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sp³ C−H Bond Arylation Directed by Amidine Protecting Group: α-Arylation of Pyrrolidines and Piperidines

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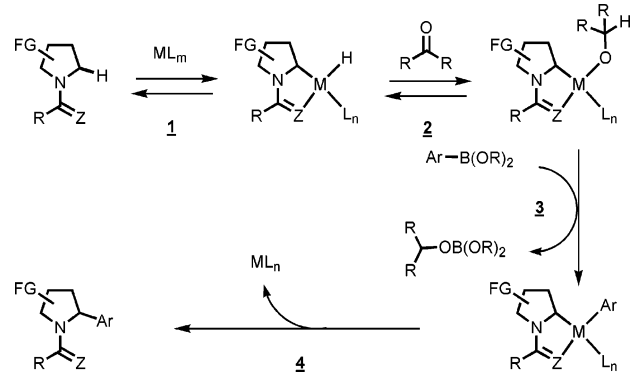
The direct arylation of sp³ C−H bonds is a process of significant synthetic potential.[1] As part of a broad program aimed at the development of catalytic methods for arylation of heterocyclic compounds,[2] we became interested in the α-arylation of saturated cyclic amines. Preliminary experiments revealed that the directed palladation−arene ring transfer sequence, developed by us[3] and others,[4] for arylation of alkyl sp³ C−H bonds would not be readily applicable to this class of substrates. In this communication, we describe a different approach to this problem based on a low-valent metal catalyst, which afforded a rare example of catalytic sp³ C−H bond arylation in substrates where *β*-hydride elimination is possible.

The first elemental step of the proposed scheme involves the insertion of a low-valent transition metal into the desired sp³ C−H bond (Scheme 1). Assuming that this is feasible, the next key issue is transforming the resulting metal hydride into the corresponding metal-aryl intermediate, without reaching a high oxidation state of the metal center. This could be achieved through the intermediacy of a metal-alkoxide, formed via ketone insertion, which could undergo transmetalation with an arylboronate ester. The subsequent reductive elimination renders the final product and regenerates the catalyst.

The inspiration for this proposal was drawn from a recent discovery by Kakiuchi and Chatani that revealed the feasibility of this sequence, albeit in the context of aromatic substrates (ruthenium-catalyzed *ortho*-arylation of ketones).[5] The success of this approach with saturated substrates was uncertain owing to several key issues. First, metal insertion at an sp³ center is much less facile than at an aromatic ring. Second, the feasibility of the C−C bond formation is questionable, as the corresponding step in directed alkylation of arenes was slow.[6] Third, all of the proposed alkyl−metal intermediates would have to be stable to *β*-hydride elimination. With respect to the third point, previous work by Jun,[7] Murai,[8] and our group[9] has established the feasibility of α-functionalization of saturated amines in preference to *β*-hydride elimination, however, in the context of C−H/alkene coupling, not C−H arylation.

As expected we found that a suitable directing group would be required to promote the metal insertion step. We considered common amine protecting groups that may also serve as directing groups for low-valent transition metals. Unfortunately, the carbonyl of the Boc carbamate moiety was unfit for this purpose.[10,11] Subsequently, a search for a better directing (and removable) element identified the amidine derived from 2-methoxy-1-pyrroline as a promising candidate (Figure 1). Importantly, $Ru_3(CO)_{12}$ as the catalyst gave the desired product in good yield. Specifically, heating substrate **1** and phenylboronate ester in the presence of 3.3 mol % of the ruthenium catalyst and 5 equiv of ketone (e.g., pinacolone) afforded good yields of diphenyl product **2** as a 3:1 ratio of trans and cis diastereomers. With regard to the catalyst, the trinuclear ruthenium cluster is required; mononuclear and dinuclear ruthenium complexes were much less effective (<10%).[12] The choice of phenylboronate ester (between pinacol- and *neo*-pentanediol-derived

Scheme 1. A Mechanistic Guide for the New sp³ C−H Bond Arylation[a]



[a] The four key steps: (1) metal insertion (directed); (2) ketone insertion; (3) transmetalation; (4) C−C bond formation.

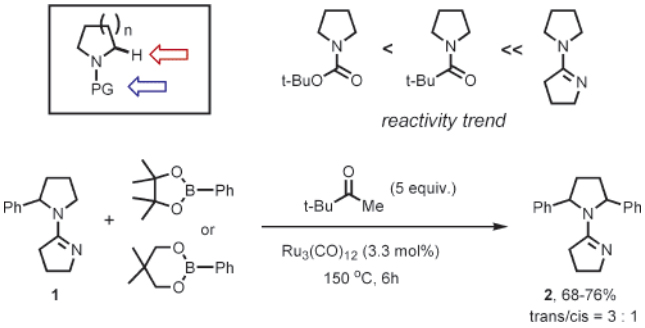


Figure 1. Pyrrolidinone-derived amidine is an effective directing group.

esters) had a minimal effect on the efficiency of the reaction. In the absence of ketone, the product was formed in 27% yield, confirming the critical role of this additive in the arylation process.[13] In analogy to other directed sp³ C−H functionalization methods,[8] the parent pyrrolidine substrate gave a mixture of mono- and bis-arylated products. Consequently, we explored the substrate scope with readily available 2-substituted pyrrolidines, which give desirable bis-substituted products. In all cases, mixtures of trans/cis diastereomers were obtained, with ratios ranging from 3:1 to 6:1, which were readily separable by column chromatography (vide infra).

This catalytic method was compatible with a variety of arene donors as demonstrated by the arylation of the 2-phenylpyrrolidine-derived substrate **1** (Table 1). Donors containing both electron-donating and electron-withdrawing substituents (CF_3, COMe, OMe, Table 1) were successfully coupled to substrate **1**. Also, ortho substitution was tolerated as illustrated by preparation of the unsymmetrical biaryl product **6**. Heteroarene boronates served as good donors too, including indole (product **7**) and pyridine (products **8** and **9**). The tolerance of this method for pyridine donors is notable since they contain a basic sp² nitrogen that can compete with the

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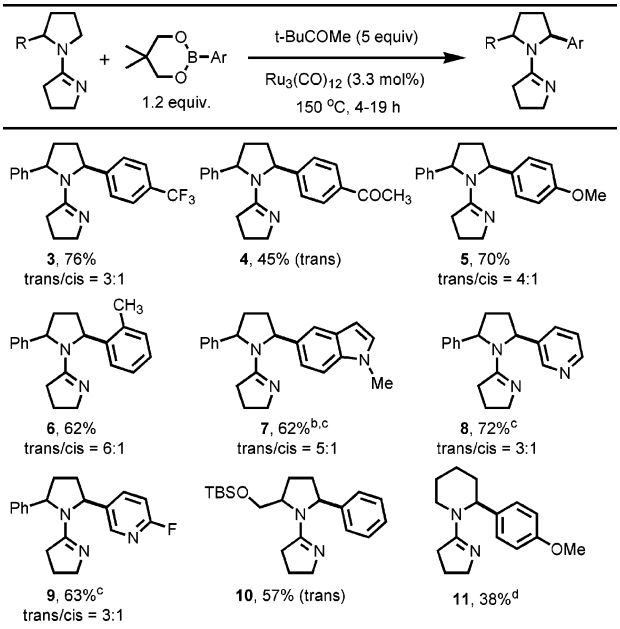
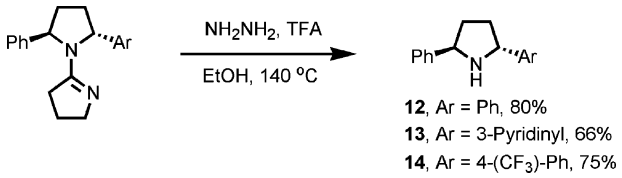
Table 1. Substrate and Functional Group Scope



[a] Isolated yields after flash chromatography are shown; all reactions were run on a 0.5 mmol scale. Diastereomeric ratio was obtained from the isolated yields of each isomer. For exact reaction times, see the Supporting Information. [b] Reaction run using 6.6 mol % of $Ru_3(CO)_{12}$. [c] Pinacol-derived ester used. [d] Reaction run on 1.0 mmol scale.

Scheme 2. Deprotection of 2,5-Disubstituted Amidines



amidine directing group for the metal center. The TBS-protected prolinol substrate also underwent regioselective phenylation to provide **10** as the major product. Saturated six-membered heterocycles have been shown to be less reactive in comparison to their five-membered ring counterparts.[14] We were pleased to see that the protected piperidine underwent α-arylation to afford product **11**, albeit in modest yield. Optimization of piperidine substrates is underway in our laboratory.

The next key question centered on the ability to remove the directing group from the sterically hindered 2,5-disubstituted amidines (Scheme 2). While treatment with NH_2NH_2/AcOH worked well for monoarylated heterocycles (see Supporting Information), these conditions were inefficient for the more hindered products. The use of stronger acid (e.g., TFA) in place of AcOH (taking advantage of significant difference in basicity between amidine and hydrazine) produced a major improvement, affording an efficient deprotection method (see Supporting Information for details). *Thus, 1-pyrroline represents an attractive directing group; it can be both installed and removed in a straightforward manner.*

Next, we investigated the reactivity of related substrates containing pyridine or pyrimidine rings as permanent directing groups (Figure 2).[8] The corresponding 2-aminopyridines or pyrimidines are desirable pharmacophore substructures in medicinal chemistry. These substrates were less reactive in comparison to the corresponding amidines discussed above, requiring higher catalyst loading and/or longer reaction time to obtain good yields. Attractive

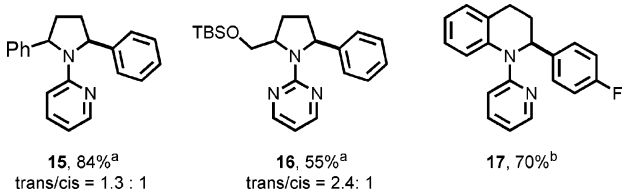


Figure 2. Pyridine and pyrimidine as permanent directing groups. These less reactive substrates required higher catalyst loading and/or longer reaction time: [a]10 mol % $Ru_3(CO)_{12}$ used; [b]3.3 mol % $Ru_3(CO)_{12}$ used.

compounds such as **15**−**17** can now be prepared in two steps from the corresponding amines.

Last, the source of relatively poor stereoselectivity of these arylation reactions was identified by submitting each stereoisomer of diphenyl product **15** (trans and cis) to the reaction conditions. These control experiments clearly showed that the product isomerization was more rapid (∼2 h) than the arylation reaction (complete in 24 h, see Supporting Information). Nevertheless, this new method is operationally simple, reactions can be performed in capped glass vials with standard benchtop handling of reagents,[15] and the isomers are readily separable by chromatography. Exploration of both the substrate scope and the mechanism of this interesting reaction is under way in our laboratories.

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Supporting Information Available: Experimental procedures, spectral data, kinetics of product isomerization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Preliminary experiments suggest that similar yields may be achieved in shorter reaction times (<1 h) in a microwave reactor.

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