Microwave-Promoted Palladium-Catalyzed Coupling Reactions

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Received July 9, 1996

Introduction

The intermolecular Heck reaction of aryl halides or aryl triflates with olefins is of the utmost importance in organic synthesis.[1] With a few exceptions,[2−4] most substrates for coupling require reaction temperatures of 70−100 °C[1e] and reaction times ranging from hours to days for full conversion. Attempts to reduce the reaction time by enhancing the temperature are seldom effective due to collapse of the catalytic system.[1d,5,6] Therefore, access to alternative and general synthetic procedures that permit fast coupling reactions would be valuable, in particular with respect to the obvious applications of such procedures to combinatorial chemistry.[7]

Many examples of the benefits of microwave irradiation, including reduction of reaction times and electricity costs, have been reported.[8] Among the transformations performed are reactions of double bonds, including hydrogenation, catalyzed by RaNi or Pd/C,[9] hydrosilylation, in the presence of CuCl and TMEDA,[10] and addition of chlorinated hydrocarbons, catalyzed by a Cu(I) complex.[11] Furthermore, vinylic substitution by the Baylis−Hillman reaction can be achieved with substantial reduction of reaction times.[12] The present investigation has been devoted to a study of the effect of microwave irradiation on the Heck arylation and briefly on the related Suzuki[13] and Stille[14] reactions, in which labile organotransition metal intermediates play a pivotal role in the catalytic cycle. We herein report that these palladium-catalyzed coupling reactions can be accomplished with reaction times ranging from 2.8 to 7.0 min and that good yields were observed in most cases.

Results and Discussion

We have reacted aryl iodides, aryl bromides, and aryl triflates with various olefins. These substrates were chosen to permit comparison of microwave-assisted reactions to conventionally heated reactions, with respect to chemo- and regioselectivity, as well as double bond isomerization. The reactions were conducted under nitrogen in sealed Pyrex vessels, and a commercially available batch reactor producing continuous irradiation was used. The primary objective was the minimization of reaction times, and the irradiation power was altered to allow full conversion of the arylating agents in less than 7.0 min. With the exception of reaction scale, solvent, and heating procedure, the reactions were performed under reaction conditions identical to the original procedures as described in the references cited, in order to enable an accurate comparison. Our initial screening experiments revealed that the microwave-promoted Heck coupling under classical conditions (without solvent or with trialkylamine as solvent) did not proceed satisfactorily.[15] The addition of DMF, a microwave-active solvent,[8,15] drastically expedited the reactions, and the desired compounds were obtained within minutes in good yield. In the Suzuki and Stille cross-couplings, the combination of ethanol/water/DME and *N*-methyl-2-pyrrolidone (NMP), respectively, was found to interact sufficiently strongly with microwaves and generate the heat required to promote the reactions.

The preparative results are summarized in Table 1. Methyl acrylate was converted smoothly in 3.8 min at 60 watt (W) to the corresponding cinnamic acid ester in the presence of DMF (Table 1, entries 1 and 2).[16,17] The same transformation could be conducted at a lower

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[1] For reviews on the Heck reaction see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp 854. (c) Heck, R. F. *Palladium Reagents in Organic Synthesis;* Academic Press: London, 1985; pp 276. (d) Heck, R. F. *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 833. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (f) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (g) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Chemistry*; John Wiley & Sons: Chichester, **1995**; pp 125. For Heck arylation of heteroatom-substituted double bonds see: (h) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

[2] Addition of phase-transfer catalysts, such as Bu_4NCl, may have a favorable effect on the reaction temperature. (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Larock, R. C. *Pure Appl. Chem.* **1990**, *62*, 653. (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113.

[3] High pressure is known to accelerate the Heck reaction. (a) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. *Synlett* **1994**, 189. (b) Sugihara, T.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 5547.

[4] Arylation of electron-rich olefins employing bidentate nitrogen ligands were performed at 40 °C. (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *Synlett* **1992**, 871. (b) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421.

[5] (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A: Chem.* **1995**, *103* 133. (b) A palladacycle acting as an efficient catalyst at up to 140 °C was recently prepared from $Pd(OAc)_2$ and $(o\text{-tol})_3P$. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C. P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.

[6] Heck reactions can be carried out with aryl chlorides at 140−160 °C when electron-rich chelating ligands are used. (a) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995, (b) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993,** *12*, 4734, (c) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

[7] For recent reviews, see: (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527. (b) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (c) DeWitt, S. H.; Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 114. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Ibid.* **1996**, *29*, 123. (e) Ellman, J. A. *Ibid.* **1996**, *29*, 132. (f) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Ibid.* **1996**, *29*, 144. (g) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555.

[8] (a) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1. (b) Abramovitch, R. A. *Org. Prep. Proc. Int.* **1991**, *23*, 683. (c) Loupy, A.; Bram, G.; Sansoulet, J. *New J. Chem.* **1992**, *16*, 233. (d) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (e) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. For a theoretical background see also: (f) Neas, E. D.; Collins, M. J. *Introduction to Microwave Sample Preparation;* Kingston, H. M., Jassie, L. B., Eds.; American Chemical Society: Washington, DC, 1988; p 7.

[9] (a) Bose, A. K.; Banik, B. K.; Barakat, K. J.; Manhas, M. S. *Synlett* **1993**, 575. (b) Leskovsek, S.; Smidovnik, A.; Koloini, T. *J. Org. Chem.* **1994**, *59*, 7433.

[10] Abramovitch, R. A.; Abramovitch, D. A.; Iyanar, K.; Tamareselvy, K. *Tetrahedron Lett.* **1991**, *32*, 5251.

[11] Adámek, F.; Hájek, M. *Tetrahedron Lett.* **1992**, *33*, 2039.

[12] Kundu, M. K.; Mukherjee, S. B.; Balu, N.; Padmakumar, R.; Bhat, S. V. *Synlett* **1994**, 444. See also ref 8d.

[13] For reviews on the Suzuki reaction see: (a) Martin, A. R.; Yang, Y. *Acta Chem., Scand.* **1993**, *47*, 221. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[14] For reviews on the Stille reaction see; (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Michell, T. N. *Synthesis* **1992**, 803. (c) Ritter, K. *Synthesis* **1993**, 735. (d) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.

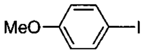
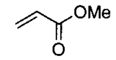
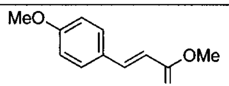
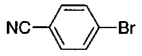
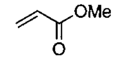
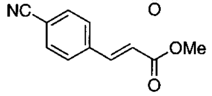
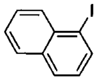
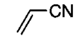
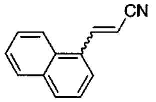
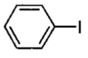
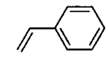
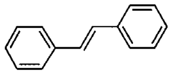
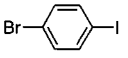
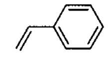
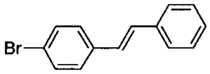
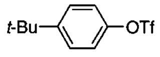
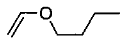
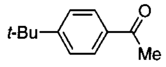
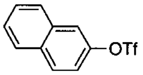
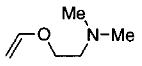
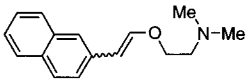
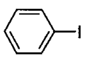
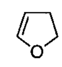
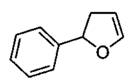
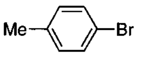
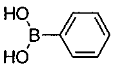
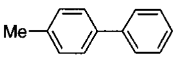
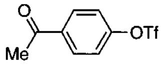
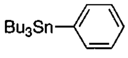
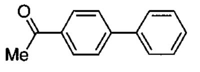
[15] A solvent with a high dipole moment (more correctly; a high dielectric loss tangent) is beneficial for efficient absorption of microwave energy. Trialkylamines are known to couple less effectively with microwave radiation than DMF. Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1988**, *66*, 17. See also ref 8.

[16] Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

[17] Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903.

S0022-3263(96)01299-6 CCC: $12.00

Table 1. Fast Palladium-Catalyzed Coupling Reactions under Microwave Irradiation*

entry	aryl halide or aryl triflate	olefin or organometallic	time and microwave power[a]	product		isolated yield[b]	thermal heating time (min)	yield
1			$\xrightarrow[\text{Pd(OAc)}_2\text{, DMF}]{\text{3.8 min 60 W}}$		1	70%[c]	300	68%[d]
2			$\xrightarrow[\substack{\text{Pd(OAc)}_2\text{, DMF}\\ o\text{-(tol)}_3\text{P}}]{\text{3.8 min 60 W}}$		2	94%[c]	120	70%[e]
3			$\xrightarrow[\text{Pd(OAc)}_2\text{, DMF}]{\text{3.8 min 80 W}}$		3	90%[c]		
4			$\xrightarrow[\text{Pd(OAc)}_2\text{, DMF}]{\text{2.8 min 90 W}}$		4	87%[c]	120	75%[d]
5			$\xrightarrow[\text{Pd(OAc)}_2\text{, DMF}]{\text{4.8 min 60 W}}$		5	63%[c]	1020	64%[f]
6			$\xrightarrow[\substack{\text{Pd(OAc)}_2\text{, DPPP}\\ \text{DMF, H}_2\text{O}}]{\text{2.8 min 55 W}}$		6	77%[g,h]		
7			$\xrightarrow[\substack{\text{Pd(OAc)}_2\text{, Ph}_3\text{P}\\ \text{DMF}}]{\text{7.0 min 35 W}}$		7	87%[g]	540	93%[i]
8			$\xrightarrow[\substack{\text{Pd(OAc)}_2\text{, Ph}_3\text{P}\\ \text{DMF, Bu}_4\text{NCl}}]{\text{6.0 min 30 W}}$		8	58%[j]	1440	76%[k]
9			$\xrightarrow[\substack{\text{Pd(Ph}_3\text{P)}_4\text{, EtOH}\\ \text{DME, H}_2\text{O}}]{\text{2.8 min 55 W}}$		9	55%[g,l]	360	88%[m]
10			$\xrightarrow[\substack{\text{Pd}_2\text{dba}_3\text{, Ph}_3\text{As}\\ \text{LiCl, NMP}}]{\text{2.8 min 50 W}}$		10	68%[g]	4200	82%[n]

*Reactions were performed on a 1.0 mmol scale in sealed Pyrex tubes under nitrogen essentially following the literature procedures, although heating was carried out utilizing microwave irradiation. >95% conversion in all cases. [a] Continuous irradiation (2450 MHz). [b] Based on the aryl halide or aryl triflate. >95% purity by GC-MS. [c] 0.50 mL of DMF was added to the reaction mixture. [d] See ref 16. [e] See ref 17. [f] See ref 19. [g] Carried out in a reduced amount of solvent. [h] 0.075 mL of water was added to the reaction mixture. [i] See ref 21c. [j] Carried out on a 0.50 mmol scale. Olefin/iodobenzene = 10/1. [k] See ref 23. [l] Reaction conditions modified according to Gronowitz. See ref 25b. [m] See ref 25. [n] See ref 26.

microwave power, although a longer reaction time was required. In order to achieve full consumption of 1-iodonaphthalene in a reaction with acrylonitrile in the same reaction time, a moderate increase in the power level (80 W) was needed. While methyl acrylate provided the *E* isomer exclusively, the reaction with acrylonitrile produced a mixture of the *E* and *Z* isomers ($E/Z = 4/1$) as expected from a related standard reaction[18] with this olefin (Table 1, entry 3). Arylation of styrene with iodobenzene[16] or 4-bromo-1-iodobenzene[19] gave the terminal product with high selectivity, in accordance with the original procedures (Table 1, entries 4 and 5). The result from the latter reaction shows that the microwave irradiation provides the same selectivity, with respect to halide displacement as compared to the original reaction,[19] and substitution of the iodo atom occurs exclusively. Products derived from bromo-substitution were not detected. To study the regioselectivity with regard to the direction of insertion, alkyl vinyl ethers[1f,1h] were selected as suitable substrates. Procedures have been developed that allow either electronically controlled internal arylation by application of bidentate ligands[20] or, alternatively, chelation-controlled terminal arylation.[21] Microwave-assisted arylation of butyl vinyl ether with aryl triflates provided mixtures of internally arylated vinyl ether and the corresponding acetophenone. However, 4-*tert*-butylacetophenone could be isolated in good yield after conducting the reaction in presence of a minor amount of water[22] (Table 1, entry 6). The reaction of [2-(dimethylamino)ethoxy]ethene with 2-naphthyl triflate constitutes an example of a relatively sluggish reaction that requires 9 h at 60 °C to afford fair yields of coupled product.[21c] In the microwave-assisted reaction we found it essential to employ a low microwave power, 35 W, to avoid decomposition of the catalytic system (Table 1, entry 7). A longer reaction time, 7.0 min, was therefore needed. A highly regioselective arylation at the terminal carbon occurred, and equal amounts of the *E* and *Z* isomers were formed, in full agreement with the reference procedures.[21c] Higher microwave power resulted in incomplete consumption of the aryl triflate,

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(18) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265.

(19) Plevyak, J. E.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1979**, *44*, 4078.

(20) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3654. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.

(21) (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Acta. Chem. Scand.* **1993**, *47*, 212. (c) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285.

(22) Many Heck arylations are known to proceed smoothly in water or in water/organic solvent mixtures. Leading references. (a) Bumagin, N. A.; More, P. G.; Beletskaya I. P. *J. Organomet. Chem.* **1989**, *371*, 397. (b) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (c) Zhang, H.-C.; Daves, G. D., Jr. *Organometallics* **1993**, *12*, 1499. (d) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051. (e) Reardon, P.; Metts, S.; Crittendon, C.; Daugherity, P.; Parsons, E. J. *Organometallics* **1995**, *14*, 3810. (f) Kiji, J.; Okano, T.; Hasegawa, T. *J. Mol. Catal. A: Chem.* **1995**, *97*, 73. See also: (g) Davison, J. B.; Simon, N. M.; Sojka, S. A. *J. Mol. Catal.* **1984**, *22*, 349. (h) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324.

clearly demonstrating the crucial interplay of reaction time and microwave power. Microwave-assisted arylation of 2,3-dihydrofuran according to Larock's original procedure C[23,24] furnished a mixture of two isomers (Table 1, entry 8). 2-Phenyl-2,3-dihydrofuran was isolated in fair yield (58%). A reaction time of 6.0 min at 30 W was needed in this case, in comparison to 24 h at 80 °C when traditional heating was employed.

Suzuki coupling of phenyl boronic acid with 4-bromotoluene[25] as well as Stille coupling of 4-acetylphenyl triflate[26] proceeded rapidly with microwave irradiation (Table 1, entries 9 and 10). The Suzuki coupling was accompanied by biphenyl formation. In the Stille reaction we encountered the formation of minor amounts of 4-butylacetophenone, which is formed frequently also when standard heating procedures are used.[26,27]

Two Heck arylations were also performed with thermal heating (preheated oil bath) at high temperature (Table 1, entries 3 and 8). For the standard heating experiments we found an optimal *initial* conversion rate of the aryl halides at 150−170 °C. The reaction in entry 3, which represents the most simple system in Table 1, is performed with no added ligand, produces a stable product, and can be conducted at 150 °C in approximately the same reaction times as with microwave technology. A minimum amount of side products are formed with both heating techniques. The reaction in entry 8 (Table 1) represents a more complex system. Thermal heating procedures (125−150 °C) produce complex product mixtures, in our case affording less than 20% of the expected 2-phenyl-2,3-dihydrofuran. The origin of this change in product pattern may result from the advantages with microwave heating, e.g., elimination of wall effects and low thermal gradients within the reaction mixture.[8d]

In summary, by employing a series of differing types of olefins, exhibiting characteristic reaction profiles, we have shown that similar product patterns are delivered in microwave-assisted Heck reactions as in reactions with traditional thermal heating. The catalytic system survives microwave irradiation, and full conversion can be achieved in a few minutes. Although we have studied only a limited number of reactions, we believe that microwave-promoted palladium-catalyzed coupling reactions should provide an attractive complement to other procedures, particularly in cases where fast reactions are desired.

Experimental Section

Procedures. Microwave heating was carried out with a MicroWell 10 single-mode microwave cavity operating at 2450 MHz from Labwell AB, Uppsala, Sweden. The reactions were performed under nitrogen in heavy-walled Pyrex tubes (8 mL, l = 150 mm) sealed with a silicon septum. If overpressurization occurred, this septum was distorted. Silicone septa (110.623−18) and screwcaps with aperture (110.627−18) were purchased from KEBO Lab AB, S-163 94 Spånga, Sweden. The reaction volume filled not more than 1/5th of the total volume of the tube, thereby allowing head space for pressure buildup during the microwave treatment. All couplings were conducted in the absence of stirring. The tube was allowed to cool before being opened carefully in a fume cupboard. Small samples were removed and partitioned between dichloromethane (DCM) and water, and the organic phase was analyzed by GC−MS. ^{1}H and ^{13}C NMR spectra were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ solution. Mass spectra were determined at 70 eV (EI). Melting points were determined with an electrothermal melting point apparatus. Column chromatography was performed on silica using Kieselgel S (0.032−0.063 mm, Riedel-de Haen).

Materials. Unless otherwise noted, starting materials, ligands, additives and solvents were obtained from commercial suppliers and used without further purification. Palladium acetate was obtained from Merck-Schuchardt, and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was obtained from Aldrich Co. and used as received. Tetrakis(triphenylphosphine)palladium(0) ($Pd(Ph_3P)_4$) was prepared according to the method described by Coulson.[28] Triphenylphosphine (Ph_3P) was recrystallized from ethanol. Phenyltributyltin[29] and [2-(dimethylamino)ethoxy]ethene[21a] were prepared as described elsewhere. The aryl triflates were synthesized from the corresponding phenols using an excess of triflic anhydride and 2,4,6-trimethylpyridine, essentially following a literature procedure,[30] and are known compounds.[21c,31,32] Structure and purity of isolated compounds were determined by NMR, melting point determination, and GC−MS (>95% purity). Products **1**,[33] **2**,[17,34] **3**,[35] **4**,[36] **5**,[19] **7**,[21c] **8**,[37] **9**,[36] and **10**[36] were described previously. Compound **6** is commercially available (Aldrich Co.), and the structure was determined by comparison with an authentic sample.

Caution! It is essential that great precautions are taken when carrying out reactions in sealed vessels due to the rapid increase in temperature and pressure associated with microwave-promoted superheating of organic material.[38] ***Unless an appropriate septum is used as a pressure relief device, the high pressure could result in an explosion.***

(*E*)-Methyl 4-Methoxycinnamate (1).[33] In the reaction tube were mixed 4-iodoanisole (0.234 g, 1.00 mmol), methyl acrylate (0.108 g, 1.25 mmol), palladium acetate (0.00225 g, 0.010 mmol), tributylamine (0.185 g, 1.00 mmol), and DMF (0.50 mL) under nitrogen. The contents of the flask were irradiated for 3.8 min with a power of 60 W. After cooling, the product mixture was poured into water (25 mL) and was extracted with DCM (3 × 25 mL). The combined extracts were washed with water (25 mL) and concentrated to an oil. The crude product was purified by column chromatography on silica gel using isohexane/diethyl ether (4/1) as the eluent. The yield was 70% (white crystals).

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support.

Supporting Information Available: Experimental details for compounds **2**−**10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9612990

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