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Graphical Abstract

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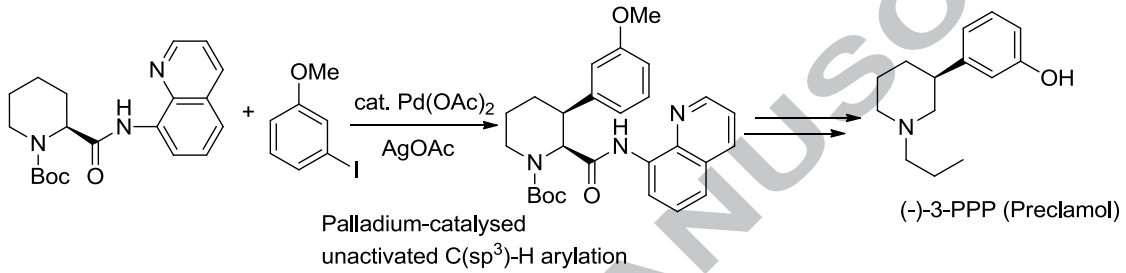
Shi-Jin Zhang,[a] Wen-Wu Sun,[b] Qun-Ying Yu,[c] Pei Cao, [c] Xiao-Ping Dong,[a] Bin Wu*[,b,c]



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ABSTRACT

An efficient route for the preparation of (-)-3-PPP(preclamol) using the highly stereoselective palladium-catalysed C(sp^3)-H arylation and radical decarboxylation reaction as the key steps is described. The chiral center at the C-3 position of L-pipecolinic acid derivative formed in the key reaction was completely induced by the adjacent stereocenter of the substrate, which was confirmed by the data of chiral HPLC analysis. Substitution effect of nitrogen on the efficiency of Pd-catalysed C(sp^3)-H arylation reaction was explored with substantial experiments including the X-ray single-crystal diffraction analysis of palladium-complex-2.

1. Introduction

3-Arylpiperidines have been attracting the chemist's interesting since the early 1980s because of their great biologically active value. The most potent therapeutically active compounds for central dopamine autoreceptor stimulating activity is (-)-3-(3-hydroxyphenyl)-*N*-(*n*-propyl)-piperidine [(-)-3-PPP, Preclamol],[1-8] which is also reported to be the first selective D_2-like dopamine autoreceptor agonist.[7,8] In addition, preclamol was tested for antipsychotic potential with therapeutic effect in the treatment of schizophrenia and Parkinson's diseases.[9-11] Furthermore, preclamol has been extensively studied as a pharmacological tool to investigate dopaminergic mechanisms.[12-15]

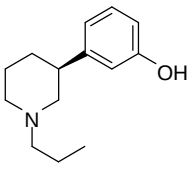

Figure 1. The structure of (-)-3-PPP

Over the past few decades, methodologies have been developed for the synthesis of the racemic proclamol, including transition-metal catalysed cross-coupling reaction with the Grignard reagents and aryl halides,[16] Heck reaction,[17] formal [3+3] cycloaddition reaction of α-sulfonyl acetamide,[18] Pd-catalysed C(sp^2)–H arylation of pyridine[19] and C(sp^3)–H arylation at the C-3 position of *N*-Boc piperidines.[20] Due to its significant biological activities, a great many methods for the stereoselective synthesis of (-)-3-PPP based on chiral-pool-derived routes, auxiliary-controlled methods, and catalytic, asymmetric reactions have been reported.[21] However, these kinds of previous procedures suffered from some limitations such as tedious chiral resolution process, expensive air- or moisture-sensitive reagents and expensive chiral ligands or auxiliary. Therefore, the development of an efficient and stereoselective route for the preparation of (-)-3-PPP is highly desirable.

Powerful synthetic methods based on the regioselective functionalization of unactivated C(sp^3)-H bonds with the assistant of various directing groups are becoming readily available.[22] Inspired by the Daugulis[23] seminal report on the palladium-catalysed arylation of unactivated C(sp^3)-H bonds using 8-aminoqunoline (AQ) as bidentate directing group, this methodology was also employed in the direct C(sp^3)-H arylation of cyclopropanes,[24] cyclobutanes,[25] acyclic amino acids,[26] and proline derivatives.[27] Recently, Bull[28] and our group[29] described the C(sp^3)-H arylation reaction at the C-3 position of L-pipecolinic acid derivatives by palladium catalysis. Encouraged by these promising results, we envisioned to develop an efficient and stereoselective route for the preparation of (-)-3-PPP using

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palladium-catalysed C(sp^3)-H arylation reaction as a key step. The chiral center at the C-3 position of L-pipecolinic acid derivative formed in the key reaction was completely induced by the adjacent stereocenter of the substrate, which was confirmed by the data of chiral HPLC analysis.

2. Results and discussion

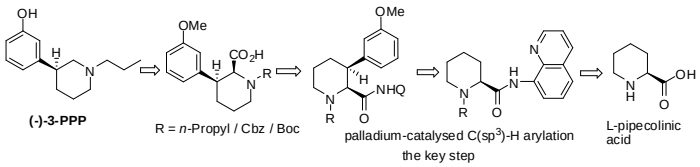
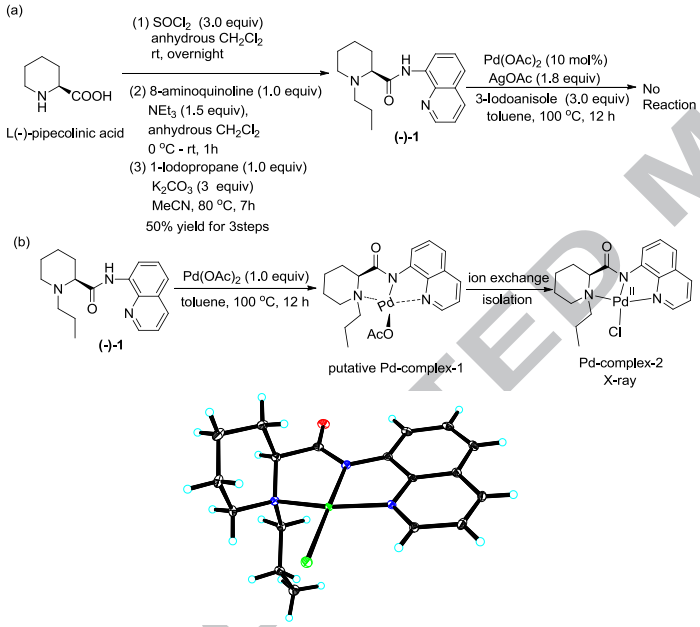


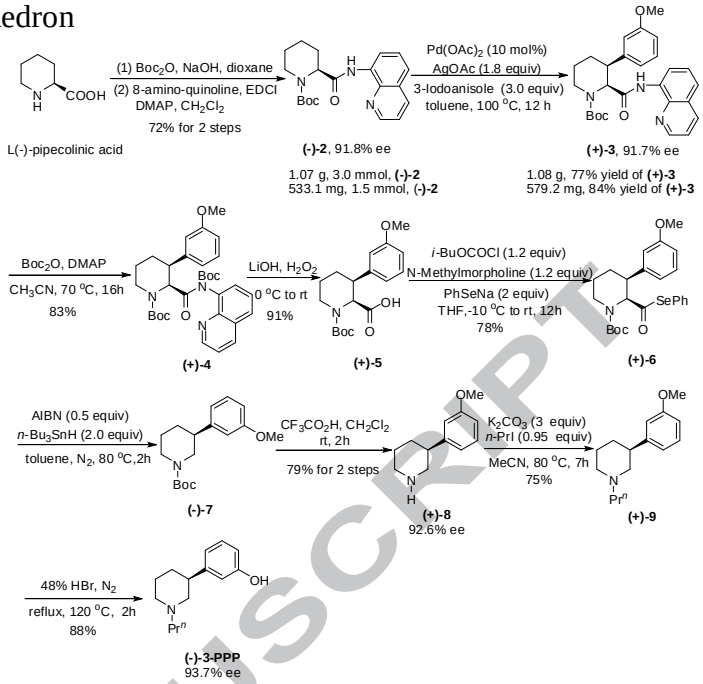
Figure 2. Retrosynthetic analysis for the preparation of **(-)-3-PPP**

In view of retrosynthetic analysis for the preparation of **(-)-3-PPP** (Figure 2), we have set up the right conditions for palladium-catalysed C(sp^3)-H arylation in our previous work.[29] However, the reaction proceeded with substrates bearing Boc or Cbz group on the piperidinyl nitrogen. Obviously, the choice of substitution groups on the nitrogen is still an issue. If the key reaction occurred with substrate bearing *n*-propyl group on the piperidinyl nitrogen, that would be a more efficient sequence to make (-)-3-PPP.



Scheme 1. Exploration of substitution effect of the piperidinyl nitrogen on the efficiency of Pd-catalysed C(sp^3)-H arylation

To test our hypothesis, we initiated our studies by preparing substrate **(-)-1** through 3 steps in 50% yield. We tried the Pd-catalysed C(sp^3)-H arylation reaction with substrate **(-)-1** in our standard conditions. However, the reaction did not work (a, Scheme 1). In order to find out the reason, the reaction with a stoichiometric amount of palladium acetate was conducted (b, Scheme 1). Some characterized signals of Pd-complex-1 were found in the ^{1}H and ^{13}C NMR spectrum of the crude sample. After isolation through a short column of diatomite, Pd-complex-2 was obtained and its structure was confirmed by X-ray single-crystal diffraction analysis.[30] These results well demonstrate that electron-donating groups on the piperidinyl nitrogen promote the nitrogen atom to coordinate strongly with palladium to form the stable palladium-complex-2, which inhibits the C(sp^3)-H arylation reaction.



Scheme 2. An efficient route for the preparation of (-)-3-PPP.

Next, we moved back to use N-Boc protected amide compound **(-)-2** as the substrate. As outlined in Scheme 2, the amide compound **(-)-2** was synthesized from the readily commercially available L-(-)-pipecolinic acid according to a literature procedure.[29] Enantioselective value of the purified compound **(-)-2** was identified to be 91.8% based on the data of chiral HPLC analysis (see Experimental Section). That means enantiopurity of the starting material L-(-)-pipecolinic acid we bought is probably not 100%. Compound **(-)-2** was smoothly arylated through palladium catalysis with 3-iodoanisole to afford compound **(+)-3** in 84% yield and 91.7% *ee*. This result indicated that the chiral center at the C-3 position of compound **(+)-3** formed in the key reaction was completely induced by the adjacent stereocenter of the substrate **(-)-2**. Furthermore, this arylation reaction proceeded successfully on a larger scale, affording 1.08 g of compound **(+)-3** in 77% yield. Removal of the 8-aminoquinoline directing group in (+)-3 delivered compound **(+)-5** through a mild, two-step sequence via (+)-4. Compound **(+)-6** was made with NaSePh under the help of isobutyl chloroformate and *N*-methylmorpholine, and then underwent radical decarboxylation reaction to afford compound **(-)-7** in excellent yield. On the other hand, after the free radical reaction, addition of CF_3COOH could remove the *N*-Boc protecting group to give the piperidine **(+)-8** in 79% yield and 92.6% *ee*. After S_N2-type reaction of (+)-8 with 1-iodopropane, compound **(+)-9** was obtained in 75% yield. Finally, *N*-alkylated piperidine **(+)-9** was converted to the target drug **(-)-3-PPP**(preclamol) in 88% yield and 93.7% *ee* after demethylation.

3. Conclusion

In conclusion, we have developed an efficient route for the preparation of (-)-3-PPP(preclamol) employing the highly stereoselective palladium-catalysed C(sp^3)-H arylation and radical decarboxylation reaction as the key steps. Substitution effect of the piperidinyl nitrogen on the efficiency of Pd-catalysed C(sp^3)-H arylation reaction was explored with substantial experiments including the X-ray single-crystal diffraction analysis of palladium-complex-2.

Acknowledgments

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30. The CIF file of Pd-complex-2 has been deposited with Cambridge Crystallographic Data Centre (# CCDC 1506812). These data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

The Supporting Information is available free of charge on the website.

X-ray crystallographic analysis, ^{1}H and ^{13}C NMR spectra of new compounds (PDF).

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Highlights

An efficient route for the preparation of (-)-3-PPP is described.

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