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

J. Krishna, A. Gopi Krishna Reddy, B. Venkat Ramulu, L. Mahendar, and G. Satyanarayana*

Indian Institute of Technology (IIT) Hyderabad, Ordnance Factory Estate Campus, Yeddumailaram – 502 205, Medak District, Andhra Pradesh, India

Fax: +91(40) 2301 6032

E-mail: gvsatya@iith.ac.in

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

Key words: Pd-catalysis; β-Arylation; Mizoroki-Heck; allylic alcohols; β-Carbonyls.

Scheme 1

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 Heck type reaction is one of the most useful reactions mediated by palladium.[1,2] In this context, Heck[3] and Chalk[4] independently but simultaneously reported Pd-catalyzed transformations of allylic alcohols with aryl halides coupling partners which resulted in the formation of β-arylcarbonyls. Subsequently, Jeffery[5] developed a method based on the catalyst directed Heck-type reaction that either leads to formation of β-aryl (or alkenyl) carbonyls or to selective β-aryl (or alkenyl) allylic alcohols. Formation of 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 Pd-catalyzed coupling of allylic alcohols, homoallylic and homologous ene-alcohols even with aryl halides, to yield arylcarbonyls and also to arylallylic alcohols have been reported in the literature.[6-12] Interestingly, Jeffery's conditions were also amenable to 1-bromo-2-iodobenzenes as coupling partners, with the resulting products having applications.[9]
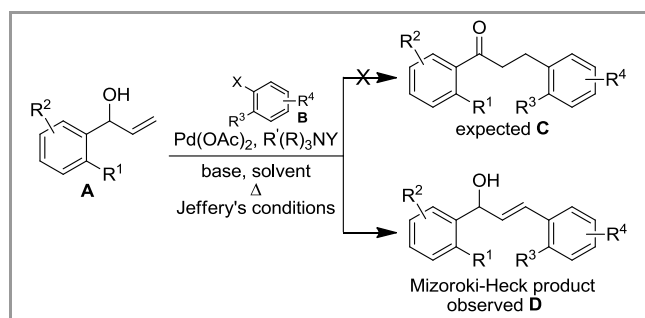
Herein we report a concise, practical, and highly regio- and stereoselective method for the synthesis of β-arylallylic alcohols based on a hitherto unexplored, substrate controlled intermolecular Pd-mediated β-arylation coupling using conventional Jeffery's conditions under which normally β-arylcarbonyls are formed, without the assistance of silver salt restricted double bond isomerization, leading predominately to the corresponding β-arylallylic alcohols.

Table 1. Optimization of reaction conditions towards the synthesis of β-arylallylic alcohol **3ab**.
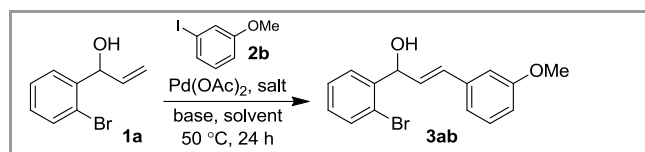
Entry[a]	Base (2 equiv)	Salt (1 equiv)	Solvent	Yield of 3ab (%)[b]
1	NaHCO₃	Bn(Et)₃NCl	DMF	67
2	NaHCO₃	TBAI	DMF	33
3	K₂CO₃	TBAI	DMF	51
4	NaHCO₃	TBAI	toluene	33
5	K₂CO₃	TBABr	toluene	50
6	NaHCO₃	Bn(Et)₃NCl	toluene	55
7	NaHCO₃	TBAI	acetonitrile	39
8	NaHCO₃	TBABr	acetonitrile	30
9	Cs₂CO₃	Bn(Et)₃NCl	acetonitrile	70
10	**NaHCO₃**	**Bn(Et)₃NCl**	**acetonitrile**	**80**
11	Cs₂CO₃	TBAI	acetonitrile	51
12	K₂CO₃	Bn(Et)₃NCl	acetonitrile	67

[a] All reactions were carried out with Pd(OAc)₂ (5 mol%), NaHCO₃ (2 equiv), Bn(Et)₃NCl (1 equiv) under nitrogen atmosphere.

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

Table 2. Pd-catalyzed reaction of **1a-c** with aryl iodides **2a-d** to give **3aa-cc**.
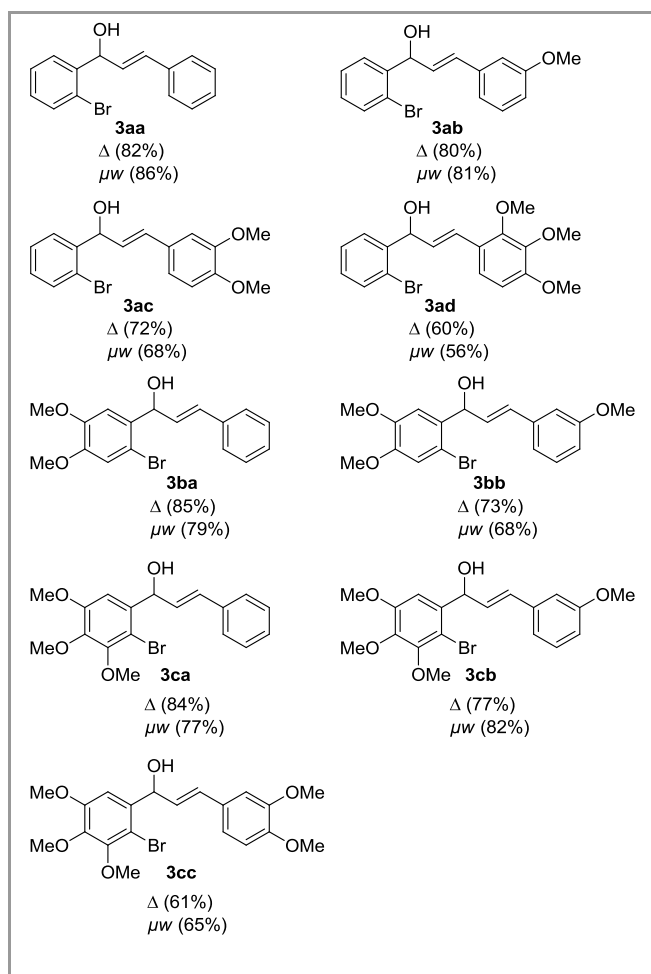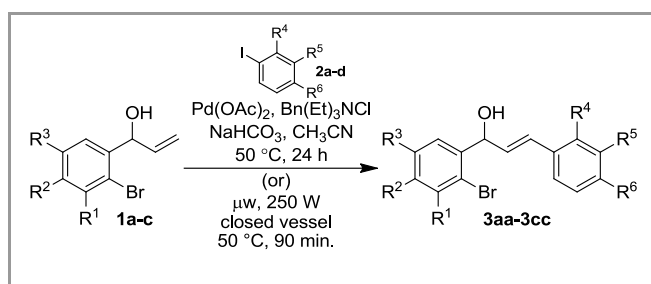
Much to our surprise, under Jeffery's conditions, the only product isolated, was the β-arylallylic alcohol **D** (Scheme 1), even though, recently Heck-type bond isomerization was reported on substrates without *ortho*-substituents on the aromatic ring of the allylic alcohol, by which β-arylcarbonyls were yielded.[13] We presumed that the substituent present at the *ortho*-position to 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-arylallylic 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-benzaldehydes (see supporting information) using vinylmagnesium bromide.

To further understand the factors that control the formation of the β-arylallylic alcohol and to delineate the scope of the observed transformation we tried to optimize reaction conditions for 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's conditions [Pd(OAc)$_2$, Bn(Et)$_3$NCl, NaHCO$_3$, DMF, 50 °C, 24 h], furnishing the β-arylallylic alcohol **3ab**, in good yield 67% (entry 1, Table 1),while reaction with TBAI in place of Bn(Et)$_3$NCl,furnished the product with inferior yield 33% (entry 2, Table 1). Switching the base to K$_2$CO$_3$ in presence of TBAI furnished the product **3ab** in moderate yield 51% (entry 3, Table 1). Changing the solvent to toluene and bases to either NaHCO$_3$ or K$_2$CO$_3$ furnished the product **3ab** in poor to moderate yields (entries 4, 5, and 6, Table 1). Change of solvent to acetonitrile and use of quaternary ammonium salts such as TBAI or TBAB, gave lower yields (entries 7 and 8, Table 1). The reaction with Cs$_2$CO$_3$/TBAI and K$_2$CO$_3$/Bn(Et)$_3$NCl furnished the product **3ab** with improved yields of 51% and 67%, respectively (entries 11 and 12, Table 1). The combination of Cs$_2$CO$_3$and Bn(Et)$_3$NCl in acetonitrile further improved yield (70%) of the product **3ab** (entry 9, Table 1). Finally, just changing the solvent from DMF to acetonitrile and keeping all other parameters constant, was found to be the best optimized condition and furnished the product **3ab** with a yield of 80% (entry 10, Table 1). Interestingly, when these optimized conditions were used in the microwave assisted (closed vessel, power: 250 W, temperature: 50 °C, time: 90 min.) reaction, the olefin **1a** was smoothly transformed to same product **3ab** in comparable yields.
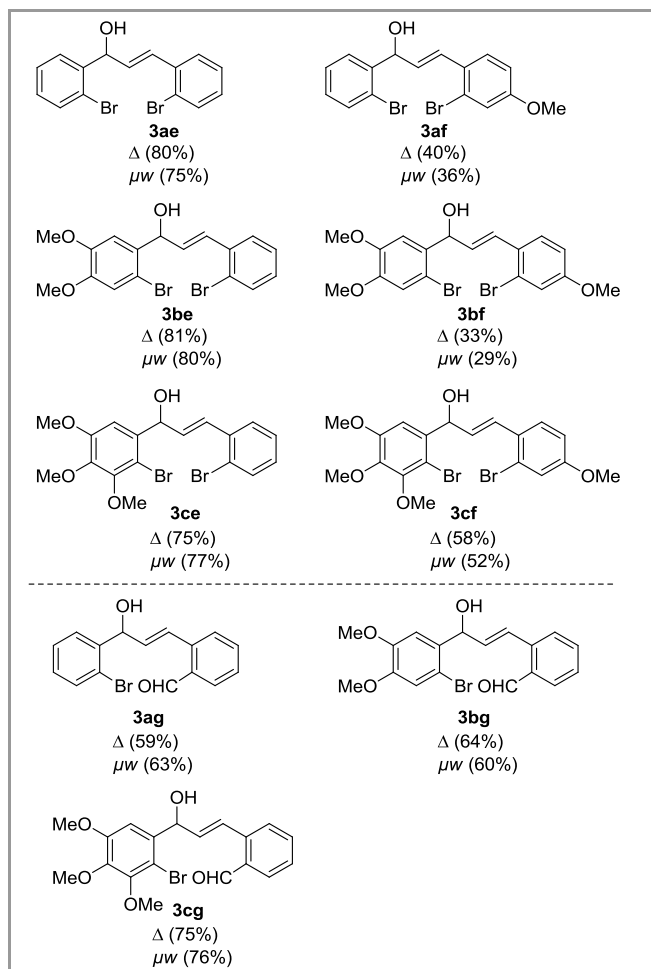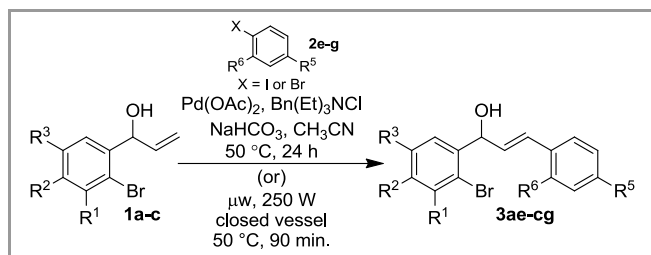
[a] Isolated yields of chromatographically pure products; for compounds **3** the first letter refers to the allylic alcohol part (**1a-1c**) whereas the second letter indicates the aromatic ring coming from the aryl halides **2e-2g**.

After optimizing the reaction conditions, the generality of the reaction was established by Pd-catalyzed reaction of allylic alcohols **1a-c** with aryl iodides **2a-d** to give the β-arylallylic alcohols **3aa-3cc**, using both conventional and microwave conditions, and the results are summarised in Table 2.

After successful accomplishment of β-arylallylic alcohols **3aa-3cc**, we turned our attention to check 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 aryl iodides **2a-d**, and furnished the products **3ae-cf** in good yields. The only exception was in the case of 2-bromo-1-iodo-4-methoxybenzene **2f** where the product was formed in poor yields (Table 3). Furthermore, to study the generality of this method, the reaction of **1a-c** with 2-bromobenzaldehyde **2g** as coupling partner was also carried out. Gratifyingly, under optimized conditions the corresponding products **3ag-cg** were obtained in good yields (Table 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 formation of aryl-palladium inserted intermediate. Finally, we studied substrates with *ortho*-methyl and *ortho*-methoxyl groups in place of bromine atom on aromatic ring of the allylicalcohol **1**. Even in these cases the alcohol products **3da-ef** were obtained as the major products along with the ketones **4da-ff**. The formation of the ketones **4da-ef** is perhaps, due to the smaller size of these *ortho*-substituents when compared to that of bromine (Table 4). The high selectivity for the formation of allylic alcohols **3** in case of *ortho*-bromosubstituent over methoxy and methyl substituents can be renationalized based on bond length and polarization effects. Presumably, because of longer C-Br bond length (1.94 Å) than C-C (1.54 Å) and C-O (1.43 Å) bond lengths, bromine resides little away from aromatic ring and closure to Pd-species at C-2, as a result might exert more steric hindrance and hence restrict the rotation about C_1-C_2 bond (Scheme 2) or due to it's high electron polarizability and ligation ability, can complex with Pd-species at C-2 carbon and could restrict the rotation and therefore affords the allylic alcohol **3** as a major product.

A possible mechanistic path can be reasoned as shown in Scheme 2. 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 hydroxyl function. 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** (ca. Scheme 1) and completes the catalytic cycle.

In summary, we have developed a highly regio- and stereoselective 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's conditions without silver salt assistance. 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.
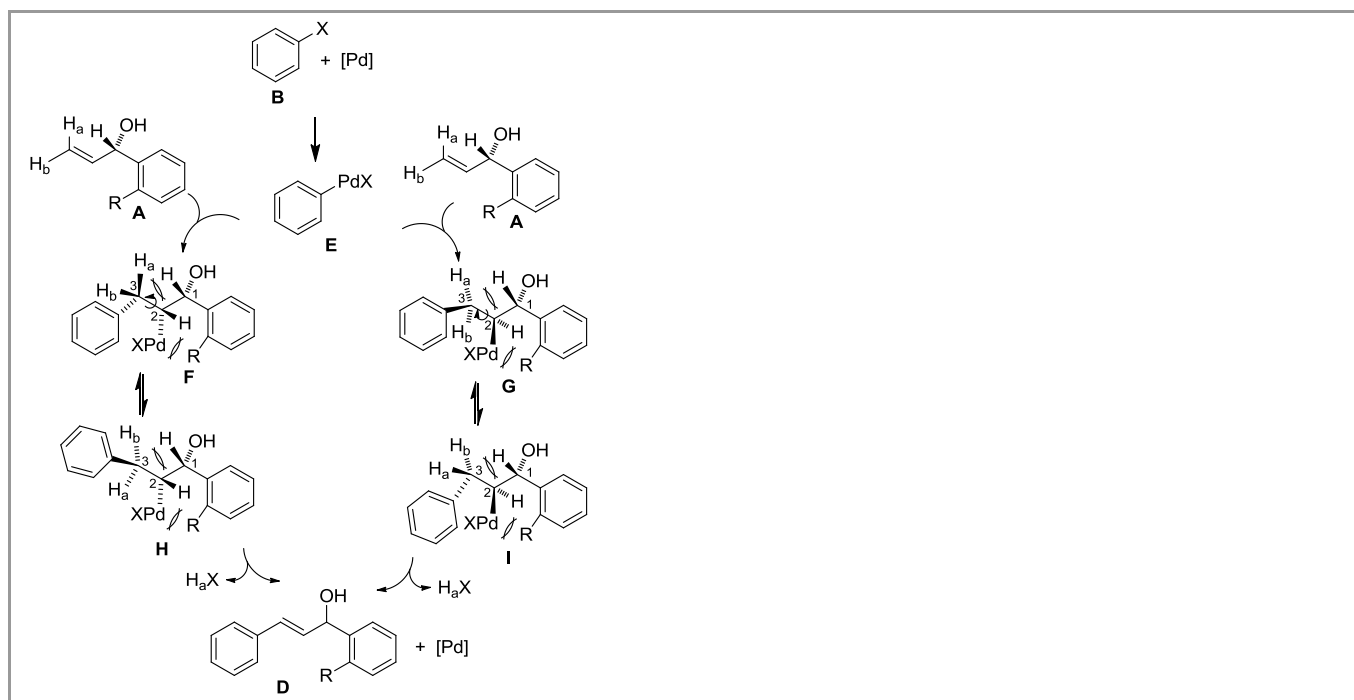
Table 4. Pd-catalyzed reaction of **1d-e** with aryl iodides **2a-c**, bromo-iodobenzene **2e-f**, and 2-bromobenzaldehyde **2g** to generate **3da-3ef and 4da-4ef**.
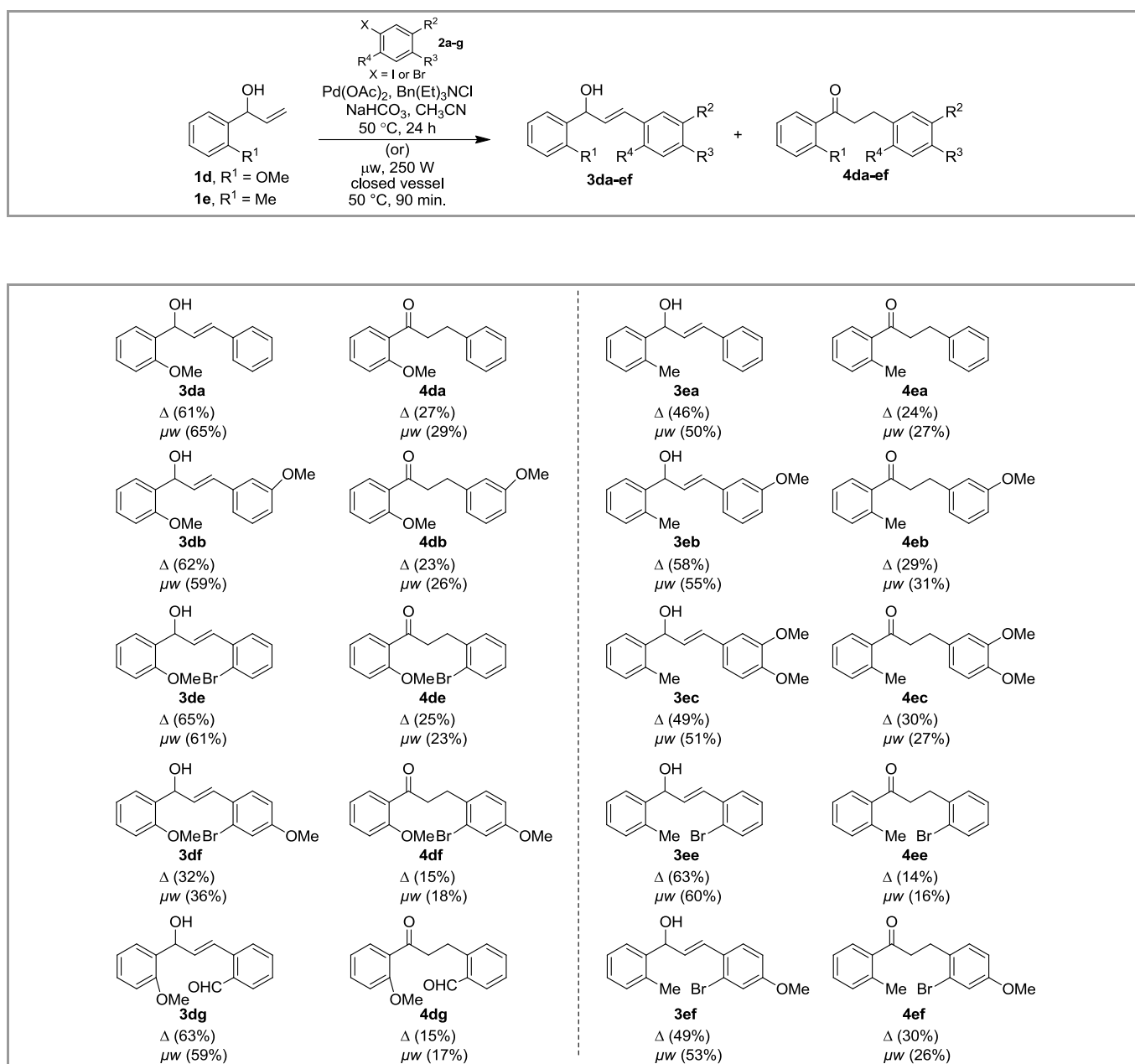
[a] Isolated yields of chromatographically pure products; for compounds **3** the first letter refers to the allylic alcohol part (**1d-1e**) whereas the second letter indicates the aromatic ring coming from the aryl halides **2a-2g**.

Scheme 2. Plausible mechanistic path, for the formation of β-arylallylicalcohol **D**. For simplicity, ligands are omitted.

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

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. *Organic Reactions* **1982**, *27*, 345.

(2)   For selected reviews, see: a) Amy B. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. b) Beletskaya, I. P.; Cheprakov, 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., Show-Yee 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 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.; Muthukumaran, 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.; 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.; Iwasaki, H.; Ryutaro 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.) 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) Bruyére, 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)   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.; Agnes Ford, A.; White, A. J. P.; Hii, K. K. (Mimi). *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) Anna Maria Zawisza, A. M.; Ganchegui, B.; Iván González, I.; Sandrine Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Mol. Catal. A: Chem.* **2008**, *283*, 240.

(12) For β-arylallylic alcohols synthesis, see: a) Tietze, L. F.; Görlitzer, J.; Schuffenhauer, A.; Hübner, M. *Eur. J. Org. Chem.* **1999**, 1075. b) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1976**, *41*, 2604. c) Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2003**, *687*, 269. d) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1996**, *36*, 6287. e) Dyker, G.; Thöne, A. *J. Prakt. Chem.* **1993**, *341*, 138.

(13) a) Briot, A.; Baehr, C.; Brouillard, R.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 1374.