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Highly Regio- and Stereoselective Heck Reaction of Allylic Esters with Arenediazonium Salts: Application to the Synthesis of Kavalactones

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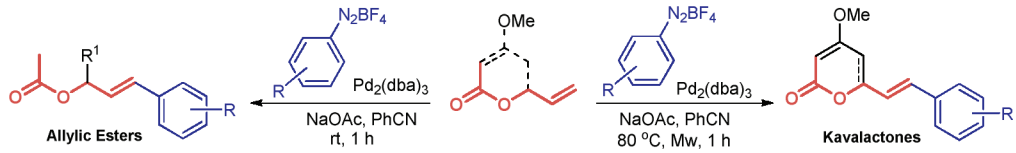
ABSTRACT



A highly efficient palladium-catalyzed Heck reaction of allylic esters with arenediazonium salts is described. The reaction proceeds under mild conditions, with excellent to total regio- and stereochemical control and with retention of the traditional leaving group. Furthermore, the generality of the present methodology is illustrated by the short total synthesis of the natural kavalactones, yangonine, (±)-methysticin, and (±)-dihydromethysticin.

The Heck arylation of olefins has been a powerful tool for the efficient formation of Csp^2-Csp^2 bonds.[1] When allylic alcohols are used as substrates for the Heck arylation, a problem with the regioselectivity arises leading to mixtures of β and γ aryl allylic alcohols, together with the formation of carbonyl products via isomerization of the allylic double bond.[2] In addition, the use of allylic esters poses additional challenges since these are common substrates for the well-known Tsuji−Trost reaction in which Pd(0) undergoes oxidative addition to the allylic C−O bond followed by the formation of a π-allyl palladium species.[3] However, some recent reports concerning the Heck reaction of allylic esters have demonstrated selectivity in favor of the Heck products when using aryl halides,[4,5] boronic acids,[6] or iodonium salts.[7]

In this regard, it is worth mentioning the recent reports of Jiao and co-workers which use aryl iodides and bromides in the presence of $AgCO_3$ at refluxing benzene for several hours[4] and the use of a very interesting oxidative Heck

(1) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I. Ed.; Wiley-Interscience: New York, 2002. (d) Tsuji, J. *Palladium Reagents and Catalyst*; Wiley: Chichester, U.K., 2004.

(2) (a) Calò, V.; Nacci, A.; Monopoli, A.; Ferola, V. *J. Org. Chem.* **2007**, *72*, 2596. (b) Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153. (c) Ambrogio, I.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sgalla, S. *Synlett* **2009**, 620. (d) Zawisza, A. M.; Ganchegui, B.; González, I.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Mol. Catal. A: Chem.* **2008**, *283*, 140. (e) Liu, S.; Thomson, N.; Pettman, A.; Hyder, Z.; Mo, J.; Xiao, J. *J. Mol. Catal. A: Chem.* **2008**, *279*, 210. (f) Batt, F.; Gozzi, C.; Fache, F. *Chem. Commun.* **2008**, 5830. (g) Scrivanti, A.; Bertoldini, M.; Beghetto, V.; Matteoli, U. *Tetrahedron* **2008**, *64*, 543. (h) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2007**, *349*, 2572. (i) Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2005**, 1367. (j) Kang, S.; Lee, H.; Jang, S.; Kim, T.; Pyun, S. *J. Org. Chem.* **1996**, *61*, 2604. (k) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073. (l) Ono, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1994**, *35*, 4133. (m) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121. (n) Masllorens, J.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822. (o) Barbero, M.; Cadamuro, S.; Dughera, S. *Synthesis* **2006**, 3443. (p) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 973. (q) Perez, R.; Veronese, D.; Coelho, F.; Antunes, O. A. C. *Tetrahedron Lett.* **2006**, *47*, 1325. (r) Sengupta, S.; Sadhukhan, S. K. *Tetrahedron Lett.* **1998**, *39*, 1237.

(3) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *106*, 395.

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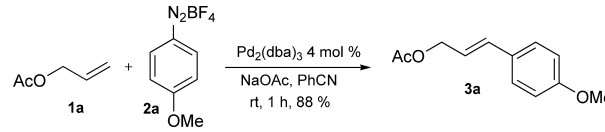
reaction with arylboronic acids to perform the regioselective arylation of allylic esters.[6b] In spite of these important advances by the Jiao group, their best results were obtained with aryl iodides under relatively harsh conditions or, in the case of the oxidative Heck arylations, with an excess of the key allylic esters in a sealed tube and the presence of oxidants and other additives in superstoichiometric amounts (AgOAc, CuF_2, and KHF_2).

Herein we present part of our ongoing research which uses a very mild, operationally simple, and synthetically attractive alternative for the highly stereo- and regioselective Heck arylation of allylic esters employing arenediazonium salts. This new Heck arylation protocol was also extended to a vinylic lactone—a conformationally restricted "allylic ester"—which was key to the efficient and straightforward synthesis of yangonin, (±)-methysticin, and (±)-dihydromethysticin, which constitute some of the major components of the kava extracts.[8] These syntheses illustrate the point that these new Heck arylations of allylic esters can also be performed without the assistance of the ester carbonyl, although more vigorous conditions are needed in these cases.

Among the several arylating agents available to perform the Heck reaction, the arenediazonium salts offer considerable advantages over traditional electrophiles.[9] They undergo an extremely facile oxidative addition with Pd(0), operating under "ligand-free" conditions to generate a highly reactive cationic ArPd(II) species.[10]

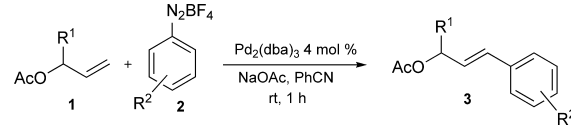
We started our investigation of the Heck arylation with allyl acetate **1a** using optimal conditions described in our recent work.[11] This procedure uses the more complex benzonitrile as solvent, $Pd_2(dba)_3$ as catalyst, and NaOAc as base. Under these conditions, the Heck adduct **3a** was obtained in 88% yield, *at room temperature after only 1 h, with total regio- and stereochemical control in favor the E isomer* (Scheme 1). The desired Heck adduct was obtained with retention of the traditional leaving group, and no product was observed from the usual π-allyl palladium pathway, the so-called Tsuji−Trost reaction. Attempts at fine-tuning the reaction parameters such as lowering the amount of palladium from 4 to 2 mol % and changing the solvent from PhCN to MeCN resulted in decreased yields.

Scheme 1. Heck Arylation of Allyl Acetate **1a**



With these initial results in hands, we decided to extend the scope of the arylation reaction to other allylic esters as well as to investigate a broader range of arenediazonium salts with respect to their electronic nature. As shown in Table 1,

Table 1. Heck Arylation of Allylic Esters **1** with Diazonium Salts **2**



entry	R^1	R^2	product yield (%)
1	H	4-OMe	**3a**, 88
2	*n*-Bu	4-OMe	**3b**, 68
3	CH_2OAc	4-OMe	**3c**, 95
4	CH_2OAc	H	**3d**, 88
5	CH_2OAc	4-Me	**3e**, 96
6	CH_2OAc	2-naphthyl	**3f**, 96
7	CH_2OAc	3,4-$(OMe)_2$	**3g**, 92
8	CH_2OAc	4-F	**3h**, 95
9	CH_2OAc	4-Cl	**3i**, 93
10	CH_2OAc	4-Br	**3j**, 89
11	CH_2OAc	4-I	**3k**, 95
12	CH_2OAc	3-NO_2	**3l**, 92
13	CH_2OAc	2-OMe	**3m**, 85
14	CH_2OAc	3,4-(−OCH_2O−)	**3n**, 93

a variety of substitution patterns are tolerated in the arenediazonium salts. Both electron-rich and electron-poor arenediazonium salts furnish the desired products in high yields. Halogen substituents are also well tolerated under the reaction conditions, and it is particularly important to mention that 4-iodobenzenediazonium tetrafluoroborate underwent selective oxidative addition at the C−N_2 bond, yielding the iodine-containing product **3k** in isolated high yields.

In all cases, the reactions proceeded within 1 h, at room temperature, with the Heck adducts formed with complete regiochemical control, with C−C bond formation exclusively at the terminal position of the double bond. Additionally, the arylation process is highly stereoselective, providing the *E* isomer as the only observable product. The only exception was the more congested 2-methoxybenzenediazonium salt (entry 13), providing the *E* Heck adduct together with the *Z* stereoisomer and the product of internal arylation in a ratio of 30:1:1.

The nature of the electrofuge group on the allylic moiety is an important aspect of this reaction. When the acetate

(4) Pan, D.; Chen, A.; Su.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4729.

(5) For Heck arylations followed by β-acetoxy elimination, see: (a) Mariampillai, B.; Herse, C.; Lautens, M. *Org. Lett.* **2005**, *7*, 4745. (b) Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2005**, *127*, 72.

(6) (a) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076. (b) Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980.

(7) Aydin, J.; Larsson, J. M.; Selander, N.; Szabó, K. J. *Org. Lett.* **2009**, *11*, 2852.

(8) (a) Bilia, A. R.; Scalise, L.; Bergonzi, M. C.; Vincieri, F. F. *J. Chromatogr. B* **2004**, *812*, 203. (b) Côté, C. S.; Kor, C.; Cohen, J.; Auclair, K. *Biochem. Biophys. Res. Commun.* **2004**, *322*, 147.

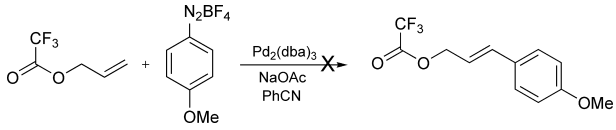
(9) Roglans, A.; Pla-Quitana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622.

(10) (a) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (b) Meira, P. R. R.; Moro, A. V.; Correia, C. R. D. *Synthesis* **2007**, 2279. (c) Burtoloso, A. C. B.; Garcia, A. L. L.; Miranda, K. C.; Correia, C. R. D. *Synlett* **2006**, 3145. (d) Pastre, J. C.; Correia, C. R. D. *Org. Lett.* **2006**, *8*, 1657. (e) da Silva, K. P.; Godoi, M. N.; Correia, C. R. D. *Org. Lett.* **2007**, *9*, 2815. For other Pd pre-catalysts operating under ligand-free conditions, see: Gruber, A. S.; Pozebon, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2001**, *42*, 7345.

(11) Moro, A. V.; Cardoso, F. S. P.; Correia, C. R. D. *Tetrahedron Lett.* **2008**, *49*, 5668.

group was replaced by the trifluoroacetate no Heck adduct was obtained. In this specific case, we believe that the π-allyl palladium complex is probably formed, which in the absence of a suitable nucleophile halts the catalytic cycle, leading to decomposition of the active palladium species (Scheme 2).

Scheme 2

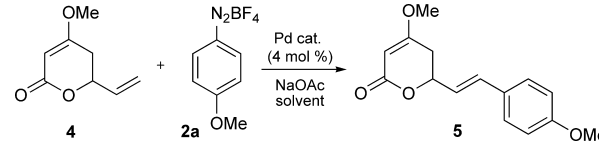


The putative catalytic cycle proposed for the Heck arylation of allylic esters with arenediazonium tetrafluoroborates is shown in Scheme 3 and parallels the one described recently by Jiao and co-workers.[4] Oxidative addition of the Pd(0) species into the C−N_2 bond occur with exclusion of nitrogen to produce a cationic palladium species **B**. This arenepalladium intermediate then coordinates to the olefin and to the acetate carbonyl oxygen. The insertion of the aryl group to the γ-position is favored by steric reasons as well as by the formation of a chelated struture **D**. Such an arrangement probably explains the high regioselectivity observed during the migratory insertion. In this step, the aryl group is transferred to the terminal carbon while the cationic palladium stays complexed to the oxygen of the ester group. This structure hinders a *syn*-relationship between the palladium and the hydrogen atom on the carbon bearing the ester group, therefore favoring β-elimination with the benzylic hydrogen atom.[2a] Thus, subsequent rotation of the C−C bond occurs to minimize steric interaction followed by β-H elimination to give the corresponding Heck adduct and the cationic hydropalladium species **F**. Coordination of cationic palladium in a six-membered ring at species **E** prevents the β-elimination of the hydrogen next to the alcoholic oxygen of the ester group. Neutralization of the hydropalladium by sodium acetate (the reductive elimination step) regenerates the Pd(0), which reinitiates the catalytic cycle.

Motivated by the success of the Heck arylation of allylic esters under mild conditions, we turned our attention to the arylation of the lactone **4**, which is structurally related to the allylic esters investigated, except for its cyclic nature. Besides putting the new methodology to a considerable new challenge, such an investigation might shed some light on the actual participation of the ester carbonyl during Heck arylation and its potential limitations. Moreover, an efficient arylation of this cyclic substrate is synthetically relevant, since this can provide advanced intermediates in the total synthesis of the kavalactone natural products such as yangonine and methysticin.[12] Yangonine is a major component of the kava extracts that is reported to display biological activities such as anxiolytic, sedative, anti-inflammatory, and analgesic.[13]

Applying the conditions depicted in Table 1 to the olefin **4**, the Heck arylation product was obtained in only 30% isolated yield, thus confirming, at least in part, the ancillary participation of the carbonyl group in the Heck process. Due to the decreased reactivity of this unsaturated lactone under those conditions, a larger screening of the reaction parameters was necessary. Therefore, different palladium catalysts, solvents, and microwave heating were evaluated as depicted in Table 2.

Table 2. Screening of the Reaction Conditions for the Heck Arylation of Olefin **4** with Arenediazonium **2a**

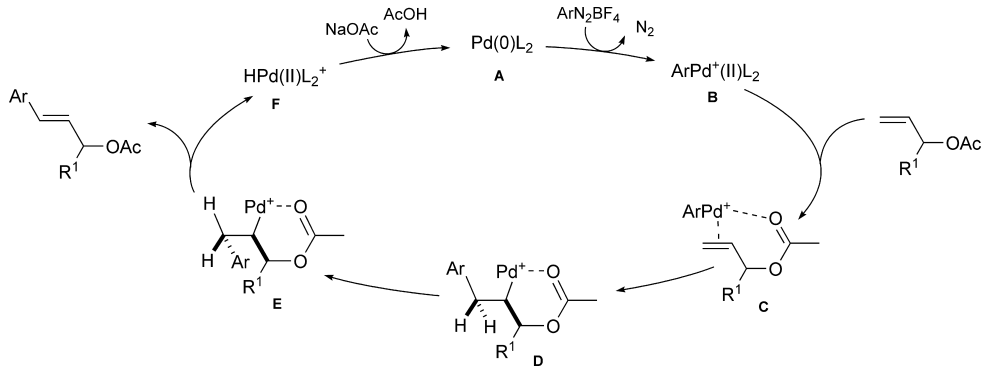


entry	Pd cat.	solvent	T (°C)	time (h)	yield (%)
1	$Pd_2(dba)_3$	PhCN	25	12	30
2	$Pd(OAc)_2$/CO	PhCN	25	12	20
3[a]	$Pd(OAc)_2$	MeOH	80	12	nr
4	$Pd_2(dba)_3$	PhCN	80	5	68
5	$Pd_2(dba)_3$	PhCN	80 (M_w)	0.5	85
6	$Pd_2(dba)_3$	MeCN	80 (M_w)	0.5	60
7	$Pd(OAc)_2$/CO	PhCN	80 (M_w)	0.5	41

[a] Reaction performed without NaOAc.

Changing the Pd precatalyst to $Pd(OAc)_2$/CO or $Pd(OAc)_2$ did not result in yield improvements. However, when the

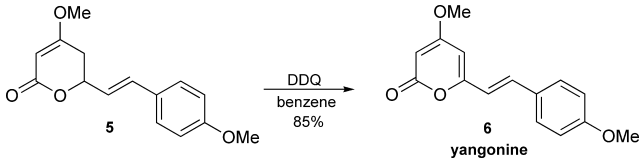
Scheme 3. Proposed Catalytic Cycle



Heck arylation reaction was performed with $Pd_2(dba)_3$ in PhCN at 80 °C the desired Heck adduct was obtained in an improved 68% yield after 5 h. Further increases in yields were obtained by performing the Heck reaction under microwave heating. The Heck adduct **5** was obtained in 85% isolated yield after 30 min.

With the Heck adduct **5** available, the synthesis of yangonine **6** was completed by a straighforward oxidation with DDQ in benzene as previously described in the literature[12] (Scheme 4).

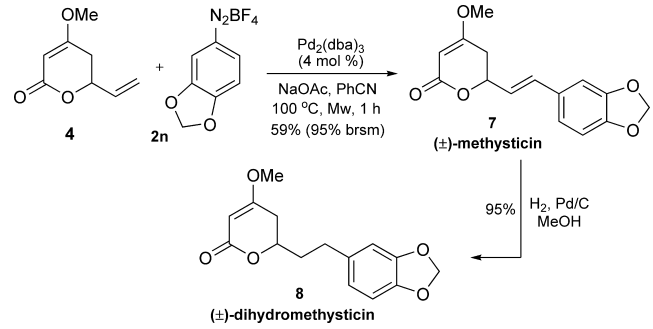
Scheme 4. Completion of the Synthesis of Yangonine



Finally, to extend the scope of the methodology we also accomplished the concise total synthesis of (±)-methysticin and (±)-dihydromethysticin by Heck arylation of olefin **4** with the arenediazonium salt **2n**. Under the same conditions employed for the synthesis of the yangonine precursor, except for the higher temperature, (±)-methysticin was obtained in 59% isolated yield (95% based on recovered starting material). Regioselective catalytic hydrogenation of the exocyclic double bond of methysticin allowed the synthesis of (±)-dihydromethysticin in 95% yield from methysticin (Scheme 5).

In summary, we describe herein a very efficient, mild, and operationally simple Heck arylation of allylic esters employing arenediazonium salts under palladium catalysis. The Heck reaction proceeds with excellent to total regio- and stereochemical control, affording the corresponding arylated allylic esters in high yields and with complete retention of the traditional leaving group. Furthermore, the present methodology was successfully applied to a conformationally restricted analogue, the vinyl lactone **4**, thus permitting the concise

Scheme 5. Synthesis of Methysticin and Dihydromethysticin



total synthesis of natural kavalactones, yangonine, (±)-methysticin, and (±)-dihydromethysticin. In these syntheses, more vigorous conditions were required for the arylation Heck reaction of a vinylic lactone, a conformationally restricted "allylic ester". These results suggest that a conformationally mobile ester group has indeed some participation in the Heck arylation process, mainly directing the regiochemistry of the arylation during the migratory insertion in the acyclic system, but it is not a requirement for obtaining an effective reaction.

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

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(12) (a) Amaral, P. A.; Gouault, N.; Le Roch, M.; Eifler-Lima, V.; David, M. *Tetrahedron Lett.* **2008**, *49*, 6607. (b) Hashimoto, T.; Suganuma, M.; Fujiki, H.; Yamada, M.; Kohno, T.; Asakawa, Y. *Phytomedicine* **2003**, *10*, 309. (c) Lygo, B. *Tetrahedron* **1995**, *51*, 12859.

(13) (a) Scherer, J. *Adv. Nat. Ther.* **1998**, *15*, 261. (b) Bilia, A. R.; Gallori, S.; Vincieri, F. F. *Life Sci.* **2002**, *70*, 2581.