN, 80 °C, 19 h	14	7a
4	PdCl ₂ (PPh ₃) ₂ (0.06), dppp (0.08), NaHCO ₃ (2.0), LiBr (0.5), DMF, 150 °C, 20 h	25	4f
5	Pd(OAc) ₂ (0.1), NaOAc (2.1), Bu ₄ NCl (1.0), DMF, 80 °C, 22 h	29	4c
6	Pd(OAc) ₂ (0.1), NaHCO ₃ (3.0), Bu ₄ NCl (1.0), DMF, 80 °C, 17 h	55	4a
7	Pd(OAc) ₂ (0.2), NaHCO ₃ (3.0), Bu ₄ NCl (1.0), DMF, 80 °C, 16 h	57	4a

^a Reactions were conducted using 0.05–0.08 mmol of the aryl iodide.

^b Yields were determined by HPLC analysis using 4-methoxybiphenyl as an internal standard.

be more generally useful in Heck-type couplings of 2-cycloalken-1-one reactants, for 4-iodotoluene was found to couple with 2-cyclohexen-1-one in quantitative yield using these conditions (eq 2). This is noteworthy and suggests that

traditional Heck couplings and decarboxylative Heck-type couplings with 2-cycloalken-1-ones may be somewhat complementary, for decarboxylative palladation is not efficient with substrates that lack ortho substituents.¹² It is interesting that the optimal conditions for both traditional Heck couplings and decarboxylative Heck-type couplings were phosphine-free. In both cases, phosphine additives served as effective catalyst poisons. This may be relevant mechanistically. Specifically, the final step of the “Heck-type” process, discussed in the introductory paragraphs, which in one extreme may be viewed as an anti elimination process,^{9,10} may require a highly electron-deficient organo-palladium center to function as an effective electrofuge.^{9,16}



In summary, we have presented both decarboxylative palladation and more traditional Heck processes to achieve the vinylic arylation of 2-cycloalken-1-one reactants. Although the latter must be regarded as poor reactants relative to styrene or derivatives of acrylic acid, we have nevertheless developed effective conditions for their coupling, which we envision to be a useful process.

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Supporting Information Available: Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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