Oxidative C-Arylation of Free (NH)-Heterocycles via Direct (sp³) C–H Bond Functionalization

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Guided by the concept of direct and systematic elaboration of heterocyclic compounds via C–H bond functionalization,1 we have recently developed new methods of C-arylation of (NH)-heterocycles such as indoles, pyrazoles, and imidazoles.1,2 In this context, we became interested in the possibility of C-arylation of saturated (NH)-heterocycles with haloarene donors. To achieve this goal we would require disfavoring known N-arylation pathways to the benefit of (sp³) C–H bond functionalization (Figure 1). Although this proposition may seem unlikely, it has been demonstrated that ruthenium fragment [RuHCl(PPr₃)₂], generated in situ, undergoes selective insertion into C–H bonds at the α-position of free pyrrolidine.3 We followed this lead, however, with no success, highlighting the challenge of translating the knowledge acquired by C–H activation (metallation) studies into direct C–H bond arylation processes. An alternative strategy would involve N–H bond metalation, followed by β-hydride elimination and arylation of the resulting imine intermediate. This latter scenario forms a mechanistic rationale for a new synthetic method described herein for oxidative C-arylation of free (NH)-heterocycles.

To explore the feasibility of this cross-coupling reaction, pyrrolidine and iodobenzene were selected as the parent substrates. A systematic study was undertaken to investigate three key variables, namely the metal source, solvent, and base. This exercise provided us with an exciting lead as well as indispensable insight into the system in question (Scheme 1). Remarkably, rhodium(I) complexes 5 and 6 catalyzed the formation of 2-phenylpyrroline (1) as the main product in 45% yield. We note that only rhodium complexes out of a broad array of examined transition metals were capable of affording appreciable amounts of C-arylation products. Compound 2 was also formed as the minor product, together with a small amount of anisole (Scheme 2). This result revealed that N-arylation pathways can be coupled in one step to furnish product 1 in very good yield. Upon acidic treatment of the crude reaction mixture, additional product 4 was detected; this compound is a result of 2'-arylation of product 1.

Interestingly, the cross-coupling between pyrrolidine and 4-iodoanisole afforded the desired product 7 in 31% yield, as well as 2-phenylpyrroline 1 and anisole (Scheme 2). This result revealed two major side reactions largely responsible for the low efficiency of this process. The formation of compound 1 reflects carbon–phosphorus bond cleavage in the triphenylphosphine ligand and subsequent phenyl group migration, while the presence of a significant amount of anisole reveals facile dehalogenation.

This insight guided our optimization studies, which began by addressing the ligand stability and phenyl group scrambling. A panel of ligands containing a plethora of phosphines and imidazolyl carbenes was examined (Supporting Information). A clear parallel between rhodium and palladium chemistry was seen in this context, as ligands known to suppress β-hydride elimination, such as bulky monodentate phosphines or bidentate phoshines, promoted N-arylation to give 3.3 In contrast, triphenylphosphine favored oxidative C-arylation, albeit with modest overall efficiency. In our search for a robust alternative to Ph₃P, we identified tri-(2-furyl)-phosphine [(Fur)₃P] as a promising candidate.5c,6 Indeed, the corresponding rhodium complex RhCl(CO)[(Fur)₃P]₂ (8) proved to be a superior catalyst, leading to a 2-fold increase in the efficiency of the coupling reaction, while no transfer of the furyl group was observed and the extent of dehalogenation was reduced. The latter process was further abated (to approximately 10–15%) by addition of tert-butylethylene (TBE) as the hydrogen acceptor (Scheme 3). Under these optimized conditions, pyrrolidine and iodobenzene can be coupled in one step to furnish product 1 in very good yield.

Figure 1. C–H bond versus N–H bond arylation.

Scheme 1. Lead Identification

Scheme 2. Ligand Degradation and Dehalogenation

Scheme 3. Optimized Conditionsa
pyrrolidine (1.2 equiv), (Het)Ar-X (1 equiv), RhCl(CO)[P(Fur)₃]₂ (5 mol %), TBE (2 equiv), Cs₂CO₃ (1.2 equiv), dioxane, 120 °C, 12–14 h. 10–15% of dehalogenation occurred for compounds 7, 9, 25–30% of dehalogenation occurred for compounds 10–12.

Table 1. Reaction Scope: Halo(hetero)arene Donors

<table>
<thead>
<tr>
<th>Heteroarene</th>
<th>Phloroglycine</th>
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<tbody>
<tr>
<td>7</td>
<td>62%</td>
</tr>
<tr>
<td>9</td>
<td>56%</td>
</tr>
<tr>
<td>10</td>
<td>39%</td>
</tr>
<tr>
<td>11</td>
<td>44%</td>
</tr>
<tr>
<td>12</td>
<td>31%</td>
</tr>
</tbody>
</table>

* X = I for compounds 7, 9, 10; X = Br for 11, 12. Conditions: pyrrolidine (1.2 equiv), (Het)Ar-X (1 equiv), RhCl(CO)[P(Fur)₃]₂ (5 mol %), TBE (2 equiv), Cs₂CO₃ (1.2 equiv), dioxane, 120 °C, 12–14 h. 10–15% of dehalogenation occurred for compounds 7, 9, 25–30% of dehalogenation occurred for compounds 10–12.

Table 2. (NH)-Heterocycle Substrate Scope

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Arylation Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Ph</td>
<td>1, 78%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>13, 65%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>14, 51%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>15, 52%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>16, 62%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>17, 53%</td>
</tr>
<tr>
<td>N-Ph</td>
<td>18, 56%</td>
</tr>
</tbody>
</table>

* Conditions: heterocycle (1.2 equiv), PhI (1 equiv), RhCl(CO)[P(Fur)₃]₂ (5 mol %), TBE (2 equiv), Cs₂CO₃ (1.2 equiv), dioxane, 120 °C, 15 h. 10% dehalogenation occurred for compounds 7, 9, 25–30% of dehalogenation occurred for compounds 10–12.

In contrast, compounds 21 and 23 were prepared from protected 3-hydroxypyrrolidine 20 and ethyl nipecotate 22 in 59% and 52% yield, respectively. Although the isolated yields were modest, the direct method described herein, even in the present state of optimization, competes favorably with traditional multistep approaches. This is particularly true in the case of more complex compounds such as 23. In contrast, β-substituted substrates worked well, showing exclusive arylation at the less hindered α-methylene group. Thus, unknown compounds 21 and 23 were prepared from protected 3-hydroxypyrrolidine 20 and ethyl nipecotate 22 in 59% and 52% yield, respectively.

The analysis of this system revealed that relatively low efficiency may be ascribed to three key processes. First, nonproductive reduction of haloarene donors (dehalogenation) is always present, to the extent of 10–15% of the halide (and up to 30% with haloheteroarene donors, Table 1). Second, heterocyclic rings larger than pyrrolidine require a higher reaction temperature, which in turn increases other haloarene degradation pathways. Third, catalyst decomposition represents the most serious limiting factor, particularly at higher reaction temperatures.

The limits of this method can be illustrated in the condensation of a mismatched reaction couple, such as ethyl nipecotate and 2-bromothiophene, which afforded a low yield of product 24 (11% yield, Scheme 4). In this case, an unreactive acceptor required a high reaction temperature, which at the same time caused fast decomposition of an unstable heteroarene donor.

Last, preliminary mechanistic studies were carried out to establish a crude framework of the catalytic cycle. The parent reaction between pyrrolidine and iodobenzene was used for these investigations. When the reaction mixture was monitored by ¹H and ³¹P NMR at 80 °C, two major products were identified as complexes 25 and 30, and their structures were confirmed by independent synthesis. Complex 25 showed identical behavior to the catalyst precursor 8 in terms of both kinetic profile and chemical yield of the catalytic reaction. Our observations showed that oxidative addition of iodobenzene to rhodium(I) complex 8 was facile and thus may represent the first, and probably reversible, step of the catalytic cycle (Figure 2, cycle A). This may be followed by a fast metalation of the N–H bond [KIE (kJmol⁻¹) = 1.0], proceeding, for instance, via Lewis-acid-promoted deprotonation of pyrrolidine to furnish rhodium(III) amido complex 26. The subsequent events involve β-hydride elimination and formation of imine rhodium hydride 27, followed by sequential carbometalation and a second β-hydride elimination to yield 2-phenyl-1-pyrroline, coordinated to the
rhodium metal (cf. 29). Replacement of the organic product by the phosphine ligand at the metal center would complete the cycle.

The key elementary reactions proposed in this cycle have firm mechanistic basis (Figure 2, cycle A). They encompass (a) oxidative arylation, facilitated by the phosphine ligand at the metal center, and (b) reductive elimination of benzene from complex 27, which represents a plausible pathway for the competing dehalogenation of arene donors. This cycle is supported by the availability of information on the partitioning between oxidative arylation and N-arylation pathways. Reductive elimination of benzene from complex 27 represents a plausible pathway for the competing dehalogenation of arene donors. An alternative cycle may begin with conversion of 8 to amido complex 30 by the displacement of the chloride with pyrrolidine (Figure 2, cycle B). This species may subsequently be converted to complex 27 in two steps involving β-hydride elimination and oxidative addition, in either order. Examination of complex 30 in detail revealed that it could function as the catalyst, however, with slower rates and significantly lower efficiency in comparison to complexes 8 and 25. The experiments involving both catalytic and stoichiometric amounts of metal complexes 8, 25, and 30 (see Supporting Information) support the notion that both catalytic cycles may be operative, wherein cycle B represents the slower and less productive one.

In summary, oxidative C-arylation of (NH)-heterocycles represents a new chemical transformation which unites two reactions, namely dehydrogenation and arylation, into one process. Thus, valuable heterocyclic compounds such as 2-aryl tetrahydropyrrolines and 2-aryltetrahydropyrrolines can be prepared in one synthetic step from the corresponding saturated (NH)-heterocycles and haloarenes. To further expand the substrate scope of this method, a deeper mechanistic insight needs to be gained, particularly with respect to the catalyst stability.

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Supporting Information Available: Experimental procedures, spectral data for all products, and kinetics of stoichiometric and catalytic experiments with complexes 8, 25, and 30. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Sezen, B.; Sames, D. J. Am. Chem. Soc. 2003, 125, 10580–10585.
(7) Piperidine did not undergo α-metalation in Caulton’s studies; see ref 3.
(8) Note that no arylation was observed at the N-methylene positions adjacent to the protected amine group in piperazine or oxygen in morpholine.

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