Modification of Natural Products via Chan-Lam Coupling: A Greener Approach for C-Heteroatom Bond Formation

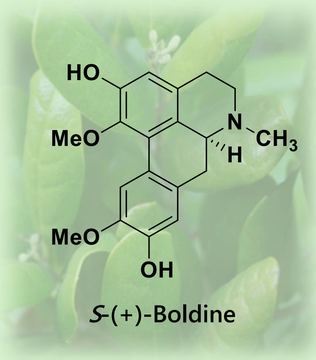
Cristóbal Hormazábal-Campos,*[,1] and Edwin G. Pérez[1]

[1] Department of Organic Chemistry, Faculty of Chemistry and Pharmacy, Pontificia Universidad Católica de Chile, Santiago 7820436, Chile.
*cihormazabal@uc.cl

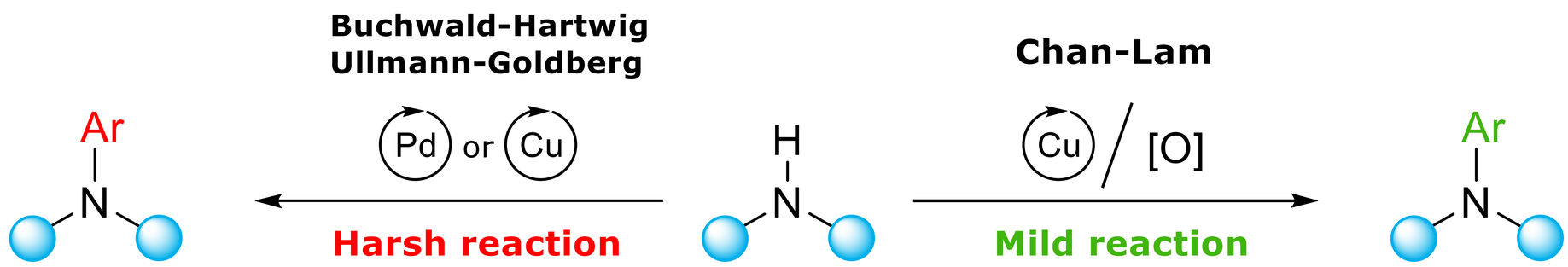
Introduction

Natural products, derived from various sources such as plants, microorganisms, and marine organisms, have long been recognized as a rich and diverse source of biologically active compounds with a wide range of therapeutic applications. Different natural products like boldine and viridicatin, both alkaloids, exhibit potential applications as anticancer, antioxidant, antihypertensive, antimicrobial, among others.

Natural products also constitute a source of renewable and sustainable substrates for the Chan-Lam coupling. The Chan-Lam reaction is a copper-catalyzed oxidative cross-coupling of amines, phenols, and other nucleophiles with aryl boron species. The Chan-Lam coupling stands out for its alignment with green chemistry principles, enabling the efficient formation of carbon-heteroatom bonds under environmentally friendly conditions, such as room temperature and open flask setups. For this reasons, this reaction offers notable advantages over the Ullmann–Goldberg and Buchwald–Hartwig reactions, as it avoids the use of palladium and proceeds under milder conditions.



Principal differences between Chan-Lam coupling and common methodologies for C-Het bond formation



Harsh reaction conditions

- ☒ High temperatures.
- ☒ Toxicity and cost of the Pd catalyst.
- ☒ The use of ligands adds complexity and cost.

Mild reaction conditions

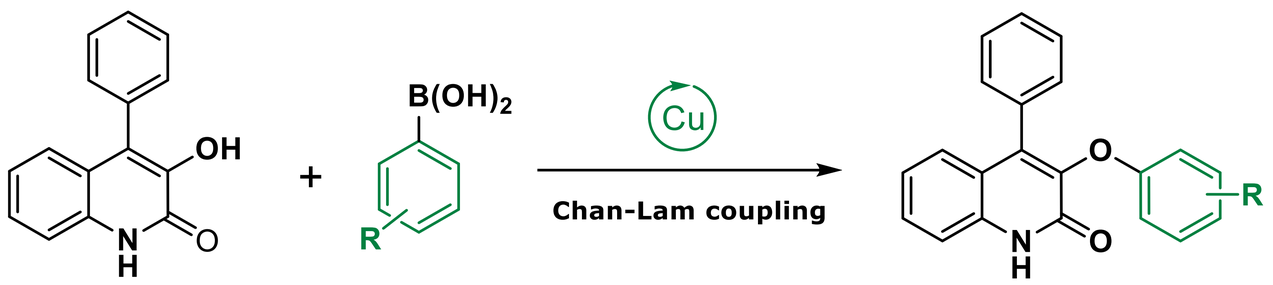
- ✓ Can be performed at room temperature and under open-flask conditions.
- ✓ Low cost and low toxicity of the catalyst.
- ✓ Does not require ligands.

Viridicatin

Viridicatin is an alkaloid of fungal origin, first isolated in 1953 from *Penicillium viridicatum* by K. G. Cunningham and G. G. Freeman.

- No cross-coupling reactions have been reported in literature for this alkaloid.
- Chemoselective Chan-Lam coupling methodologies are rare in literature, with this study the oxygen in position 3 can be arylated without any *N*-aryl byproduct formation.
- Some derivatives exhibit antibacterial activity against Gram-positive bacteria.

Chemoselective synthesis of 3-*O*-arylviridicatin derivatives by Copper-Catalyzed Chan-Lam coupling

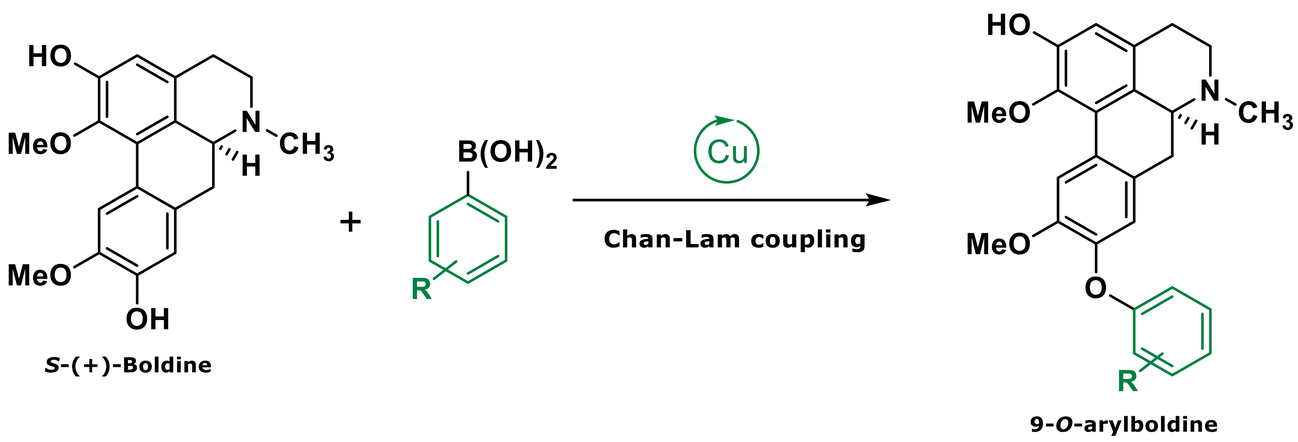


Boldine

(*S*)-(+)-Boldine is the main alkaloid found in the bark of the Chilean boldo tree. It was first isolated over 160 years ago by Bourgoin and Verne.

- A single nearly 50-year-old study of the *O*-arylation of boldine under Ullmann conditions was reported.
- Although the substitution at the C-9 phenol group was not unequivocally confirmed.
- In this study we unequivocally demonstrate the 9-*O*-arylation of boldine based on NOESY correlations.
- The reaction conditions allow the formation of this new derivatives at room temperature employing copper salts as catalyst.

Regioselective synthesis of 9-*O*-arylboldine derivatives by Copper-Catalyzed Chan-Lam coupling



Conclusions

This poster presents two novel synthetic approaches for the chemoselective modification of viridicatin and the regioselective modification of boldine, employing the copper-catalyzed Chan-Lam coupling reaction. The development of the Chan-Lam coupling it is important to make progress in new sustainable practices in organic synthesis, due the inherent strong alignment with green chemistry principles, as it enables the efficient formation of carbon-heteroatom bonds under environmentally friendly conditions.