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Effects of High Pressure on the Heck Reaction. Is It Possible to Control Dehydropalladation of Alkylpalladium Intermediates Having β -Hydrogens?¹

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Abstract: The palladium-catalyzed arylation of acrylates, so-called the Heck reaction, was accelerated and partially controlled under high pressure conditions.

It is well known that reactions in the solution state having negative activation volumes ($\Delta V^\ddagger < 0$), such as intermolecular incorporations, are accelerated, while those having positive activation volumes ($\Delta V^\ddagger > 0$), such as extrusion reactions, are suppressed under high pressure conditions.²

The palladium-catalyzed alkenylation or arylation of olefins is well known as the Heck reaction³ and has been widely used in the field of synthetic organic chemistry.⁴ The following three reactions in this type of catalytic carbon-carbon bond formations are considered to be accelerated under high pressure conditions, because these might have negative activation volumes; (1) formation of active Pd(0) species, (2) oxidative addition of Pd(0) to alkenyl or aryl halides, and (3) complexation of Pd species with olefins. On the contrary, decomplexation might be suppressed on the basis of their positive reaction volumes. These predictions suggest that the steps for the carbon-carbon bond formations in the Heck reaction will be accelerated and that for the termination will be retarded under high pressure conditions. We focused our study on this point and report herein the preliminary results concerning effects of high pressure on the Heck reaction.

The Predictive Influences of High Pressure on the Reactions Commonly Observed in Organometallic Chemistry

Intermolecular Incorporation ($\Delta V^\ddagger < 0$)	»	Intramolecular Reaction ($\Delta V^\ddagger \approx 0$)	»	Extrusion Reaction ($\Delta V^\ddagger > 0$)
oxidative addition complexation		insertion migration deinsertion		reductive elimination decomplexation

At first, we examined the effect of high pressure on the Heck reaction.⁵ A mixture of iodoarenes **1** (1.0 equiv), ethyl acrylate (1.0 equiv), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (2% mol), and Et_3N (2.0 equiv) in MeCN was pressured under a variety of conditions (Table 1).⁶ Comparison of Entry 1 with Entries 2 and 3 revealed that the rate of the Heck reaction was accelerated dramatically by high pressure and was completed even at 25 °C. At higher temperature, diarylated product **3a** was also formed (Entries 5 and 6), which could not be obtained either

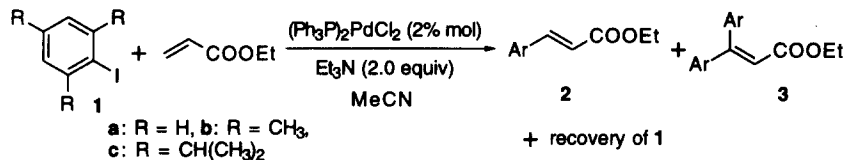


Table 1. Results of the Heck Reactions under Atmospheric and High Pressure Conditions

Entry	Starting Material	Pressure (x10 ⁵ Pa ^a)	Temperature (°C)	Reaction Time (h)	Yield (%)		
					2	3	1
1	1a	1	25	12	-	99	
2	1a	1x10 ⁴	25	12	62	32	
3	1a	1x10 ⁴	25	24	80	-	
4	1a	1	90	20	80	-	
5	1a	1x10 ⁴	90	26	54	38	
6	1a	1x10 ⁴	140 ^b	4	-	76	
7	1b	1	25	18	7	75	
8	1b	1x10 ⁴	25	20	21	67	
9	1b	1x10 ⁴	90	9	92	7	
10	1c	1x10 ⁴	90	20	37	57	

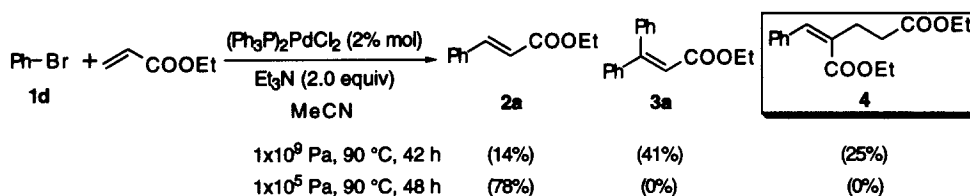
a) Pa is Pascal, one Newton per square meter: 1x10⁵ Pa = 1 bar = 1.013 atm

b) The reaction was carried out in DMF instead of MeCN.

under high pressure conditions at room temperature (Entries 2 and 3) or under atmospheric pressure conditions in boiling MeCN (Entry 4). This result tells us that the reactivities between acrylate and cinnamate toward phenylpalladium intermediate differ markedly under atmospheric pressure, but are much the same under high pressure conditions. The high pressure conditions might accelerate the complexation of the phenylpalladium intermediate with the acrylate and might cause the formation of diphenylacrylate **3a**. In the case of iodoarenes **1b** and **1c**⁷ (Entries 7–10), only cinnamate derivatives **2** were formed and 3,3-diarylacrylates **3** were not obtained at all. Since the *ortho*-dialkyl groups protect sterically the reaction center at C₃-position of cinnamate, the second arylpalladium species might not approach the reaction center of **2b** and **2c** even under high pressure conditions.

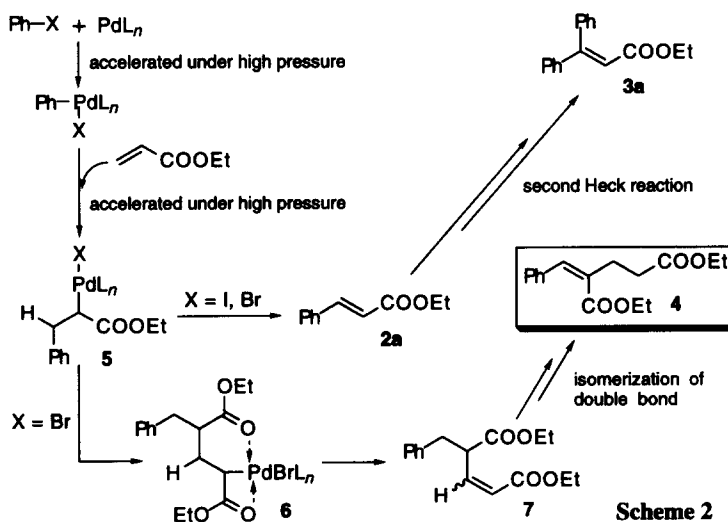
When a mixture of iodobenzene **1a** (1.0 equiv), ethyl acrylate (1.0 equiv), (Ph₃P)₂PdCl₂ (2% mol), and *N,N*-dimethylaniline (2.0 equiv) in MeCN was pressured (8.4x10⁸ Pa, 25 °C, 54 h, then 55 °C, 20 h), ethyl cinnamate **2a** (18% yield) and 3-phenylcinnamate **3a** (4%) were produced together with the recovery of iodobenzene **1a** (76%). Without an amine base, using either (Ph₃P)₂PdCl₂ or (Ph₃P)₄Pd as a catalyst, the Heck reaction did not proceed at all and resulted in recovery (92%) of **1a**. The basicity of amines influenced the rate of the Heck reaction.

The reaction of bromobenzene **1d**, instead of iodobenzene **1a**, with ethyl acrylate under the compatible conditions (1x10⁹ Pa, 90 °C, 42 h) afforded ethyl cinnamate **2a** (14% yield), ethyl 3-phenylcinnamate **3a** (41%), and **4**⁸ (25%) (Scheme 1). No polymerized product was detected by the analysis of ¹H NMR spectroscopy of the crude product. The product **4** could not be obtained from any reaction shown in Table 1 and was amazingly produced from the reaction with 2 equiv of ethyl acrylate! In the compatible conditions under atmospheric pressure (refluxed in MeCN for 48 h), the reaction only gave ethyl cinnamate **2a** (78% yield). This means that *the termination steps in the Heck reaction is not only suppressed partially but also controlled under high pressure conditions*. The production of **4** indicates two important features of this reaction: One is that the alkylpalladium intermediates even having β-hydrogens could react further with the acrylate under these conditions^{9–11} and the other is that the carbon-carbon bond formation catalyzed by



Scheme 1

palladium complexes was terminated when two molecules of the acrylate were incorporated. Comparison of Entry 3 with the result shown in Scheme 1 also tells us that the kind of halogen on the intermediary alkylpalladium species is playing a key role to control the course of the reaction with the acrylate. The proposed mechanism is shown in Scheme 2. Using iodobenzene, the alkylpalladium intermediate **5** gave cinnamate **2a** via the β -elimination and then the second Heck reaction followed. In the case of bromobenzene, some part of **5** behaved like in the case of iodobenzene. The other part of **5** might partially have the "living" nature^{12,13} and reacted with the second acrylate to afford **6**, because the complexation of **5** with the acrylate might be accelerated under forcing conditions. The intermediate **6** might be suppressed for further reaction with the acrylate because of its stabilization by the chelation of two ester groups, and finally affords **4** via the β -elimination followed by the palladium-catalyzed isomerization of the olefin.



Scheme 2

In conclusion, the Heck reaction is accelerated dramatically and is partially controlled under high pressure conditions depending on the kind of alkylpalladium intermediates. We are now investigating the role of halogens and studying the mechanism of this reaction.

References and Notes

- 1) This paper is dedicated to Professor Ei-ichi Negishi on the occasion of his 60th birthday.
- 2) The typical reviews for high pressure reaction: a) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407. b) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis*, **1985**, 1 and 999.
- 3) a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. b) Heck, R. F. *Org. React.* **1982**, *27*, 345. c) Heck, R. F. *Palladium Reagents in Organic Syntheses*, Academic Press, London, **1985**.

- 4) An excellent review has been published recently dealing with the applications of the Heck reaction in the field of synthetic organic chemistry: de Meijere, A.; Meyer, F. E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.
- 5) Recently the Heck reaction under high pressure conditions was investigated in two different groups, but none of them discussed on the influence of high pressure to the steps of the termination in the Heck reaction: a) Hillers, S.; Reiser, O. *Tetrahedron Lett.* **1993**, *34*, 5265. b) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *Synlett*, **1994**, 189.
- 6) All reactions under high pressure conditions were carried out in 4 mL Teflon tube using Koukouatsu Kiki PK 15 B instrument.
- 7) Iodoarenes **1b** and **1c** were prepared according to the literature: Suzuki, H. *Org. Synth.* **1988**, *Coll. Vol. 6*, 700.
- 8) **4**: >99% Z selectivity. IR (neat) 1740, 1712 cm^{-1} . ^1H NMR (Me_4Si , CDCl_3) δ : 1.24 (t, $J = 7.0$ Hz, 3 H), 1.36 (t, $J = 7.0$ Hz, 3 H), 2.55-2.6 (m, 2 H), 2.85-2.9 (m, 2 H), 4.11 (q, $J = 7.0$ Hz, 2 H), 4.28 (q, $J = 7.0$ Hz, 2 H), 7.25-7.4 (m, 5 H), 7.73 (s, 1 H). ^{13}C NMR (CDCl_3) δ : 14.25, 14.38, 23.16, 33.63, 60.54, 61.04, 128.66, 128.69, 129.24, 131.54, 135.38, 140.22, 167.92, 172.85. EI-MS 276 (M^+), 230, 202, 129 (100%). High-resolution MS calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ (M^+) 276.1361, found 276.1325. The stereochemistry of the double bond of **4** was determined by NOE experiment.
- 9) A few examples are reported in which cyclic carbopalladations proceed via alkylpalladium intermediates having β -hydrogens: Grigg, R.; Mitchell, T. R. B.; Ramasubbu, A. *J. Chem. Soc., Chem. Commun.* **1979**, 669.
- 10) To our knowledge, there is no report concerning with that two molecules of olefins are incorporated in the intermolecular Heck reaction.
- 11) There is an example that the alkylpalladium intermediates having β -hydrogens cross-coupled with vinylstannanes intermolecularly before β -eliminations: Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta.* **1993**, *76*, 1266.
- 12) The "living" nature of organopalladium species is pointed out by Professor Ei-ichi Negishi. The "living" is used for the species of alkynyl-, alkenyl-, allyl-, and alkylpalladiums lacking β -hydrogens which don't readily undergo dehydropalladations. See: a) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323. b) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron*, **1993**, *49*, 5471.
- 13) The "living" nature of organopalladium species were utilized both in the cascade mode cyclic carbopalladations and in the polymerizations: a) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93. b) Catellani, M.; Chiusoli, G. P.; Sgarabotto, P. *J. Organomet. Chem.* **1982**, *240*, 311. c) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. d) Wu, G.; Lamaty, F.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2507. e) Zhang, Y.; Wu, G.; Agnel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590. f) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. g) Negishi, E.; Harring, L. S.; Owczarczyk, Z.; Mohamud, M. M.; Ay, M. *Tetrahedron Lett.* **1992**, *33*, 3253. h) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E. *J. Am. Chem. Soc.* **1994**, *116*, 7923. i) Silverberg, L. J.; Wu, G.; Rheingold, A. L.; Heck, R. L. *J. Organomet. Chem.* **1991**, *409*, 411. j) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255. m) Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923. n) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.* **1992**, *114*, 9836. o) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. p) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2329. q) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ticca, D. *J. Pure Appl. Chem.* **1992**, *64*, 1813. r) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. s) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. t) Reiser, O.; Weber, M.; de Meijere, A. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1037. u) Meyer, F. E.; de Meijere, A. *Synlett*, **1991**, 777. v) Albrecht, K.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 2539. w) Grigg, R.; Fretwell, P.; Meerholtz, C.; Sridharan, V. *Tetrahedron*, **1994**, *50*, 359. x) Grigg, R. *J. Heterocyclic Chem.* **1994**, *31*, 631. y) Suzuki, M. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 141. z) See also ref. 4) and 11), and references cited therein.

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