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A New Approach to the Synthesis of Peptidomimetic Renin Inhibitors: Palladium-Catalyzed Asymmetric Allylation of Acyclic Alkyl Aryl Ketones

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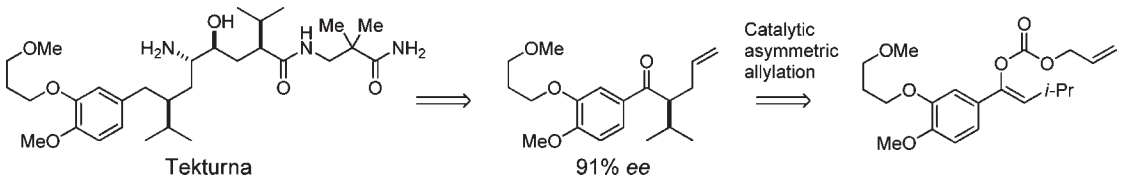
ABSTRACT



A new approach to the synthesis of Tekturna, a recently marketed drug for hypertension, takes advantage of a modified protocol of the Stoltz palladium-catalyzed asymmetric allylation with a *t*-BuPHOX ligand for the synthesis of allylated acyclic alkyl aryl ketones. The method led to an α-isopropyl α-allyl aryl ketone in 90% yield and 88 to 91% *ee*, which was used in the synthesis of an advanced intermediate toward Tekturna. A beneficial effect of protic additives, such as BHT (2,6-di-*tert*-butyl-*p*-cresol), on the time and enantioselectivity of the reaction was discovered.

Interest in the inhibition of the enzyme renin over the past two decades[1] has culminated with the discovery of the antihypertensive drug aliskiren, marketed under the trade name Tekturna.[2] Extensive studies involving cocrystal structures of promising inhibitors with renin led to refinements that eventually provided the optimized drug candidate.[3] Although a number of synthetic approaches have been reported,[4] details of the total synthesis of Tekturna are more likely to be found in the patent literature.[5] In 2010, we disclosed an 11-step total synthesis

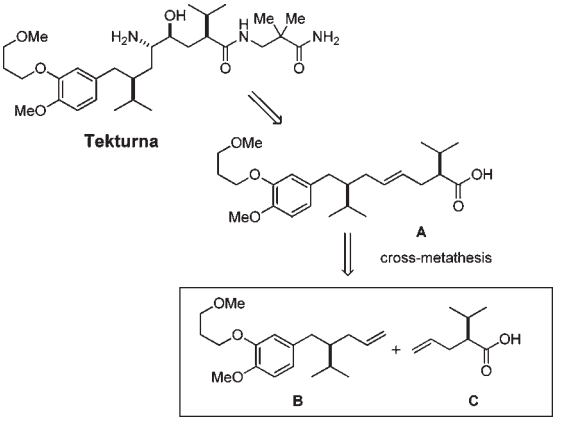


Figure 1. Retrosynthetic analysis toward Tekturna.

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(2) (a) For recent reviews, see: Maibaum, J.; Feldman, D. L. *Annu. Rep. Med. Chem.* **2009**, *44*, 105. (b) Jensen, C.; Herold, P.; Brunner, H. R. *Nat. Rev. Drug Discovery* **2008**, *7*, 399. (c) Siragy, H. M.; Kar, S.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 779.

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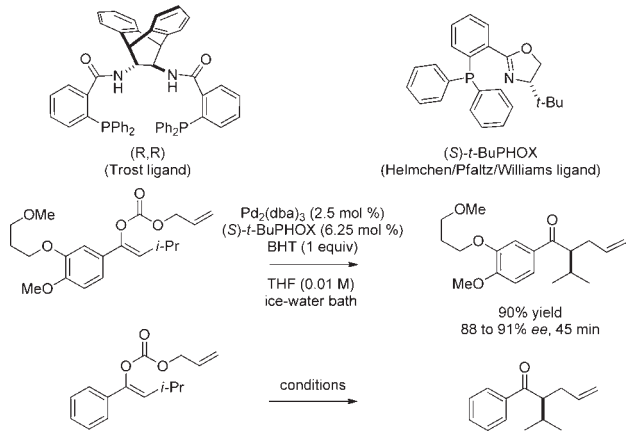
of Tekturna, in an overall yield of 7%,[6] which to the best of our knowledge, is the shortest linear sequence to date.

Scheme 1. Palladium-Catalyzed Asymetric α-Allylation of Acyclic Isopropyl Aryl Allyl Enol Carbonates



We now report on the efficient synthesis of a key advanced intermediate to Tekturna, previously prepared by a multistep procedure.[5] Besides its novelty with regard to published reports,[4,5] our approach features a catalytic step that provides a key intermediate expeditiously and in high enantiomeric purity. Disconnection of Tekturna in a retrosynthetic sense leads to the two olefinic chirons **B** and **C** that can be joined in a cross-metathesis reaction, to give the known advanced intermediate **A**, which has been previously converted to the intended target compound (Figure 1).[5]

The venerable Tsuji palladium-catalyzed α-allylation of ketones[7,8] has been adapted to an asymmetric variant by Stoltz[9,10] and Trost[11] independently, using optimized chiral ligands.[12] Although there were only a few examples of the asymmetric allylation of acyclic aryl ketones at the inception of our work, we initiated studies to assess the feasibility of such a reaction with an isobutyl phenyl ketone corresponding to chiron **B** (Figure 1). Trost and coworkers[13] had reported that while α-allylation of ethyl phenyl ketone took place with 94% enantiomeric excess, the selectivity and yield were drastically diminished in the case of the more sterically demanding isobutyl phenyl ketone (32% *ee*, 30% yield) (Scheme 1). We were pleased to find that under optimized conditions, the Stoltz protocol, using the (*S*)-*t*-BuPHOX ligand,[9] was highly effective in converting the enol carbonate prepared from isobutyl phenyl ketone to the corresponding α-allyl ketone in 84% *ee* and 95% isolated yield intended for Tekturna (entry 2, Table 1). We found that addition of 1 equiv of BHT had a significant effect on the rate of the reaction (3 h to 45 min) at 0 °C while also improving the degree of enantioselectivity with up to 91% *ee* (entry 15, Table 1 and Scheme 1). To the best of our knowledge, the palladium-catalyzed asymmetric allylation of acyclic enol carbonates with the PHOX ligand has only been recently reported.[14,15] A demonstrable 12% improvement in enantiomeric excess was shown for ethyl phenyl ketone, in the presence of 40 mol % of AgBr (75%, 79% *ee*).

Studies on the screening of other BuPHOX and related catalysts were done with regard to reaction time and the nature of the additive (Table 1). The following observations are noteworthy: (a) the $Pd_2(dba)_3$/(*S*)-*t*-BuPHOX catalyst was optimal at a ratio of $Pd_2(dba)_3$ 2.5 mol %/ligand 6.25 mol %; (b) protic additives including 2-methyl diethylmalonate[13] did not adversely affect the reaction rate, except for 1-naphthol and binol; (c) *t*-BuOH and especially BHT decreased the reaction time and increased the *ee* in some cases; (d) reactions were more reproducible with a freshly prepared ligand.

The role of the BHT as an additive is not fully understood at this time. Murakami[16] reported that the addition of phenol or 1-naphthol was essential to attain a good yield and an improved *ee* in an asymmetric Carroll rearrangement. In contrast, 1-naphthol and related compounds were detrimental in our case (entries 11 and 16, Table 1).

Trost and co-workers[11,17] reported an increase in reaction rate by adding 2-methyl dimethylmalonate when

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(6) Hanessian, S.; Guesné, S.; Chénard, E. *Org. Lett*. **2010**, *12*, 1816.

(7) (a) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992. See also: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: U.K., 2004. (b) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett*. **1980**, *21*, 3199. (c) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, *6*, 4387.

(8) For a recent review on metal catalyzed decarboxylative allylation, see: Weaver, J. D.; Recio, A., III; Grenning, A. J.; Tunge, J. A. *Chem. Rev*. **2011**, *111*, 1846.

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(10) For reviews, see: (a) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323. (b) Mohr, J. T.; Stoltz, B. M. *Chem.—Asian J*. **2007**, *2*, 1476. (c) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed*. **2006**, *45*, 5246.

(11) Trost, B. M.; Xu, J. *J. Am. Chem. Soc*. **2005**, *127*, 2846.

(12) For the design, synthesis, and reactivity of chiral phosphinooxazolines (PHOX) ligands, see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, *33*, 336 and references therein. (b) Williams, J. M. J. *Synlett* **1996**, 705. (*S*)-*t*-BuPHOX is commercially available from L-*tert*-leucinol. (*R*)-*t*-BuPHOX was prepared from D-*tert*-leucine. For the synthesis of modified PHOX ligands, see: (c) Bélanger, E.; Pouliot, M.-F.; Courtemanche, M.-A.; Paquin, J.-F. *J. Org. Chem*. **2012**, *77*, 317. (d) McDougal, N. T.; Streuff, J.; Mukerjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett*. **2010**, *51*, 5550. (e) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth*. **2009**, *86*, 181. (f) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett*. **2007**, *9*, 2529. For examples of palladium-catalyzed allylation with bis(oxazoline) ligands, see: (g) Liu, L.; Ma, H.; Fu, B. *Molecules* **2012**, *17*, 1992. (h) Bayardon, J.; Sinou, D.; Guala, M.; Desimoni, G. *Tetrahedron: Asymmetry* **2004**, *15*, 3195 and references therein.

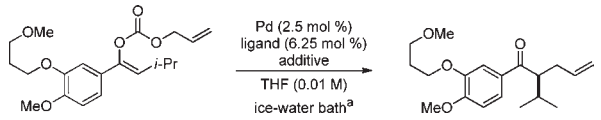
(13) Trost, B. M.; Xu, J.; Schmidt, T. *J. Am. Chem. Soc*. **2009**, *131*, 18343.

(14) For example, see: Behenna, D. C.; Stoltz, B. M.; Mohr, J. T.; Harned, A. M. U.S. 7,235,698, B2 2007.

(15) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem.—Eur. J*. **2011**, *17*, 14199.

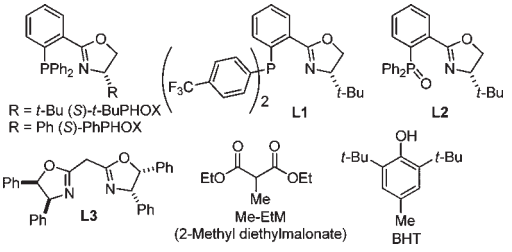
(16) Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun*. **2005**, 3951.

Table 1. Screening of Palladium Catalysts and Additives in the Asymmetric Allylic Reaction



entry	Pd / ligand[b]	additive	time (h)	yield (%)	% *ee*[c]
1	$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX	---	1[d]	95	76
2	**$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX**	**---**	3	**95**	**84**
3	$Pd_2(dba)_3$ / (*S*)-PhPHOX[e]	---	24	67	60
4	$Pd_2(dba)_3$ / **L1**	---	24	<10	81
5	$Pd_2(dba)_3$ / **L2**	---	24	0	---
6	$Pd_2(dba)_3$ / **L3**[e]	---	24	0	---
7	$Pd_2(dba)_3$ / (*S*)-BINAP[e]	---	24	ND	–7
8	$Pd(PPh_3)_4$ / (*S*)-*t*-BuPHOX	---	24	ND	43
9	$Pd(OAc)_2$ / (*S*)-*t*-BuPHOX	---	24	70	68
10	$Pd(dppe)_2$ / (*S*)-*t*-BuPHOX	---	24	0	---
11	$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX	1-naphthol (1 equiv)	24	0	---
12	$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX	Me-EtM (1 equiv)	1	ND	64
13	**$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX**	***t*-BuOH** (5 equiv)	1-3	**90**	**88**
14	$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX	BHT (1 equiv)	5 min[d]	68	75
15	**$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX**	**BHT** (1 equiv)	45 min	**90**	**88 to 91**
16	$Pd_2(dba)_3$ / (*S*)-*t*-BuPHOX	(*R*)- or (*S*)-binol (1 equiv)	24	0	---

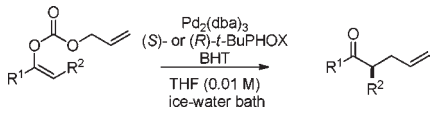
[a] After 5 h, reactions were allowed to slowly reach room temperature. [b] Freshly prepared ligands. For the synthesis of **L1** and **L2**, see refs 12d, 12e, 12f, and 15. [c] Enantiomeric excess were determined by chiral HPLC separations; see Supporting Information for details. [d] Reaction was performed at room temperature. [e] Purchased ligand. For examples of asymmetric allylation with bis(oxazoline) ligands (**L3**), see ref 12g and 12h. ND = Not determined.

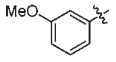
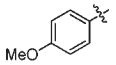
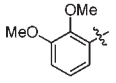
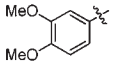
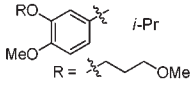
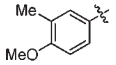
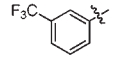


conducting palladium-catalyzed asymmetric allylations on alkyl aryl enol carbonates. Although simple alcohols such as *i*-PrOH and *t*-BuOH were also effective in our case, the reactions were more reproducible with regard to time, yield, and *ee* when using 1 equiv of BHT, especially with 3,4-dialkoxy aryl ketones. In order to expand the scope of the reaction, while maintaining the functionally important isopropyl appendage,[3] we varied the nature of the substituents on the aromatic ring. It is known that such variants of Tekturna also maintain substantial in vitro activity against the enzyme renin.[3]

Depending on the nature of the substituent on the aromatic ring, reactions with or without BHT appeared to vary with regard to time especially. The enantiomeric excess could be improved at −20 °C, but reaction times were longer compared to those at 0 °C. A definitive shortening of reaction times and increases in *ee* were consistently evident in the case of 4-alkoxy and 3,4-dialkoxy aryl enol carbonates (entries 4, 6, and 7, Table 2). This was particularly interesting for the substrate corresponding to

Table 2. Reaction Scope



entry	R^1	R^2	no BHT yield, % *ee*,[a,b] time	BHT yield, % *ee*,[a,b] time
1		*i*-Pr	84%, 78, 3 h (ND,[c] 84, 10 d)[d]	88%, 84, 2 h (85%, 85, 3 d)[d]
2		*i*-Pr	96%, 80, 90 min	84%, 82, 90 min
3		*i*-Pr	86%, 84, 90 min	85%, 89, 90 min
4		Me *i*-Pr	91%, 83, 7 h 89%, 79, 7 h[e]	90%, 88, 7 h 83%, 83,[f] 3 h
5		*i*-Pr	97%, 81, 2 h	87%, 82, 2 h
6		*i*-Pr *i*-Pr	95%, 87, 2 h (67%,[c] 93, 10 d)[d]	(90%, 91, 45 min)[g] (86%, 93, 2 d)[d,g]
7		*i*-Pr	95%, 84, 3 h	90%, 88 to 91, 45 min (85%, 91, 2 d)[d,g]
8		*i*-Pr	82%, 79, 14 h[e]	95%, 84, 7 h
9		*i*-Pr	92%, 70, 2 h	57%, 74, 2 h

[a] See Supporting Information for SFC and HPLC conditions. [b] Average *ee* of ≥2 runs. [c] Reaction did not achieve full conversion. [d] Reaction performed at −20 °C. [e] After 5 h, reaction solution was allowed to slowly reach room temperature. [f] Observed 76% *ee* when the reaction was performed with *t*-BuOH as the additive. [g] Same results were observed with *t*-BuOH as the additive. ND = Not determined.

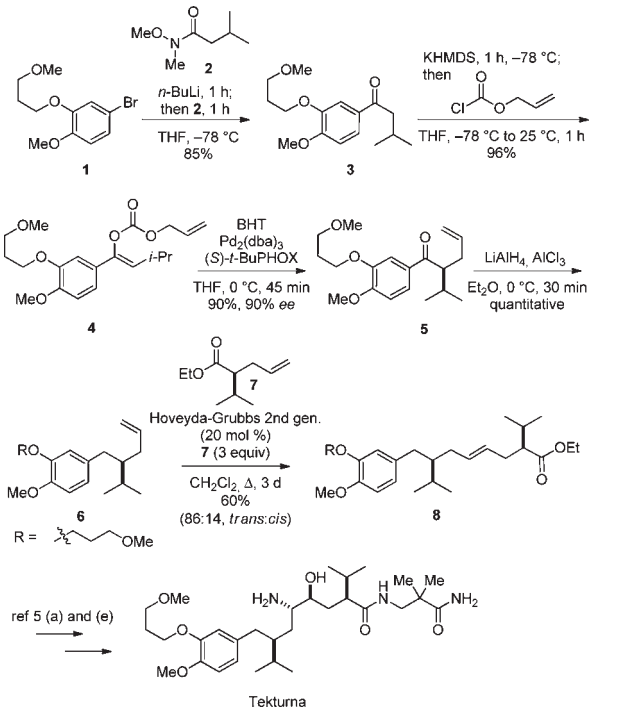
Tekturna (entry 7, Table 2). Steric bulk or chelating properties of an *ortho*-methoxy group required longer reaction times (entries 2 and 5, Table 2). The beneficial effect of 3,4-dialkoxy groups was evident when compared to the 3-methyl-4-methoxy variant (entry 8, Table 2), in which case the reaction time was considerably longer, especially when no BHT was added to the reaction mixture.

The mechanism of the catalytic asymmetric allylation of alkyl aryl allyl enol carbonates has been recently investigated in detail by Stoltz[15,18] and Trost,[13] employing their respective catalyst−ligand combinations (see Figure 1). Although "inner sphere" and "outer sphere" nucleophilic additions to π-allyl palladium species have been proposed

(17) For the effect of an alkoxide in a related reaction, see: Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480.

(18) (a) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876.

Scheme 2. Synthesis of the Patented Key Intermediate **8**



depending on the nature of the nucleophile, it is difficult at this point to define the role of protic additives such as BHT or *t*-BuOH in our case, other than to speculate their involvement as a proton source or a palladium-bound species[19,20] in one of the discrete intermediates in the catalytic cycle. The significant difference in the reaction times between the methyl and the isopropyl enol carbonates (entry 4, Table 2) can be attributed to a release of strain of the *Z*-isopropyl enol carbonate upon decarboxylation of a charged carbonate-palladium enolate (or its protonated counterpart).

With an efficient method to prepare the enantioenriched ketone **5** (Scheme 1), we turned our attention to an advanced key intermediate previously reported in the patent literature toward the synthesis of Tekturna (Scheme 2).[5]

Thus, treatment of **1** with *n*-BuLi, followed by addition of the Weinreb amide **2**, gave the ketone **3**. Formation of the potassium enolate and treatment with allyl chloroformate afforded the *Z*-enol carbonate **4**, as evidenced by NMR, in excellent overall yield. Application of the catalytic asymmetric allylation reaction led to the intended ketone **5**,[21] which was deoxygenated in the presence of $LiAlH_4$ and $AlCl_3$, leading to the corresponding olefin **6** in four steps from **1** in 73% overall yield. A cross metathesis reaction of **6** and the enantiopure ester **7**[6,22] in the presence of the Hoveyda–Grubbs second generation catalyst[23] led to **8** in 60% yield as a 84:16 *trans*/*cis* mixture.

In conclusion, we have studied the enantioselective α-allylation of alkyl aryl enol carbonates using a modified Stoltz protocol. Further transformation of the α-allylated isopropyl 3-methoxypropoxy-4-methoxyphenyl ketone **5** allowed the synthesis of an advanced key intermediate **8** in five linear steps from **1** and in 38% overall yield. This intermediate was previously prepared in a multistep convergent synthesis[5] and was used for the synthesis of Tekturna. The inclusion of BHT as an additive had a beneficial effect on reducing the reaction time and increasing the enantioselectivity of the α-allylation reaction leading to **5**. Further studies on the role of additives in the palladium-catalyzed enantioselective α-allylation of alkyl aryl and related ketones are in progress.

Acknowledgment. We thank NSERC (Canada) and FQRNT (Québec) for financial assistance. We thank Professor Collins and his group member (Université de Montréal) for the use of their GC and HPLC facilities.

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

(19) NMR spectroscopic studies showed no association of BHT with either the ligand or the starting isobutyl aryl enol carbonate. No nonlinear effect was observed. ^{31}P NMR indicated the presence of a new peak at 22.2 ppm, after addition of BHT to a freshly prepared Pd-ligand complex. In most of the cases, direct proton transfer on an enolate to give starting ketone was only observed in part (5 to 15%, on the crude NMR) when reactions were done at −20 °C or when reaction times were prolonged.

(20) Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341.

(21) Attempts to directly allylate the potassium enolate from ketone **3** in the presence of 2.5 mol % of $Pd_2(dba)_3$, 6.25 mol % of (*S*)-*t*-BuPHOX, and 1 equiv of (bis)-allyl carbonate yielded ketone **5** with a poor 13% isolated yield and 86% *ee*.

(22) Dowling, M. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 15090.

(23) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. 1–3.

The authors declare no competing financial interest.