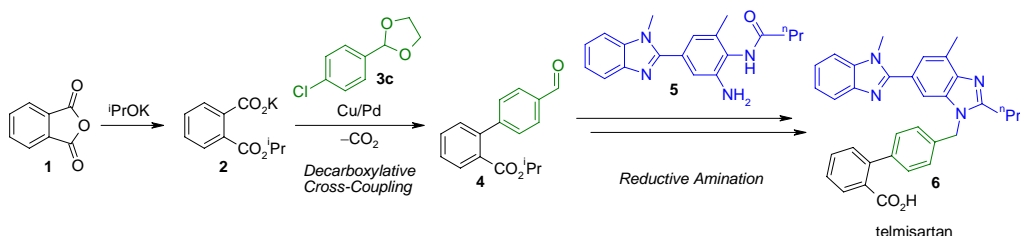




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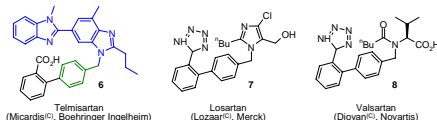
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**Abstract:** An efficient synthesis of the angiotensin II receptor antagonist telmisartan (**6**) (Micardis) is presented involving a decarboxylative cross-coupling<sup>1</sup> of isopropyl phthalate (**2**) with 2-(4-chlorophenyl)-1,3-dioxolane (**3c**) as the key step (85% yield). The benzimidazole moiety is constructed regioselectively via a reductive amination-condensation sequence instead of the traditional nonselective alkylation of the pre-formed benzimidazole. The product is obtained in an overall yield of 36% in a convergent synthesis, the longest sequence consisting of eight steps.



## Essential Hypertension – A widespread Disease

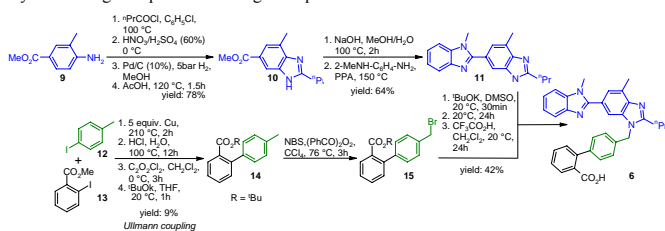
Essential hypertension is a major risk factor for cardiovascular disease, and responsible for one third of global deaths.<sup>2</sup> Therefore a huge market for effective anti-hypertension drugs is opened up. Since the early 90's Merck's Losartan<sup>®</sup> caused a landslide of novel, highly effective and compliant Angiotensin-II-Receptor-Antagonists. They inhibit the binding of Angiotensin II, the most important effector peptide for the regulation of blood pressure in the Renin-Angiotensin-Aldosteron-System RAS, to its AT<sub>1</sub>-receptor.<sup>3</sup> The most common drugs are shown in the figure below.



The *ortho*-substituted biaryl is one of the pharmacophores and can be found in all the sartans. Among them telmisartan has the strongest binding affinity to the AT<sub>1</sub>-receptor.

## Traditional Synthesis of Telmisartan

The first total synthesis of telmisartan starts with 4-amino-3-methylbenzoic acid methyl ester (**9**) transformed in a multistep synthesis in the bisbenzimidazole derivative **11** and finally alkylated with 4'-(bromomethyl)-2-biphenylcarboxylic acid *tert*-butyl ester (**15**) to give telmisartan (**6**) in 21% overall yield and eight steps over the longest sequence.<sup>4</sup>



Several improvements to this protocol have been reported.<sup>5</sup> However, the two major shortcomings of this synthesis remained: namely the unsatisfactory regioselectivity in the alkylation of **11** with **15**, and the intricate synthesis of the biaryl intermediate which was synthesized *via* an Ullmann coupling of the aryl iodides **12** and **13**. Modern syntheses of **14** involve cross-couplings of sensitive arylmagnesium, -zinc or -boron compounds with alkyl 2-halo-benzoates.

## Development of a Concise Synthesis of Telmisartan

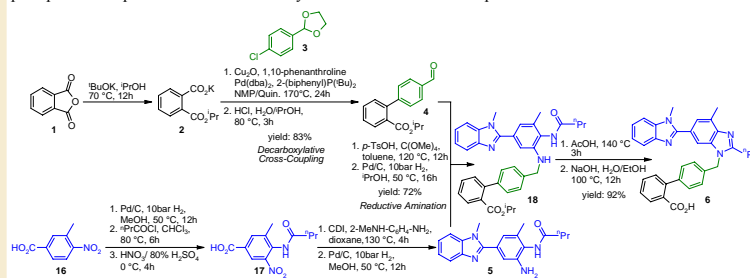
We envisioned that our Pd/Cu-catalyzed decarboxylative biaryl synthesis as the key step had the potential to overcome both these weaknesses: the use of an inexpensive aryl chloride substituted in the 4-position by an aldehyde or derivative in the cross-coupling followed by a reductive amination-condensation sequence would allow a regioselective entry into the 2-propylbenzimidazole fragment. Thus the use of stoichiometric amounts of organometallic reagents could be avoided, as the biaryl would become accessible from a stable potassium monoalkylphthalate instead, which could be prepared in one simple step from the bulk chemical phthalic anhydride (**1**) by anhydride esterification with a potassium alkoxide. In our search for an optimal set of starting materials, catalyst components and conditions for the synthesis of the biaryl intermediate **4**, we started our investigation with a catalyst system consisting of CuI / 1,10-phenanthroline and PdBr<sub>2</sub> / 2-(*tert*-butylphosphino)-biphenyl (John-Phos) facilitating the coupling of 2-nitrobenzoates with arylchlorides.<sup>1</sup>

A combination of Cu<sub>2</sub>O and Pd(dba)<sub>2</sub> proved to be the best precursors for the coupling of **2** with the arylchlorides **3a-c**. Expectedly, the choice of phosphine played a critical role – best yields were obtained with the sterically crowded, electron-rich 2-(*tert*-butylphosphino)biphenyl (John-Phos). Under these optimized conditions, we were delighted to see that the corresponding dioxolane (**3c**) was converted in very good yield. The preparation of the other key intermediate of our telmisartan synthesis, heterocyclic aniline **5**, the coupling partner for the reductive amination of the biaryl **4**, is outlined below. Reduction of the nitro group of compound **16** followed by acylation with butyrylchloride and nitration afforded compound **17** in an excellent overall yield of 87%. The carboxyl group of this compound was condensed with *N*-methyl-2-phenyldiamine to the benzimidazol derivative and its nitro group was smoothly reduced to afford the key intermediate **5**. At this point of our synthetic route, both key fragments **4** and **5** were coupled *via* a reductive amination reaction which was followed by cyclisation to construct the second benzimidazol ring.

Entry	Alk	R	Cu-Source	Pd-Source	Ligand	Yield [%]
1	Me	Xa	CuI	PdBr <sub>2</sub>	John-Phos	7
2	<i>t</i> Bu	"	"	"	"	3
3	<i>i</i> Pr	"	"	"	"	39
4	"	"	CuF <sub>2</sub>	"	"	43
5	"	"	CuBr	"	"	49
6	"	"	Cu <sub>2</sub> O	"	"	52
7	"	"	"	Pd(acac) <sub>2</sub>	"	55
8	"	"	"	Pd(OAc) <sub>2</sub>	"	59
9	"	"	"	Pd(dba) <sub>2</sub>	"	63
10	"	"	"	"	John-Phos	65
11	"	"	"	"	BINAP	11
12	"	"	"	"	PCy <sub>3</sub>	34
13	"	"	"	"	P( <i>t</i> Bu) <sub>3</sub>	53
14	"	"	"	"	Dave-Phos	61
15	"	X	"	"	John-Phos	64
16	"	Xb	"	"	"	78
17	"	Xc	"	"	"	86

*General conditions:* 1.50 mmol of potassium monoisopropyl phthalate, 1.00 mmol aryl chloride, 10 mol% Cu-source (5 mol% for Cu<sub>2</sub>O), 2 mol% Pd-source, 10 mol% 1,10-phenanthroline, 1.5 mL NMP, 0.5 mL quinoline, 170 °C, 24h. Yields were determined by GC analysis using *n*-tetradecane as the internal standard. *a*: 3 mol% of ligand was used. *b*: 6 mol% of ligand (3 mol% for *rac*-BINAP) was used.

The resulting telmisartan isopropyl ester was saponified and subsequent acidification led to precipitation of pure telmisartan in 92% yield over the two final steps.



In conclusion, a concise and selective synthesis of the antihypertensive drug telmisartan has been developed, featuring a decarboxylative cross-coupling for the construction of the biaryl moiety and a regioselective reductive amination / condensation sequence for the synthesis of the central benzimidazole. It demonstrates the high synthetic potential of decarboxylative coupling reactions, which draws on easily accessible carboxylate salts rather than sensitive organometallic reagents as sources of carbon nucleophiles.

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## Literature and Further Reading (see also [www.chemie.uni-kl.de/goossen](http://www.chemie.uni-kl.de/goossen))

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