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Pd-Catalyzed Aminations of Aryl Triazolones: Effective Synthesis of Hydroxyitraconazole Enantiomers.

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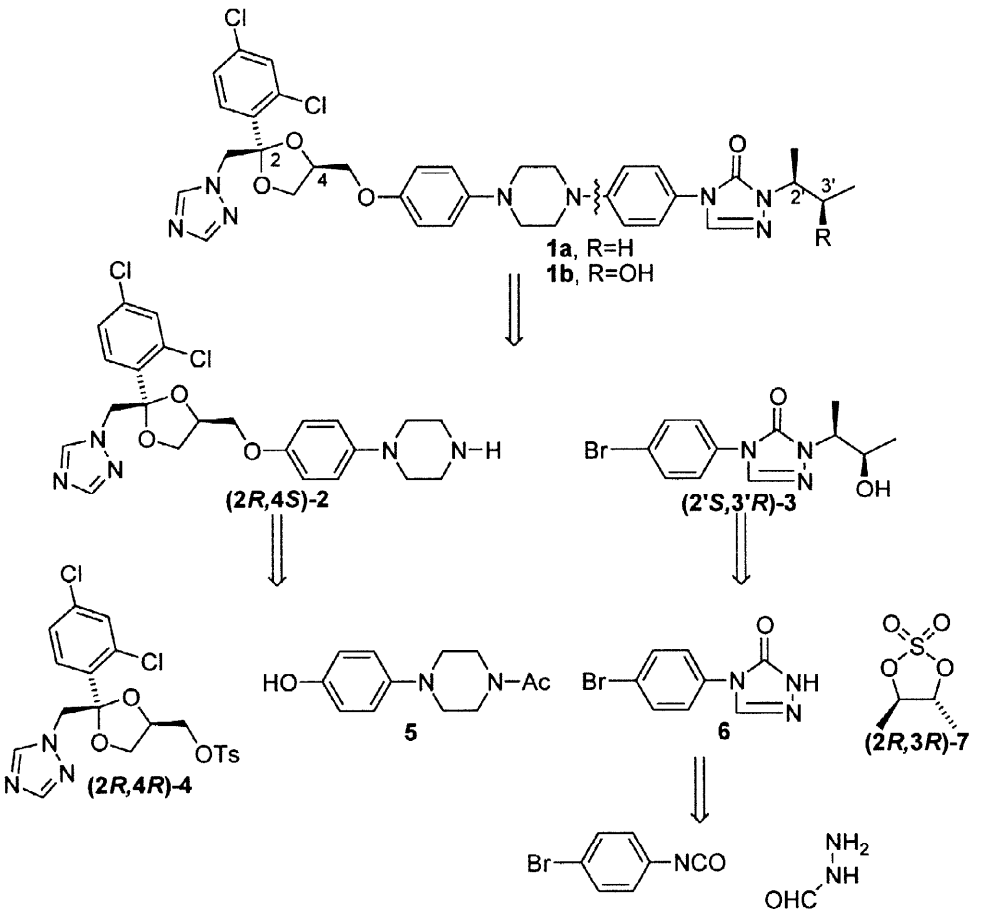
Abstract: A palladium-catalyzed amination of triazolone **3** by piperazine **2** was used as the key step in an efficient synthesis of highly enantiomerically-pure hydroxyitraconazole isomers. Compound **2** (>99%ee) was prepared by reaction of an achiral phenol precursor with the corresponding dioxolyl tosylate (>99% ee), and **3** was made by alkylation of **6** with **7** (>99%ee).

Itraconazole (**1a**) (Sporanox) and its active metabolite, hydroxyitraconazole (**1b**),[1] are members of a large class of azole antifungal and anti-yeast compounds.[2] Both compounds have a high molecular weight (706 and 722, respectively), when compared to other pharmaceutical agents, and contain a high degree of chemical complexity. An efficient synthesis of enantiomerically-pure *cis,syn*-hydroxyitraconazole isomers via alkylative ring-opening of an enantiomerically-pure cyclic sulfate by the triazolone anion of the central aromatic core has been reported.[3] Upon further analysis of the target molecule, two key C-N bond disconnections between the aromatic rings and the piperidine moiety were noted. In light of the recent advances in the Pd-catalyzed aminations of aromatic halides,[4,5] this synthetic approach toward the target molecule seemed viable. This manuscript highlights a novel synthesis of hydroxyitraconazole enantiomers via application of a Pd-catalyzed amination reaction. This is the first demonstration of the utility of a Pd-catalyzed C-N bond-forming reaction between two highly functionalized heterocyclic systems leading toward the synthesis of an active antifungal compound.

Scheme I



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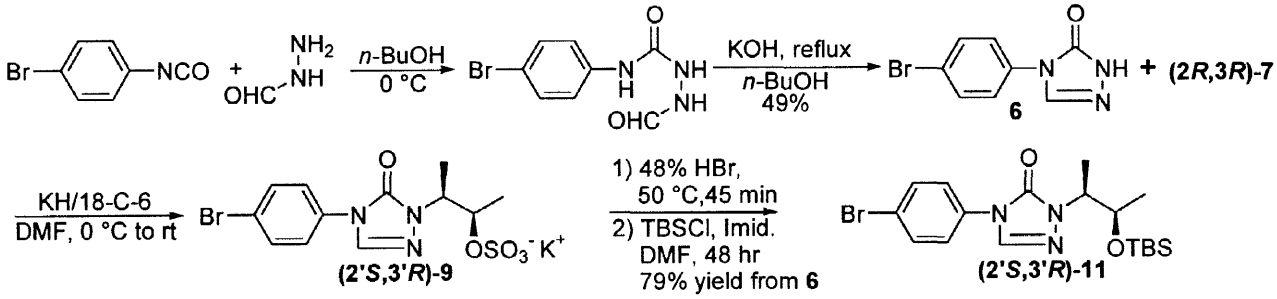
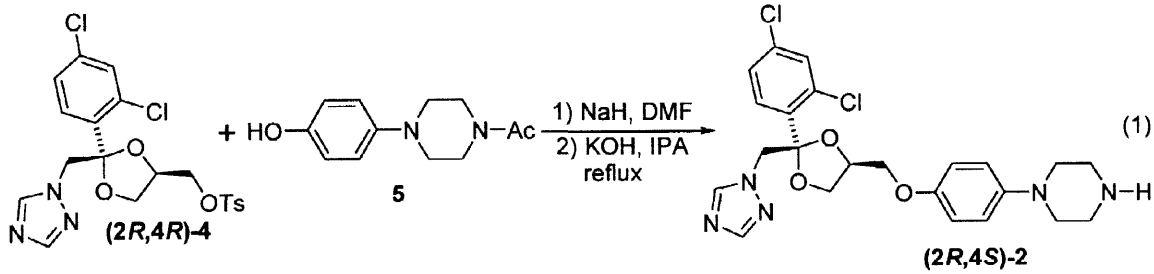
A retrosynthesis of hydroxyitraconazole is outlined in Scheme I. After evaluation of several synthetic strategies, we envisaged that the key bond disconnection would be the N-aryl bond, liberating the complex heteroatom segments (2*R*,4*S*)-**2** and (2'*S*,3'*R*)-**3**. Potentially, this critical bond could be formed by a palladium-catalyzed process as developed by Buchwald et al[4] and Hartwig et al.[5] Compound **2** could be prepared by the reaction of piperazine derivative **5** with tosylate (2*R*,4*R*)-**4** followed by hydrolysis, and (2'*S*,3'*R*)-**3** could be assembled by the alkylation of triazolone **6** with cyclic sulfate (2*R*,3*R*)-**7**[6] according to the methods of our previous synthesis of itraconazole and hydroxyitraconazole.[3] Compound **6** should be available from 4-bromophenyl isocyanate and formylhydrazine.

The silylated derivative of (2'*S*,3'*R*)-**3** was prepared according Scheme II. Reaction of readily available 4-bromophenyl-isocyanate and formyl hydrazine in *n*-butanol at 0 °C gave intermediate **8**. Addition of KOH and warming to reflux for 3 hr resulted in cyclization and dehydration to generate **6**. After diluting with water and acidifying, compound **6** was isolated in 49% yield by filtration. Deprotonation of **6** with KH/18-crown-6 in DMF followed by addition of cyclic sulfate (2*R*,3*R*)-**7** (99.78% ee)[7] at 0 °C resulted in a ring-opening alkylation with inversion to generate the *syn*-sulfate adduct (2'*S*,3'*R*)-**9**. The sulfate was hydrolyzed by treatment with 48% HBr at 50 °C for 45 min to give the corresponding alcohol, and the sterically-hindered hydroxyl group was converted to the TBS ether (TBSCl, imidazole, DMF, 48 hr, rt) to give (2'*S*,3'*R*)-**11** in 79% yield from **6**.[8] Chiral HPLC analysis showed that (2'*S*,3'*R*)-**11** was obtained in 99.78% ee.[9]

Scheme II



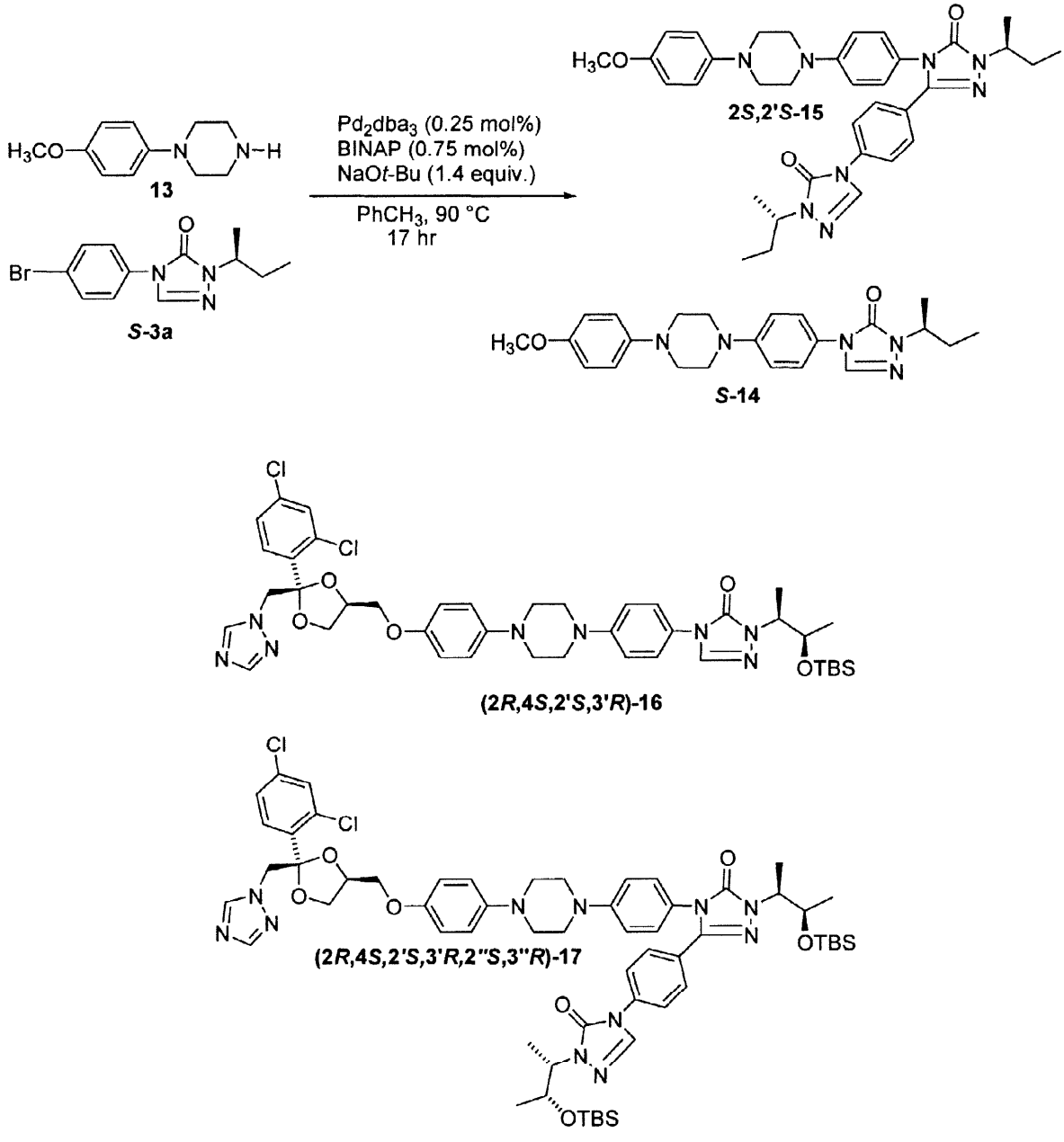
The synthesis of the left half of hydroxyitraconazole, (2*R*,4*S*)-**2**, is outlined in eq. 1. Reaction of (2*R*,4*R*)-**4** (>99% ee) with phenol **5** in DMF in the presence of NaH, followed by hydrolysis with KOH in refluxing 2-propanol, gave (2*R*,4*S*)-**2** in 85% yield.



Before embarking on the key synthetic step, preliminary experiments were conducted to understand the Pd-catalyzed amination process of triazolone-containing aryl bromides. Hence, as shown in Scheme III, the amination of *S*-**3a**[10] by **13** was studied. Coupling of *S*-**3a** with **13** using 0.25 mol% $Pd_2(dba)_3$, 0.75 mol% BINAP and 1.4 equiv. NaO*t*-Bu in toluene at 90 °C resulted in a 65% isolated yield of adduct *S*-**14** and a 7% isolated yield of (2*S*,2'*S*)-**15**, the product of a Heck coupling of *S*-**14** with *S*-**3a**. The structure of (2*S*,2'*S*)-**15** was determined by ^{1}H NMR, ^{13}C NMR, and mass spectral analysis (*m/e* 921, M^+). Attempts to minimize Heck adduct formation during the Pd-catalyzed amination reaction were unsuccessful. To the best of our knowledge, this is the first observation of a Heck coupling on a triazolone under the Pd-catalyzed amination conditions.

After understanding the competition between the two reaction processes (amination vs Heck), our attention was turned to the synthesis of hydroxyitraconazole. Reaction of the triazolone-containing aryl bromide (2'*S*,3'*R*)-**11** with 1.1 equivalents of the complex piperazine (2*R*,4*S*)-**2** in the presence of 0.5 mol% $Pd_2(dba)_3$, 1.5 mol% BINAP and 1.4 equivalents NaO*t*Bu in toluene at 85 °C for 3hr provided (2*R*,4*S*,2'*S*,3'*R*)-**16** in 81% yield, along with the Heck adduct (2*R*,4*S*,2'*S*,3'*R*,2''*S*,3''*R*)-**17** in 4%.[11] Surprisingly, less of the Heck product was observed with this more complex system. Deprotection with tetra-*n*-butylammonium fluoride in THF at room temperature for 17h gave hydroxyitraconazole in 91% yield and 99.78% ee.[12]

Scheme III



In conclusion, a novel synthesis of hydroxyitraconazole has been achieved via a key palladium-catalyzed amination reaction of two highly functionalized subunits. The synthesis is general and could be applied to all enantiomers of the target molecule. A

competition between C-N bond formation and Heck coupling to a triazolone moiety was observed. The scope of the Heck coupling process on to triazolones (and other heterocyclic systems) is being explored.

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7. The enantiomeric purity of **7** and its enantiomer were determined by chiral HPLC analysis of the dibenzyl ester of the 2,3-butanediol precursor. The analysis gave the following results: (*R,R*)-2,3-butane diol dibenzyl ester-99.89% (*R,R*), 0.11% (*S,S*) and (*S,S*)-2,3-butanediol dibenzyl ester-99.16%(*S,S*), 0.23% (*R,R*), 0.61% *meso*. HPLC conditions: Chiralpak AD, 10 μm, 4.6 mm X 25 cm, hexane/2-propanol (97:3), 1.0 mL/min, 220 nm
8. The steric hiderance of the hydroxyl group was evidenced by its reluctance to be converted to the corresponding benzyl ether. Use of benzyl trichloroacetamidate/TfOH in CH_2Cl_2 resulted in 60% conversion after 16 hr at room temperature.
9. The enantiomeric purity of **11** and its enantiomer were determined by chiral HPLC analysis. The analysis gave the following results: (2'*S*,3'*R*)-**11**-99.89% (2'*S*,3'*R*), 0.11% (2'*R*,3'*S*) and (2'*R*,3'*S*)-**11**-99.16%(2'*R*,3'*S*), 0.23% (2'*S*,3'*R*), 0.61% (2'*R**,3'*R**). HPLC conditions: Chiralpak AD, 10 μm, 4.6 mm X 25 cm, hexane/ethanol (95:5), 1.0 mL/min, 220 nm
10. Compound *S*-**3a** can be prepared analogously to (2'*S*,3'*R*)-**9** by the alkylation of **6** with 2*R*-tosyloxybutane without racemization.
11. Attempts to couple the desilylated analog of (2'*S*,3'*R*)-**11** resulted in partial product formation (<10%) and catalyst deactivation, even in the presence of 2.8 equivalents of NaO*t*Bu.
12. Synthesis of (2*R*,4*S*,2'*S*,3'*R*)-**16**: **16:** (2*R*,4*S*)-4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine ((2*R*,4*S*)-**5**) (110 mg, 0.28 mmol), 2,4-dihydro-4-bromophenyl-2-[(1*S*,2*R*)-[2-(1,1-dimethylethyl)dimethylsiloxy-1-methylpropyl]]-3H-1,2,4-triazol-3-one ((2*S*,3*R*)-**26**) (110 mg, 0.25 mmol), tris(dibenzylideneacetone)dipalladium (2.3 mg, 0.0025 mmol), BINAP (4.7 mg, 0.0075 mmol) and sodium *tert*-butoxide (34 mg, 0.35 mmol) were combined into a dry flask. The contents were vacuum purged with argon (3x). To this was added degassed toluene (1.25 ml), and the entire solution was purged by bubbling argon through it. The reaction mixture was warmed to 85 °C for 3 hr, cooled to room temperature, and ethyl acetate and water were added. The phases were separated and the aqueous phase was extracted with ethyl acetate (3x). After drying the combined organic phases over anhydrous magnesium sulfate, filtering and removing the solvent *in vacuo*, the crude material was purified by flash chromatography (98:2 chloroform:methanol) followed by purification on a Chromatotron (the plate wetted with chloroform and eluted with 98:2 chloroform:methanol) to give 171 mg (81% yield) of the desired product (2*R*,4*S*,2'*S*,3'*R*)-**16**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.89 (s, 1H), 7.64 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.25 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.85 (d_{AB}, *J* = 14.7 Hz, 1H), 4.75 (d_{AB}, *J* = 14.7 Hz, 1H), 4.36 (m, 1H), 4.27 (m, 1H), 4.21 (m, 1H), 3.92 (t, *J* = 6.7 Hz, 1H), 3.79 (m, 2H), 3.67 (d, *J* = 2.5 Hz, 1H), 3.48 (dd, *J* = 9.8, 6.5 Hz, 1H), 3.36 (m, 4H), 3.24 (m, 4H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6, 152.0, 151.3, 150.7, 145.9, 144.9, 136.0, 134.3, 134.0, 133.1, 131.4, 129.6, 127.2, 125.3, 123.7 (2C), 118.4 (2C), 116.6 (2C), 115.2 (2C), 107.6, 74.7, 69.8, 67.6, 67.4, 57.3, 53.5, 50.5 (2C), 49.1 (2C), 19.4, 12.4.