A new synthetic route for Valsartan via a novel Decarboxylative Biaryl Synthesis

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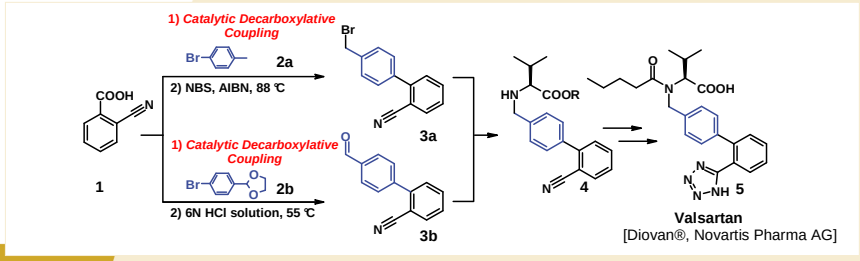
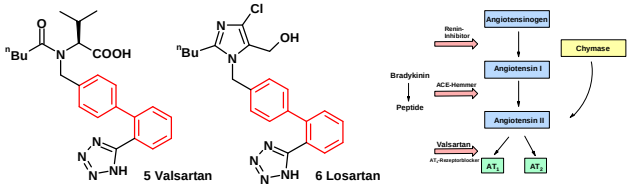
Abstract : A new catalytic system composed of copper and palladium has been recently reported by our group for the decarboxylation of aromatic carboxylates and the cross-coupling of the resulting aryl metal species with aryl halides. Already at its current state of development, this biaryl synthesis has opened up new opportunities for the industrial synthesis of high-value pharmaceutical intermediates, such as the Sartans or Boscalid analogs. Herein, we present the synthesis of Valsartan as one example of the many possible applications of the novel decarboxylative coupling in the synthesis of bioactive molecules. Our proposed synthetic route not only promises to be more environmentally benign, but also significantly cheaper in comparison to the literature synthesis.



Valsartan, the perfect angiotensin-II-receptor antagonist

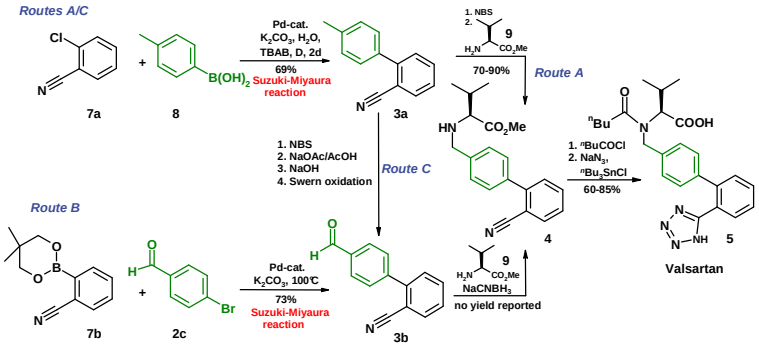
Hypertension is one of the most prevalent diseases in developed countries with an estimated one billion cases worldwide,[1] conferring its treatment an enormous social and economic importance. The therapeutic standard was significantly improved in the 1980s by the introduction of Losartan **6** (Lorzaar®, Merck)[2] as the first non-peptidic angiotensin-II-receptor antagonist. An entire therapeutic class, the sartans, has since been developed, among which Valsartan **5** (Diovan®, Novartis: US$ 4.2 bn sales in 2006) currently holds the largest market share.[3,4]



Their common structural element, a biphenyl unit (red), is essential for the binding affinity to the receptor and for the oral bioavailability.

Literature syntheses of Valsartan *via* Suzuki-Miyaura coupling

The formation of its aryl–aryl bond represents the key step in the synthesis of sartans: While for the synthesis of Losartan,[2] the uses of Negishi and Ullmann couplings is described in the literature, the published methods for the preparation of Valsartan make use of Suzuki-Miyaura couplings.[5]

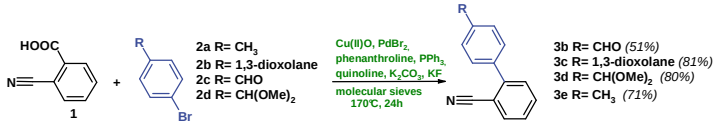


The main shortcoming common to these syntheses originates from the use of expensive boronic acid substrates in the cross-coupling step. We believed to be able to overcome this weakness with the biaryl synthesis recently developed in our group, which instead draws on carboxylic acid salts as a stable, inexpensive and widely available source of the aryl nucleophile.[6]

The Decarboxylative Biaryl Synthesis: the key step in our Valsartan synthesis

In this method carboxylic acid salts are decarboxylated by a copper/phenanthroline system, and the resulting aryl-copper species are coupled *in situ* with aryl halides by a palladium co-catalyst.

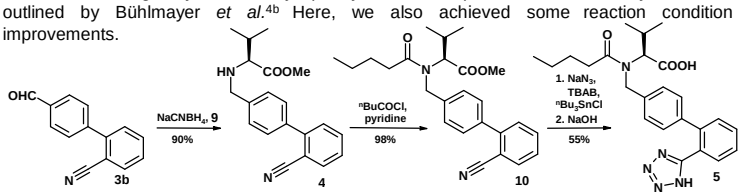
In order to allow a more concise Valsartan synthesis, a decarboxylative coupling of 2-cyanobenzoic acid **1** with the aryl bromides **2a-d,** leading to the intermediate biaryls **3a-e** had to be developed. It soon became clear that this was not an easy task: 2-cyanobenzoic acid **1** had previously been found to be particularly resistant against decarboxylation, which we rationalize with a competing coordination of cyano-groups to copper.



Thus, under previously optimized conditions (2% $PdBr_2$, 30% $CuCO_3$/1,10-phenanthroline, K_2CO_3, NMP/quinoline mixture),[6a] the yields did not exceed 36%. So, we began our search for a better catalyst system for the coupling of 2-cyanobenzoic acid **1** with **2a** by varying the copper source and found copper(II) oxide to be more effective, allowing us to reduce the amount of copper to 15%. Added phosphines like triphenylphosphine had a beneficial effect, presumably by stabilizing the palladium catalyst. In an attempt to further facilitate the speed of the copper mediated decarboxylation step, we tested metal salts as additives and found that with potassium fluoride, the yield could finally be improved for the first time beyond 60%. Finally, we reinvestigated the influence of the solvent system and found that in sharp contrast to the reaction of other benzoic acids, NMP/quinoline mixtures were inferior to pure quinoline, with which the best yield (71%) was achieved for the synthesis of 2-cyano-4'-methylbiphenyl **3e**. These optimized conditions gave reasonable yields in the coupling of **1** with the sensitive 4-bromobenzaldehyde **2c** (51%). However, best results were obtained with the corresponding acetals, *i.e.* the dioxolane **2b** and the commercially available dimethyl acetal **2d**, which hydrolyzed quantitatively during the standard acidic work-up and so the desired 2-cyano-4'-formylbiphenyl **3b** could be directly isolated in an overall yield of 80%.[7]

Completion of the Valsartan synthesis:

Completion of the Valsartan synthesis starting from 2-cyano-4'-methylbiphenyl **3e** *via Route A* required bromination to give 4'-bromomethyl-2-cyanobiphenyl **3a** which turned out to be sluggish as the use of NBS caused low yields (45%) and a double bromination of the product. So, we decided to abandon *Route A* and instead, focus on the alternative pathway *Route B* involving 2-cyano-4'-formylbiphenyl **3b** to complete the Valsartan synthesis as outlined by Bühlmayer *et al.*[4b] Here, we also achieved some reaction condition improvements.



Overall, we were able to significantly improve the decarboxylative biaryl coupling of 2-cyanobenzoic acid and demonstrate for the first time the advantages of this concept in the synthesis of complex, biologically active molecules. Thus, Valsartan was synthesized in four isolated steps and an overall yield of 39%.

Outlook: Currently, we are testing new ligands for our biaryl synthesis to achieve couplings with aryl-chlorides instead of aryl-bromides. And at the current state of development we already have received yields about 30% for the 2-cyano-4'-methylbiphenyl **3e**.

Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

[1] U.S. Department of Health and Human Services; National Heart, Lung, and Blood, Institute; National High Blood Pressure Education Program, NIH Publication No. 03 – 5233, December **2003**.
[2] D. Carini, J. Duncia, P. Aldrich, A. Chiu, A. Johnson, M. Pierce, W. Price, J. Santella III, G. Wells, R. Wexler, P. Wong, S. E. Yoo, P. Timmermans, *J. Med. Chem.* **1991**, *34*, 2525-2547.
[3] For sales figures, see: *Novartis Annual Report 2006*, Novartis International AG, Basel (**2007**).
[4] For published syntheses, see: a) P. Bühlmayer, F. Ostermayer, T. Schmidlin, *Eur. Pat. Appl.* EP443983, **1991**; b) P. Bühlmayer, P. Furet, L.Ciscione, M. de Gasparo, S. Whitebread, T. Schmidlin, R. Lattmann, J. Wood, *J. Bioorg. Med. Chem. Lett.* **1994**, *4*, 29-34.
[5] For state-of-the-art Suzuki couplings, see: a) A. F. Littke, G. C. Fu, *Angew. Chem. Int. Ed.* **2002**, *41*, 4176-4211; b) J. Kristensen, M. Lysén, P. Vedsø, M .Begtrup, *Org. Lett.* **2001**, *3*, 1435-1437.
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[7] L. J. Gooßen, B. Melzer, *J. Org. Chem.* **2007**, *72*, 7473-7476.