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Carbon Dioxide-Mediated C(sp^2)−H Arylation of Primary and Secondary Benzylamines

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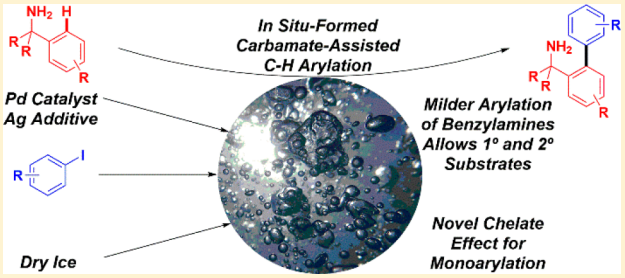
Supporting Information

ABSTRACT: C−C bond formation by transition metal-catalyzed C−H activation has become an important strategy to fabricate new bonds in a rapid fashion. Despite the pharmacological importance of *ortho*-arylbenzylamines, however, effective *ortho*-C−C bond formation of free primary and secondary benzylamines using Pd^{II} remains an outstanding challenge. Presented herein is a new strategy for constructing *ortho*-arylated primary and secondary benzylamines mediated by carbon dioxide (CO_2). The use of CO_2 with Pd is critical to allowing this transformation to proceed under relatively mild conditions, and mechanistic studies indicate that it (CO_2) is directly involved in the rate-determining step. Furthermore, the milder temperatures furnish free amine products that can be directly used or elaborated without the need for deprotection. In cases where diarylation is possible, an interesting chelate effect is shown to facilitate selective monoarylation.



INTRODUCTION

Amines are a ubiquitous functional group, being especially important in polymers[1−3] and pharmaceuticals.[4,5] Despite many classical[6−8] and modern[9−12] approaches to their synthesis, however, new methods are still in demand to access new chemical space surrounding these functional groups.[13] One strategy for preparing amines that has recently been gaining traction has been to functionalize C−H bonds through C−H activation[14−17] and C−H functionalization[18−20] methods. These approaches can allow rapid access to compounds that were either inaccessible with conventional synthetic methods, or required more lengthy synthetic routes, thereby expediting and improving drug library synthesis.[21] Although primary and secondary aliphatic amines often require prefunctionalization with *static* directing groups to facilitate C−H bond activation and prevent undesirable substrate oxidation under palladium-catalyzed protocols,[22−29] aromatic C−H bonds have generally been more easily targeted. For this reason free homobenzylamines[30,31] have been widely used as substrates for a variety of palladium-catalyzed C−H activation reactions without the need to prefunctionalize the amine. It is therefore interesting to note that there was until recently no example in the literature whereby free primary *ortho*-aryl benzylamines could be directly accessed via C−H arylation,[32] and there is still no method for the same transformation on free secondary benzylamine substrates. Because of the importance of the biaryl moiety in a number of biologically active molecules (Figure 1),[33−35] we considered that the ability to directly access free primary and secondary *ortho*-aryl benzylamines directly under milder conditions would have utility to the synthetic community.

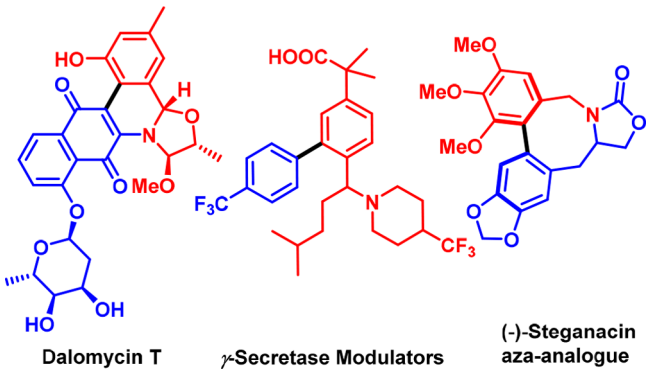


Figure 1. Examples of biologically active *ortho*-aryl benzylamines.

Ortho-aryl benzylamines are generally prepared directly from biaryl nitriles via reduction[36,37] or an azidation/reduction sequence, also from a preformed biaryl species.[38] Alternatively, they can be prepared from *protected* benzylamines via Suzuki−Miyaura cross-coupling[39,40] or directed C−H arylation.[41] However, it was not until 2006 that Daugulis was able to show the first example of Pd-catalyzed *ortho*-arylation utilizing free primary and secondary benzylamines as substrates.[42] Though the arylation strategy was successful, the harsh conditions led to partial protection of the substrate and product as acetamides, which led to the need to fully protect the amines for isolation. Furthermore, the substrate scope of secondary amines was only demonstrated for *N*-methylbenzyl-

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