

Palladium-Mediated Highly Regio- and Stereoselective Intermolecular β -Arylation on Allylic Alcohols: Synthesis of Functionalized Allylic Alcohols

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Abstract: An efficient and highly regio- and stereoselective Pd-catalyzed β -arylation method for the formation of β -aryl allylic alcohols, employing aryl iodides, 1-bromo-2-iodobenzenes, and 2-bromobenzaldehydes as coupling partners, is presented. The β -aryl allylic alcohols formed in this Pd-catalyzed transformation is unexpected under conventional Jeffery conditions without the assistance of silver salt. It is proposed that the reaction is substrate controlled, and the selective formation of the product depends on the size or nature of the substituent at the *ortho* position on the aromatic ring of the allylic alcohol part.

Key words: Pd catalysis, β -arylation, Mizoroki–Heck, allylic alcohols, β -carbonyls

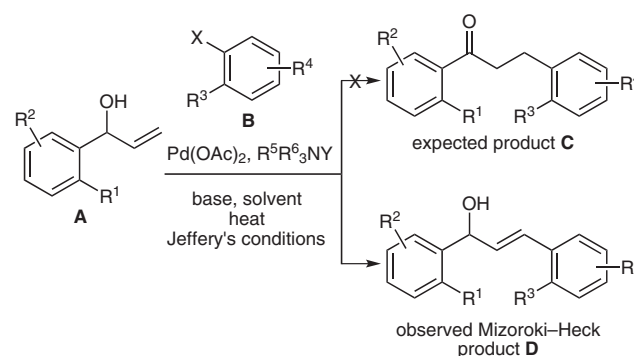
Transition-metal catalysis is a powerful tool that permits C–C bond-forming reactions quite efficiently. In this context, palladium is one of the most used metals suitable for oxidations, reductions, and many efficient cross-coupling reactions. Among these the Heck-type reaction is one of the most useful reactions mediated by palladium.^{1,2} In this context, Heck³ and Chalk⁴ independently but simultaneously reported Pd-catalyzed transformations of allylic alcohols with aryl halides coupling partners which resulted in the formation of β -aryl carbonyls. Subsequently, Jeffery⁵ developed a method based on the catalyst-directed Heck-type reaction that either leads to the formation of β -aryl (or alkenyl) carbonyls or to the selective formation of β -aryl (or alkenyl) allylic alcohols. Formation of the latter was controlled by the use of silver salts (either AgOAc or Ag₂CO₃) as additive to the catalytic system, which was crucial for the controlled formation of β -aryl (or alkenyl) allylic alcohols, by preventing further double-bond isomerization. Subsequently, many useful applications of the Pd-catalyzed coupling of allylic alcohols, homoallylic and homologous ene-alcohols even with aryl halides, to yield aryl carbonyls and also aryl allylic alcohols, have been reported in the literature.^{6–12} Interestingly, Jeffery conditions were also amenable to 1-bromo-2-iodobenzenes as coupling partners, the resulting 2-bromoaryl aldehydes were further successfully extended for the synthesis of various benzo-fused carbocyclic^{9a,b} and het-

erocyclic systems,^{9c} benzomorphans,^{9c} and heterospirocyclic systems.^{9d}

Herein we report a concise, practical, and highly regio- and stereoselective method for the synthesis of β -aryl allylic alcohols based on a hitherto unexplored, substrate-controlled intermolecular Pd-mediated β -arylation coupling using conventional Jeffery conditions. Under these conditions normal β -aryl carbonyls are formed, without the assistance of silver salt restricted double-bond isomerization, leading predominantly to the corresponding β -aryl allylic alcohols.

In the course of our investigations on Pd catalysis for the synthesis of dihydrochalcones, we envisioned the Pd-catalyzed Jeffery conditions would be ideally suited for the formation of desired dihydrochalcone **C** using allylic alcohol **A** and aryl halide **B** as coupling partners.

Much to our surprise, under Jeffery conditions the only product isolated was the β -aryl allylic alcohol **D** (Scheme 1), even though a Heck-type bond isomerization on substrates without *ortho* substituents on the aromatic ring of the allylic alcohol, by which β -aryl carbonyls were yielded, has been reported.¹³ We presumed that the substituent present at the *ortho* position of the aromatic ring is crucial to make the entire aryl moiety bulky enough to restrict the rotation around the C–C bond of the PdCH=CH(OH)Ar intermediate, thus suppressing the enol formation, which ultimately would lead to the β -aryl allylic alcohol. To understand well the scope and limitations of the method and to explore further whether it is specific to our substrate, we attempted to optimize the reaction conditions. Thus, the desired allylic alcohols **1** were easily prepared in excellent yields, from *ortho*-substituted benz-



Scheme 1

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aldehydes (see Supporting Information) using vinylmagnesium bromide.

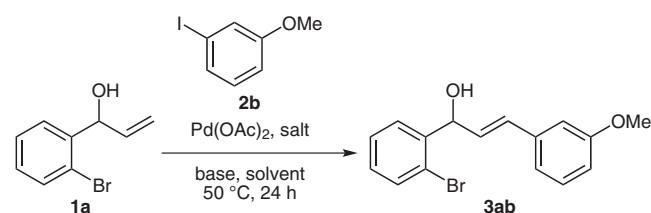
To further understand the factors that control the formation of the β -aryl allylic alcohol and to delineate the scope of the observed transformation we sought to optimize the reaction conditions for the coupling of various substrates.

With the allylic alcohol **1a** in hand, we studied the key Pd-mediated coupling with aryl iodide **2b** under conventional Jeffery conditions [$\text{Pd}(\text{OAc})_2$, $\text{Bn}(\text{Et})_3\text{NCl}$, NaHCO_3 , DMF, 50 °C, 24 h], furnishing the β -aryl allylic alcohol **3ab** in a good yield of 67% (Table 1, entry 1), while the reaction with TBAI in place of $\text{Bn}(\text{Et})_3\text{NCl}$ furnished the product with an inferior yield of 33% (Table 1, entry 2). Switching the base to K_2CO_3 in the presence of TBAI furnished the product **3ab** in a moderate yield of 51% (Table 1, entry 3). Changing the solvent to toluene and bases to either NaHCO_3 or K_2CO_3 furnished the product **3ab** in poor to moderate yields (Table 1, entries 4–6). Change of solvent to acetonitrile and use of quaternary ammonium salts such as TBAI or TBAB gave lower yields (Table 1, entries 7 and 8). The reaction with $\text{Cs}_2\text{CO}_3/\text{TBAI}$ and $\text{K}_2\text{CO}_3/\text{Bn}(\text{Et})_3\text{NCl}$ furnished the product **3ab** with improved yields of 51% and 67%, respectively (Table 1, entries 11 and 12). The combination of Cs_2CO_3 and $\text{Bn}(\text{Et})_3\text{NCl}$ in acetonitrile further im-

proved the yield (70%) of the product **3ab** (Table 1, entry 9). Finally, just changing the solvent from DMF to acetonitrile (and keeping all other parameters constant) was found to be the best set of optimized conditions and furnished the product **3ab** with a yield of 80% (Table 1, entry 10). Interestingly, when these optimized conditions were used in the microwave-assisted reaction (closed vessel, 250 W, 50 °C, 90 min), the olefin **1a** was smoothly transformed to the same product **3ab** in comparable yields.

After optimizing the reaction conditions, the generality of the reaction was established by the Pd-catalyzed reaction of allylic alcohols **1a–c** with aryl iodides **2a–d** to give the β -aryl allylic alcohols **3aa–cc**, using both conventional and microwave conditions, and the results are summarized in Scheme 2. It was observed that the reaction was quite successful with various aryl iodide coupling partners **2a–d** and allylic alcohols **1a–c**, possessing simple to electron-rich, substituted aromatic rings on either side. Slight reduction in yield was observed in cases (**3ac**, **3ad**, and **3cc**) where the methoxy group is either at the *ortho* or at the *para* position on the ring which was originated from aryl iodides **2c** and **2d**. This can be attributed to the fact that the more positive mesomeric effect of methoxy group(s), substituted *ortho* and/or *para* to the allylic double bond, may make the products more sensitive.

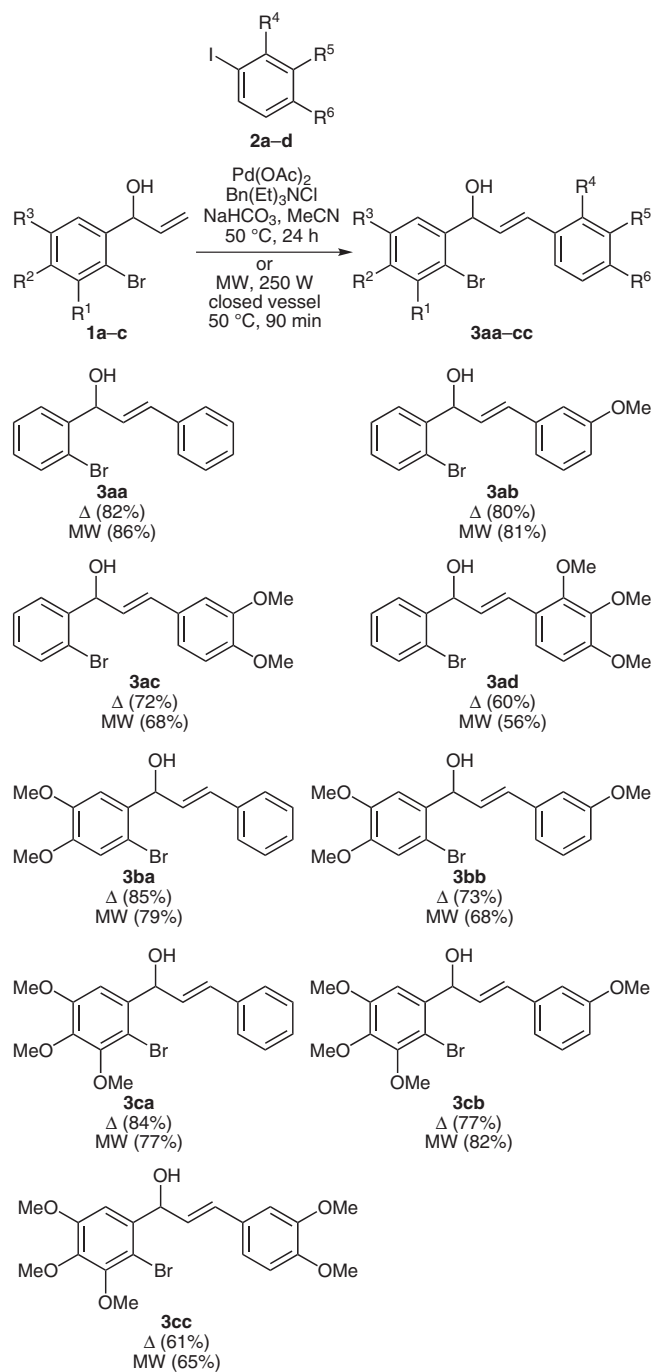
Table 1 Optimization of Reaction Conditions in the Synthesis of β -Aryl Allylic Alcohol **3ab**



Entry ^a	Base (2 equiv)	Salt (1 equiv)	Solvent	Yield of 3ab (%) ^b
1	NaHCO_3	$\text{Bn}(\text{Et})_3\text{NCl}$	DMF	67
2	NaHCO_3	TBAI	DMF	33
3	K_2CO_3	TBAI	DMF	51
4	NaHCO_3	TBAI	toluene	33
5	K_2CO_3	TBABr	toluene	50
6	NaHCO_3	$\text{Bn}(\text{Et})_3\text{NCl}$	toluene	55
7	NaHCO_3	TBAI	MeCN	39
8	NaHCO_3	TBABr	MeCN	30
9	Cs_2CO_3	$\text{Bn}(\text{Et})_3\text{NCl}$	MeCN	70
10	NaHCO_3	$\text{Bn}(\text{Et})_3\text{NCl}$	MeCN	80
11	Cs_2CO_3	TBAI	MeCN	51
12	K_2CO_3	$\text{Bn}(\text{Et})_3\text{NCl}$	MeCN	67

^a All reactions were carried out with $\text{Pd}(\text{OAc})_2$ (5 mol%), NaHCO_3 (2 equiv), and $\text{Bn}(\text{Et})_3\text{NCl}$ (1 equiv) under nitrogen atmosphere.

^b Isolated yields of chromatographically pure products; for compounds **3** the first letter refers to the allylic alcohol part (**1a**) whereas the second letter indicates the aromatic ring coming from the aryl iodide **2b**.

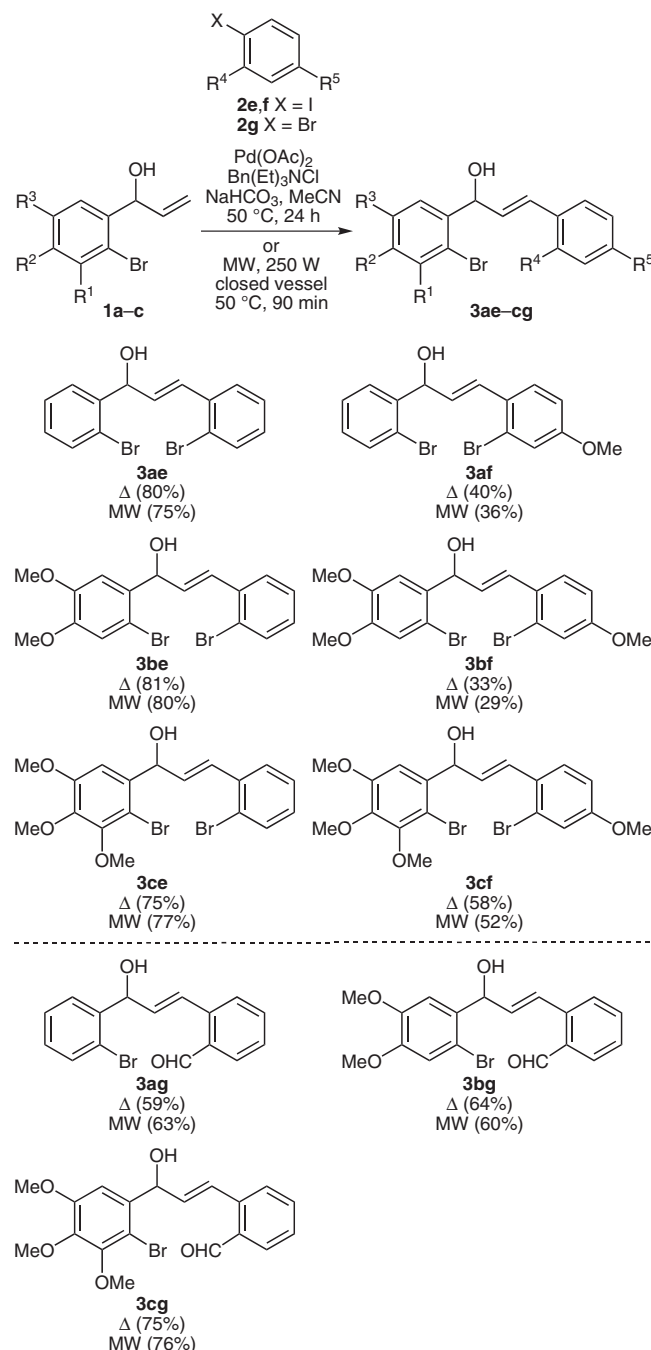


Scheme 2 Pd-catalyzed reaction of **1a–c** with aryl iodides **2a–d** to give **3aa–cc**. Isolated yields of pure chromatographically products; for compounds **3** the first letter refers to the allylic alcohol moiety **1**, whereas the second letter indicates the aromatic ring coming from the aryl iodide **2**.

After accomplishing the synthesis of β -aryl allylic alcohols **3aa–cc**, we turned our attention to determine the scope and limitation of the method. Hence, Pd catalysis with 1-bromo-2-iodobenzenes **2e,f** on allylic alcohols **1a–c** was also investigated.

In general, the results were quite consistent as to those observed in the case of the coupling between aryl iodides **2a–d** and allylic alcohols **1a–c** and furnished the products **3ae–cf** possessing simple to electron-rich aromatic func-

tionality on either side of the allylic alcohol in good yields. The only exception was in the case of the coupling partner 2-bromo-1-iodo-4-methoxybenzene (**2f**) where the corresponding products (**3af**, **3bf**, and **3cf**) were obtained in poor to moderate yields (Scheme 3). This was expected due to a similar positive mesomeric effect of the methoxy group *para* to the allylic double bond, as described above for **3ac**, **3ad**, and **3cc**. Furthermore, to study the generality of this method, the reaction of **1a–c** with electron-deficient 2-bromobenzaldehyde **2g** as coupling partner was

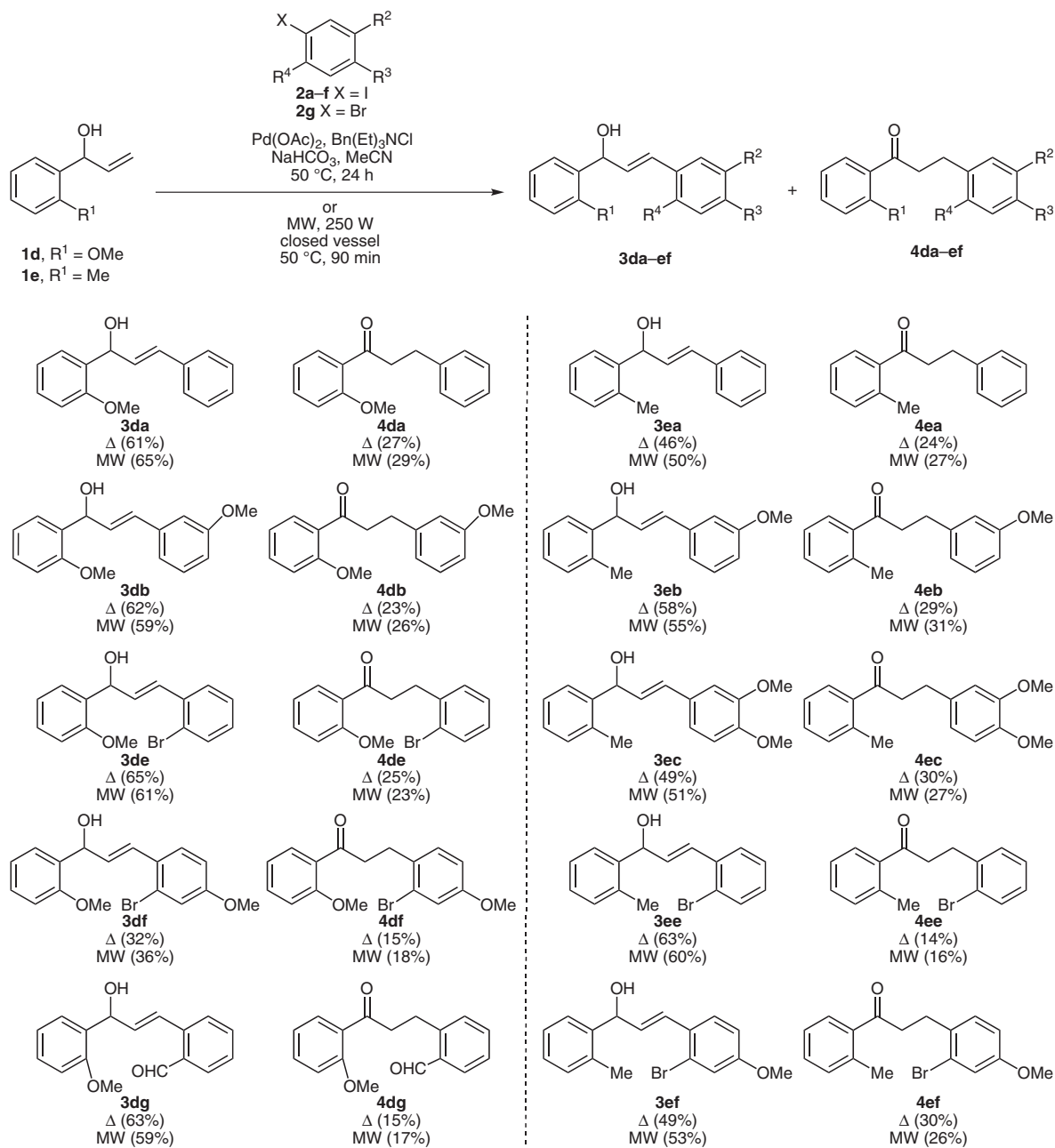


Scheme 3 Pd-catalyzed reaction of **1a–c** with bromiodobenzenes **2e–f**, and 2-bromobenzaldehyde **2g** to furnish **3ae–cg**. Isolated yields of chromatographically pure products; for compounds **3** the first letter refers to the allylic alcohol moiety **1**, whereas the second letter indicates the aromatic ring coming from the aryl halide **2**.

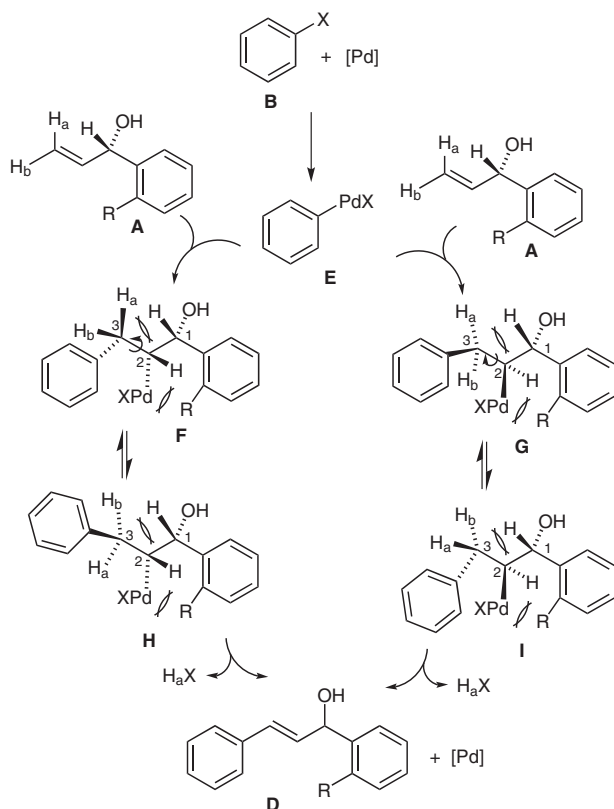
also carried out. Gratifyingly, under the optimized reaction conditions the corresponding products **3ag–cg** were obtained in good yields (Scheme 3). The unusual chemoselectivity in these cases can be attributed the electron-withdrawing nature of the aldehyde moiety of 2-bromobenzaldehyde **2g** which makes the aromatic ring more reactive towards the Pd catalyst for the formation of the aryl–palladium intermediate.

Finally, we studied substrates with *ortho*-methyl and *ortho*-methoxy groups in place of bromine atom on the aromatic ring of the allylic alcohol **1**. Even in these cases the alcohol products **3da–ef** were obtained as the major products along with the ketones **4da–ff** (Scheme 4). As expected, based on the substituent effect observed above,

products **3df**, **3ec**, and **3ef** were afforded in poor to moderate yields. The high selectivity for the formation of allylic alcohols **3** in the case of an *ortho*-bromo substituent over methoxy and methyl substituents can be rationalized based on bond length and polarization effects. Presumably, because of the C(sp²)–Br bond length (1.85 Å) that is longer than the C(sp²)–C(sp³) (1.50 Å) and C(sp²)–O (1.35 Å) bond lengths, bromine resides further away from the aromatic ring and closer to Pd species at C-2. As a result it might exert more steric hindrance and hence restrict the rotation about the C1–C2 bond (Scheme 5). An alternative explanation would be that due to its high electron polarizability and ligation ability, the bromine atom can complex with the Pd species at the C-2 carbon which as



Scheme 4 Pd-catalyzed reaction of **1d,e** with aryl iodides **2a–c**, bromiodobenzenes **2e,f**, and 2-bromobenzaldehyde **2g** to generate **3da–ef** and **4da–ef**. Isolated yields of chromatographically pure products; for compounds **3** the first letter refers to the allylic alcohol moiety **1**, whereas the second letter indicates the aromatic ring coming from the aryl halide **2**.



Scheme 5 Plausible mechanistic path for the formation of β -aryl allylic alcohol **D**. For simplicity, ligands are omitted.

well could restrict the rotation and therefore afford the allylic alcohol **3** as a major product.

A possible mechanistic path can be reasoned as shown in Scheme 5. It appears that the addition of the initially formed aryl palladium species **E** to the double bond of the allylic alcohol **A** gives both the *syn* (**F**) and *anti* intermediates (**G**) with respect to the hydroxy group. Even though *syn*- β -hydride-PdX elimination in the case of intermediate **G** seems possible, this process might be restricted due to the bulky nature of the benzylic alcohol part. In addition C-1–C-2 bond rotation could be restricted in the right half of both intermediates **F** and **G**, respectively. Now, the possible rotation of 120° around C-2–C-3 bond of the left hand part of the intermediates **F** and **G**, towards the direction of minimal eclipsed interaction, leads to the formation of intermediates **H** and **I**, respectively. Finally, *syn*- β -hydride-PdX elimination from both **H** and **I** yields the same allylic alcohol as product **D** (Scheme 1) and completes the catalytic cycle.

In summary, we have developed a highly regio- and stereo-selective Pd-catalyzed β -arylation on allylic alcohols using aryl iodides, 1-bromo-2-iodobenzenes, and 2-bromobenzaldehydes as coupling partners. The observation was unexpected under conventional Jeffery conditions without using silver salts as additives. The method is efficient and functioned smoothly on a variety of electron-rich and electron-deficient aromatic systems and lead to the products with dense functionality on aromatic rings.

Furthermore, this method may be useful for the synthesis of different flavonoid derivatives.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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References

- (1) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5526. (b) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, **1985**. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345.
- (2) For selected reviews, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Beletskaya, I. P.; Chepurkov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (e) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365.
- (3) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265.
- (4) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273.
- (5) (a) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121. (b) Jeffery, T. *Tetrahedron Lett.* **1990**, *31*, 6641. (c) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1991**, 324.
- (6) For the relevant topic, see review: Muzart, J. *Tetrahedron* **2005**, *61*, 4179.
- (7) (a) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329. (b) Aslam, M.; Elango, V.; Davenport, K. G. *Synthesis* **1989**, 869. (c) Beller, M.; Zapf, A. *Synlett* **1998**, 792. (d) Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153. (e) Caló, V.; Nacci, A.; Monopoli, A.; Spinelli, M. *Eur. J. Org. Chem.* **2003**, 1382. (f) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (g) Reymond, J.-L.; Jahangiri, C. K.; Stoudt, C.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 3909. (h) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970. (i) Kumareswaran, R.; Vankar, Y. D. *Synth. Commun.* **1998**, *28*, 2291. (j) Larock, R. C.; Yum, E. K.; Yang, H. *Tetrahedron* **1994**, *50*, 305. (k) Basavaiah, D.; Muthukumar, K. *Tetrahedron* **1998**, *54*, 4943. (l) Ferreira, B. R. V.; Pirovani, R. V.; Souza-Filho, L. G.; Coelho, F. *Tetrahedron* **2009**, *65*, 7712. (m) Sidler, D. R.; Sager, J. W.; Bergan, J. J.; Wells, K. M.; Bhupathy, M.; Volante, R. P. *Tetrahedron: Asymmetry* **1997**, *8*, 161. (n) Kim, J. M.; Kim, K. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 7712. (o) Ohno, H.; Okumura, M.; Maeda, S.-i.; Iwasaki, H.; Wakayama, R.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 7722.
- (8) For domino reactions, see: (a) Dyker, G.; Thöne, A. *J. Prakt. Chem.* **1993**, *341*, 138. (b) Dyker, G.; Kadzimirsz, D.; Henkel, G. *Tetrahedron Lett.* **2003**, *44*, 7905. (c) Catellani, M.; Deledda, S.; Ganchegui, B.; Hénin, F.; Motti, E.; Muzart, J. *J. Organomet. Chem.* **2003**, *687*, 473. (d) Dyker, G.; Grundt, P.; Markwitz, H.; Henkel, G. *J. Org. Chem.* **1998**, *63*, 6043.

- (9) (a) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem. Eur. J.* **2002**, 8, 401. (b) Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, 60, 4007. (c) Satyanarayana, G.; Maier, M. E. *Tetrahedron* **2008**, 64, 356. (d) Satyanarayana, G.; Maier, M. E. *J. Org. Chem.* **2008**, 73, 5410. (e) Gibson (née Thomas), S. E.; Jones, J. O.; McCague, R.; Tozer, M. J.; Whitcombe, N. J. *Synlett* **1999**, 954.
- (10) For reports on long-chain allylic alcohols, see: (a) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, 30, 6629. (b) Wong, Y.; Dong, X.; Larock, R. C. *J. Org. Chem.* **2003**, 68, 3090. (c) Satyanarayana, G.; Maichle-Mössmer, C.; Maier, M. E. *Chem. Commun.* **2009**, 1571. (d) Dyker, G.; Markwitz, H. *Synthesis* **1998**, 1750. (e) Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2005**, 3589. (f) Cropper, E. L.; Yuen, A.-P.; Ford, A.; White, A. J. P.; Hii, K. K. *Tetrahedron* **2009**, 65, 525.
- (11) For intramolecular Heck-type reaction, see: (a) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, 48, 3894. (b) Gaudin, J.-M. *Tetrahedron Lett.* **1991**, 32, 6113. (c) Kelly, S. A.; Foricher, Y.; Mann, J.; Bentley, J. M. *Org. Biomol. Chem.* **2003**, 1, 2865. (d) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, 34, 4219. (e) Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. *Synthesis* **1993**, 920. (f) Dyker, G.; Grundt, P. *Eur. J. Org. Chem.* **1999**, 323. (g) Mal, S. K.; Ray, D.; Ray, J. K. *Tetrahedron Lett.* **2004**, 45, 277. (h) Zawisza, A. M.; Ganchegui, B.; González, I.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. J. *Mol. Catal. A: Chem.* **2008**, 283, 140.
- (12) For β -aryl allylic alcohol synthesis, see: (a) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1976**, 41, 2604. (b) Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2003**, 687, 269. (c) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, 36, 6287. (d) See ref. 8a. (e) Leese, M. P.; Williams, J. M. J. *Synlett* **1999**, 1645. (f) Fang, X.; Yang, X.; Yang, X.; Zhao, M.; Chen, G.; Wu, F. *Tetrahedron Lett.* **2006**, 47, 8231. (g) Alacida, E.; Nájera, C. *Adv. Synth. Catal.* **2007**, 349, 2572.
- (13) Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, 69, 1374.

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