

Carbon Dioxide-Mediated C(sp³)-H Arylation of Amine Substrates

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S Supporting Information

ABSTRACT: Elaborating amines via C–H functionalization has been an important area of research over the past decade but has generally relied on an added directing group or sterically hindered amine approach. Since free-amine-directed C(sp³)-H activation is still primarily limited to cyclization reactions and to improve the sustainability and reaction scope of amine-based C–H activation, we present a strategy using CO₂ in the form of dry ice that facilitates intermolecular C–H arylation. This methodology has been used to enable an operationally simple procedure whereby 1° and 2° aliphatic amines can be arylated selectively at their γ -C–H positions. In addition to potentially serving as a directing group, CO₂ has also been demonstrated to curtail the oxidation of sensitive amine substrates.

Amines are a key functional group in pharmaceuticals¹ and agrochemicals² (Figure 1) as well as materials³ and have

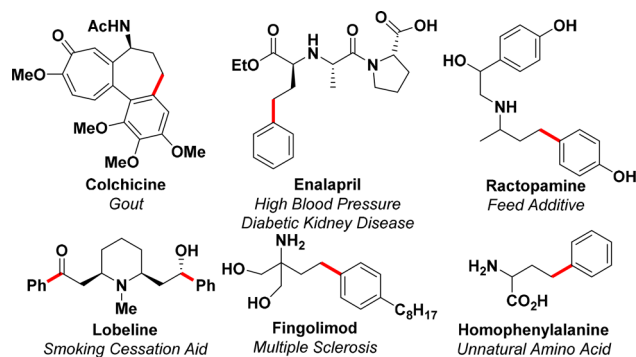


Figure 1. Biologically active compounds bearing a γ -arylamine motif.

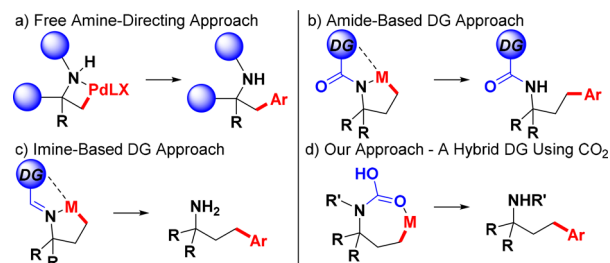
been the subject of numerous synthetic approaches.⁴ Although transition-metal-catalyzed C–H activation has revolutionized the installation of functional groups at otherwise inert C–H bonds,⁵ amines are still a complicated substrate class for this strategy because of their reactivity. Primary (1°) and secondary (2°) amines are especially sensitive to oxidation, making them a challenge for organometallic reactions:⁶ palladium, for example, is well-known for its ability to oxidize 1° and 2° amines.⁷ Furthermore, amines can react with organometallics to produce substituted amines, such as in the Buchwald–Hartwig coupling.⁸ Despite these challenges, there are examples of palladium-catalyzed C–H activation of both 1° and 2° free-amine substrates in the literature, yet these have generally

featured either activation of more reactive C(sp²)-H bonds⁹ or intramolecular cyclization.¹⁰ We present herein an alternative strategy for overcoming these barriers using carbon dioxide to mediate C–H activation.

Recent work has suggested that *in situ* protection of the amine as an ammonium ion can be used to protect it from oxidation, thereby facilitating remote C(sp³)-H oxidation reactions by deactivation,¹¹ while a recent report even suggests 1° amine- or ammonium-directed C(sp³)-H oxidation.¹² However, 1° and 2° amines generally require the presence of a directing group (DG) to facilitate C–C bond-forming C(sp³)-H activation.¹³ The only exception to this is when 2° amine substrates bearing fully substituted α,α' -centers are used.¹⁴ The strategy can also be applied to primary β -amino alcohols by first converting them into highly substituted aminoketals, although neither strategy enjoys a particularly broad substrate scope.¹⁵

The traditional method to facilitate DG-mediated C(sp³)-H arylation of amines has been to use static functional groups such as amides with or without a second chelating moiety (Scheme 1b),¹⁶ while a recent trend has focused on *transient*

Scheme 1. Strategies for Amine-Directed C(sp³)-H Arylation



DGs (Scheme 1c).¹⁷ Though each can be used to facilitate C(sp³)-H activation reactions, both possess disadvantages that might be alleviated. Static DGs require additional stoichiometric reagents and are both atom- and step-uneconomical. Meanwhile, transient DGs, which are generally aldehyde-based, suffer from the presence of oxidation-sensitive imines as intermediates. Furthermore, static DGs are rarely used for C–H activation of 2° amine substrates, while transient DG methods are nonexistent.

To circumvent the challenges of these two strategies, we sought a *hybrid DG* strategy (Scheme 1d). Carbon dioxide was

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