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Synthesis of Pyrrolo[1,2-*b*]isoquinolines through Carbopalladation Initiated Domino Reactions. Evaluation as New Antileishmanial Agents

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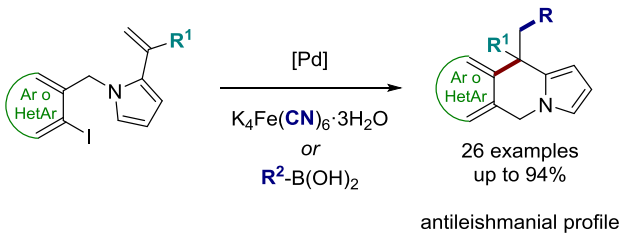
Graphical Abstract



Abstract. A series of C-10 substituted pyrrolo[1,2-*b*]isoquinolines have been synthesized via palladium-catalyzed Heck/Suzuki and Heck/anion capture cascade reactions. These compounds have shown antileishmanial activity against cutaneous (*L. amazonensis*) leishmaniasis, being even 10-fold more potent and selective than the drug of reference, Miltefosine. A Perturbation Theory Machine Learning (PTML) model has also been developed for the prediction of the probability with which a query compound reaches a desired level for multiple parameters *vs.* different *Leishmania* species and target proteins.

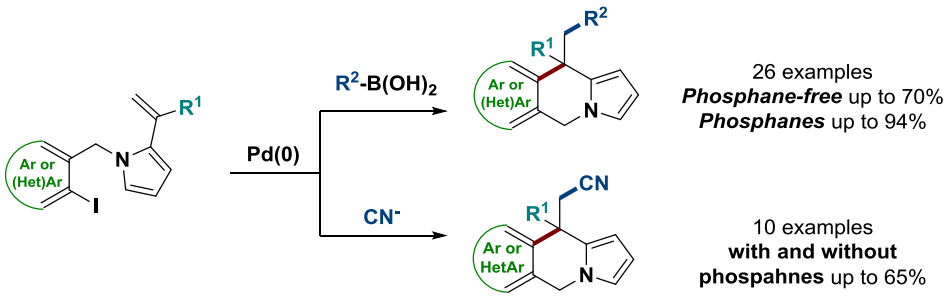
Introduction

Palladium-catalyzed carbopalladation-initiated domino reactions (cascade cyclizations) are powerful carbon-carbon bond-forming processes for the construction of functionalized carbocycles and heterocycles with quaternary stereocenters.[1] The starting point is an intramolecular Mizoroki-Heck reaction, which leads to an σ-alkylpalladium intermediate that can be involved in another cross-coupling reaction or in an anion capture event. The Heck-type cascade processes reported in literature have been mainly applied to the construction of five-membered rings, so our aim will be to expand the scope of the procedure to the synthesis of six-membered rings. Taking advantage of our experience in palladium-catalyzed reactions for the synthesis of heterocycles,[2] we have developed palladium-catalyzed Heck/Suzuki and Heck/cyanation cascade reactions over 2-alkenyl substituted

benzylpyrroles for the construction of different pyrrolo[1,2-*b*]isoquinolines with a quaternary center a C-10, whose antileishmanial activity has also been investigated.

Results and Discussion

Our first goal was to perform an intramolecular palladium(0)-catalyzed 6-*exo* carbopalladation/Suzuki coupling cascade reaction on 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles to access pyrrolo[1,2-*b*]isoquinoline scaffolds with a quaternary center at C-10. We have been able to control the chemoselectivity of the process to favor the 6-*exo* carbopalladation by choosing the adequate catalytic systems and experimental conditions. Although environmentally friendly phosphane-free precatalytic systems [e.g. $Pd(OAc)_2$, Na_2CO_3, nBu$_4$NCl (2 equiv.) in DMF] favor the 6-*exo* carbopalladation reaction vs. the direct Suzuki coupling, in some cases the 7-*endo* process could not be completely suppressed. However, no 7-*endo* process occurred when $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of phosphane ligands, as tri(furan-2-yl)phosphane, were used. In both cases, the use of nBu$_4$NCl is essential to allow the 6-*exo* carbopalladation to occur at a competitive rate, avoiding the direct Suzuki coupling.[3] The procedure has a wide scope, being compatible with both electron-rich and electron-deficient arylboronic acids, and different substitution patterns on the alkene and the aromatic ring. Thus, an efficient route to substituted pyrrolo[1,2-b]isoquinolines (yields up to 94%, 22 examples) has been developed.[4]



Scheme 1

On the other hand, a palladium-catalyzed intramolecular Heck/anion capture cascade reaction over the 2-alkenyl *N*-(*o*-iodobenzyl)pyrroles led to the C-10b cyanomethyl substituted pyrrolo[1,2-*b*]isoquinolines generating a quaternary stereocenter. In this domino process, the use of ligands has not a beneficial effect in the Heck/cyanation sequence, while the use of $K_4Fe(CN)_6{\cdot}3H_2O$ as cyanation agent, nBu$_4$NCl as additive and water as co-solvent were crucial to control the chemoselectivity. Although this Heck/cyanation sequence can be applied to various substrates with different substitution patterns on the aromatic ring, the yields were moderate yields, as direct cyanation process was always competitive (Scheme 1).

At this point, we decided to investigate the antileishmanial activity of C-10 substituted pyrrolo[1,2-*b*]isoquinolines, as it is known that isoquinoline alkaloids may present biological activity against tropical diseases caused by protozoan parasites, such as leishmaniasis.[5] Thus, biological assays of leishmanicidal activity against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis revealed that some of the C-10 substituted pyrrolo[1,2-*b*]isoquinolines were more active and less toxic than the drug of reference, Miltefosine, for cutaneous leishmaniasis (Figure 1).

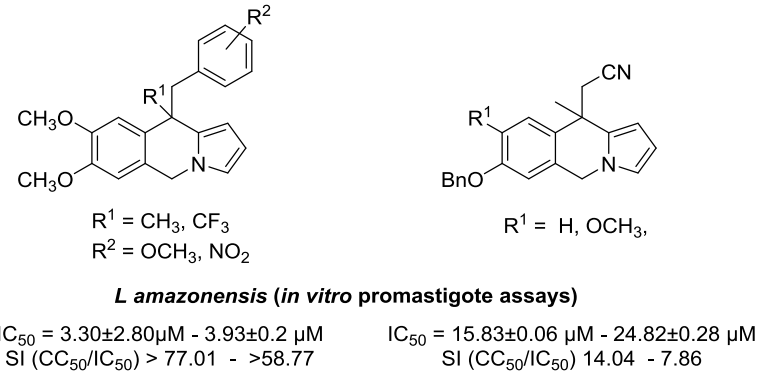


Figure 1

Finally, the developed Perturbation Theory Machine Learning (PTML) model with > 145,000 antileishmanial assays reported in ChEMBL for > 65,000 compounds can predict the probability of a query compound to reach a desired level for multiple parameters (IC_{50}, K_i, etc.) of pyrroloisoquinoline scaffolds *vs*. different *Leishmania* species and target proteins.

Conclusions

It has been demonstrated that C-10 disubstituted pyrrolo[1,2-*b*]isoquinolines with a quaternary center can be efficiently synthetized through a palladium-catalyzed 6-*exo* carbopalladation of 2-alkenyl substituted *N*-(*o*-iodobenzyl)pyrroles, followed by an intermolecular Suzuki coupling reaction or a cyanide trapping process. In addition, several compounds have shown promising *in vitro* antileishmanial profile against visceral (*L. donovani*) and cutaneous (*L. amazonensis*) leishmaniasis. Finally, the developed Perturbation Theory Machine Learning (PTML) model can be utilized to explore the antileishmanial activity against other *Leishmania* species, so it could be a useful tool to reduce biological assay costs.

References

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