Citation for published version:

DOI:
10.1002/anie.201708961

Publication date:
2017

Document Version
Peer reviewed version

Link to publication

This is the peer reviewed version of the following article: Leitch, JA, Mcmullin, CL, Paterson, AJ, Mahon, MF, Bhonoah, Y & Frost, CG 2017, 'Ruthenium-Catalyzed para-Selective CH Alkylation of Aniline Derivatives' Angewandte Chemie-International Edition., which has been published in final form at https://doi.org/10.1002/anie.201708961. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

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Ruthenium-Catalyzed para-Selective C-H Alkylation of Aniline Derivatives

Abstract: The para-selective C-H alkylation of aniline derivatives furnished with a pyridine auxiliary is herein reported. This is proposed to take place via a N-H activated cyclometalate formed in situ. Experimental and DFT mechanistic studies elucidate a dual role ruthenium catalyst. Here the ruthenium catalyst can undergo cyclometalation via N-H metatation (as opposed to C-H metatation in meta-selective processes) and form a redox active ruthenium species, to enable site selective radical addition at the para position.

Transition-metal catalyzed C-H functionalization has evolved into a widespread and effective technique to derive (hetero)arenes and especially biologically relevant motifs.[1] The innate hurdle in C-H functionalization is the differentiation of electronically and sterically similar C-H bonds in an organic structure. To overcome this, a directing group strategy is often employed to enable selective ortho-C-H functionalization via chelation assistance with respect to the directing group.[2] Recent developments have allowed carefully tailored catalytic systems to permit meta-selective C-H functionalization.[3] These methods utilize three primary techniques; template directed group design,[4] the use of a transient mediator,[5] and σ-activation by a metal center.[6] Accessing complementary para-selective methodologies typically takes advantage of electronic effects to permit C-H functionalization at the para position of an electron rich arene, with pioneering reports from Gaunt,[7] Niecewicz,[8] and Ritter[9] (Scheme 1a). There have been examples of the use of extended templates by Maiti,[10] and the careful manipulation of steric effects by Itami[11] and Nakao.[12,13] In a recent report Weng and Lu described the use of 5-membered aminopyridine-based bidentate cyclometalates in the para-C-H functionalization of aminonaphthalene derivatives.[14,15] Herein, we demonstrate that certain aniline derivatives can undergo para-selective C-H alkylation reactions catalyzed by ruthenium complexes. σ-Activation focuses on the use of strongly bound ruthenacycles which can activate remote positions via electronic effects.[6] Ackermann applied this concept to aniline derivatives furnished with a pyridine directing groups to enable meta-selective alkylations (Scheme 1b).

We were intrigued to investigate whether complementary Ru-N cyclometalation of anilines (as opposed to Ru-C in in meta-selective sigma activation strategies), could lead to an active catalyst which may permit complementary para-C-H functionalization (Scheme 1c). Anilines have been widely used as templates for C-H functionalization development,[16] due to their ubiquity in active pharmaceuticals[17] and agrochemicals.[18] This concept was initially investigated by submitting aniline to slightly modified conditions from our previous work on meta-alkylation methodology (Scheme 2).[6c]

Scheme 1. Previous Reports on Site Selective Catalytic C-H Functionalization in the Context of this Work.

Scheme 2. Ruthenium Catalysed para-C-H Alkylation of Aniline

This led to primarily the ortho/para-substituted aniline (3a), whereby an in situ lactamization can take place on at the ortho

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position, amongst multiple other products. No C-H alkylation products were observed in the absence of ruthenium catalyst or in the presence of radical scavenger TEMPO. This suggests a redox catalyst is formed in situ enabling radical arene functionalization. Encouraged by this, we endeavored to promote a solely para-selective transformation by using a bespoke N-substituted auxiliary (Table 1).

**Table 1.** Ruthenium-Catalyzed para-C-H Alkylation of Aniline Derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aux</th>
<th>Ligand</th>
<th>Solvent</th>
<th>3 %[^i]</th>
<th>4 %[^i]</th>
<th>5 %[^i]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>35</td>
<td>6[^j]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>39</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>16</td>
<td>10[^j]</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>NaOAc</td>
<td>1,4-dioxane</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>1c</td>
<td>PhMe</td>
<td></td>
<td>56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>NaOAc</td>
<td>DCE</td>
<td>56</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>NaOAc</td>
<td>TBME</td>
<td>81</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>1c</td>
<td>MesCO2H</td>
<td>TBME</td>
<td>77</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>Piv-Val-OH</td>
<td>TBME</td>
<td>70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>DMEDA</td>
<td>TBME</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>1c</td>
<td>TBME</td>
<td></td>
<td>66[^h]</td>
<td>(55)[^i]</td>
<td>-</td>
</tr>
<tr>
<td>14[^d]</td>
<td>1c</td>
<td>TBME</td>
<td></td>
<td>55</td>
<td>-</td>
<td>38</td>
</tr>
<tr>
<td>15[^e]</td>
<td>1c</td>
<td>TBME</td>
<td></td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16[^d]</td>
<td>1c</td>
<td>TBME</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Aux = auxiliary [a] Standard Conditions: aniline derivative (0.25 mmol), methyl α-bromoisobutyrate (0.75 mmol), [RuCl₃(p-cymene)]₂ (0.0125 mmol), ligand (0.075 mmol), K₂CO₃ (0.5 mmol), solvent (1 mL) under a N₂ atmosphere. [b] ¹H NMR yield. [c] * denotes position of di-functionalization. [d] isolated yield. [e] at 140 °C. [f] under an air atmosphere. [g] no ruthenium catalyst.

Despite its use in other meta-alkylation methodologies a pyrimidine auxiliary (1b) gave the para-substituted structure in modest conversions (entry 1).[^6][^8][^9] No meta-functionalization was observed, however competing di-C-H alkylation occurred on the auxiliary (4b), albeit in low amounts. It is worth noting throughout the auxiliary optimization, there was no observation of the ortho/para-disubstituted structure. Pleasingly the use of 5-chloropyrimidine as the auxiliary (1c) led to completely selective para-functionalization (entry 2). Pyridyl (1e) and Acetanilide (1f) did not lead to any C-H functionalized products (entries 4-5), and pyridyl derivative (1g) was also unsuccessful (entry 6). A screen of solvents identified TBME (tert-butyl methyl ether) as the optimal reaction medium (entries 6-8). A ligand screen manifested that removal of the ligand entirely was of benefit to the reaction (entries 10-13), and could be due to a reduction in undesired ortho-cyclometalation. Unfortunately, isolated yields in this methodology were found to be substantially lower than NMR yields, primarily due to polymeric byproducts formed which were indistinguishable via proton NMR (see ESI, Scheme S3).

Interestingly on increasing the temperature to 140 °C, we observed formation of competing meta-selectivity (entry 13), and importantly no reactivity was observed in the absence of the ruthenium catalyst (entry 16). With suitable conditions in hand to access para-substituted structures, we applied this methodology to a range of coupling partners and substituted arenes (Scheme 3).[^20]

**Scheme 3.** Scope of Ruthenium-Catalyzed para-Selective C-H Alkylation of Aniline Derivatives
This scope showed that a variety of tertiary alkyl esters could be applied in modest yields (3c-3e). A cyclohexyl derivative was also shown to be amenable to the reaction (3cf), and must be noted that all of these examples proceeded with absolute selectivity for the para position. On varying the ring electronics, it was found that 3-substitution was tolerated well (3h-m) and that the none of the electronic influences of these substituents overrode the selectivity dictated by the N-substitution pattern. The quinazoline heterocycle was also shown to be applicable to this methodology, again in modest yields (3na-3nd).

We anticipated that under certain conditions, the regioselectivity of functionalization could be switched to a meta-selective protocol using identical an starting material and coupling partner (Scheme 4). With carboxylate assistance as well as a change of solvent from 1,4-dioxane to DME, the meta-selective reaction was strongly favored and led to corresponding meta-C-H alkylated product with very high selectivity (99:1 m:p) (Scheme 4). It must be noted removal of the AcOH still favors meta-selectivity, however this is less pronounced. This suggests that in a proposed equilibrium between N-H and C-H cyclometalated complexes, the use of a carbonate base (K$_2$CO$_3$) could favor an N-H cyclometalation to form para-substituted products, whereas acetate bases (KOAe) could favor an ortho-C-H cyclometalation to form meta-substituted products.

Scheme 4. Ruthenium-Catalyzed meta-C-H Alkylation of Aniline Derivative

As we were observing a definitive shift in selectivity from meta to para, it was of interest to perform experimental and computational mechanistic studies to provide rationale to a proposed Ru-N cyclometalation/activation pathway. Initially we carried out radical scavenger studies using TEMPO where the use of stoichiometric amounts led to complete suppression of reactivity. The isolation of polymeric byproducts, and the unique reactivity of α-halocarbonyls are also indicative of a radical mechanism.

The proposed mechanism for the remote para C-H alkylation does not involve cyclometalation on the aromatic ring via ortho-C-H cyclometalation. In order to explore this an isotopically labelled derivative 1c-d$_5$ was submitted to the reaction conditions (Scheme 5a). This showed that under the para conditions there was negligible H/D scrambling (~2%) in either the unreacted starting material or the product. This suggests readily reversible ortho-C-H cyclometalation is not possible. The complementary meta-selective conditions did however give rise to substantial scrambling in both recovered starting material and meta-alkylated product. Despite this, Huang and co-workers did not observe deuterium scrambling in their report. It must be noted there was no substantial hydrogen incorporation at either meta or para positions in either investigation, which demonstrates there is no reversible direct C-H metalation responsible for the selectivity observed.

Scheme 5. Mechanistic Studies on para Alkylation Methodology

Acetanilide was chosen as a model comparison for a crossover study due to similar electronic influence on the ring, pK$_a$ of the N-H, and that it contains a metal coordinating group (Scheme 5b). If the pyrimidine is only generating a redox active species capable of forming the tertiary radicals, which can then interact with an electron rich organic structure, one would expect to see a mixture of para-C-H alkylated pyrimidine (3c) and acetanilide (3f). No presence of 3f was observed and 3c was isolated in equable yields. This strongly suggests that the C-H functionalization taking place at the para position is directly influenced by electronic effects of a coordinated ruthenium species. This result along with the previous insights suggest a α-activation/redox pathway analogous to previous meta-selective methodology, however in this case unlocking the complementary para-selective chemistry.

Density Functional Theory (DFT) calculations of the competing N-H and C-H activation of 1c have been computed for acetate or carbonate as the base (see Figure 1 and SI for discussion). A change in preferred activation and hence mechanism occurs, with acetate favoring C-H activation and hence a meta-selective mechanism, whilst carbonate has a lower barrier to N-H activation and a para-selective product.
In summary, we have reported the selective para-C-H alkylation of aniline derivatives, making use of pyrimidine and quinazoline auxiliaries. Experimental and computational mechanistic studies suggest that the addition takes place via a radical process to a ruthenium species cyclometalated at N-H rather than C-H (previously seen). This positional cyclometalation has been proposed to dictate the selectivity, which permits functionalization para to the metal center which in this case is para to the N-substituted auxiliary.

Acknowledgements

J. A. L. would like to thank the University of Bath and Syngenta for funding. This research made use of the Balena High Performance Computing (HPC) Service at the University of Bath.

Keywords: Ruthenium para-Selective Homogeneous Catalysis C-H Functionalization Aniline

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Figure 1: Summary of DFT calculated free energies (kcal mol⁻¹) relative to the most stable intermediate, for the competing C-H and N-H activations of 1ce at [Ru(p-cymene)O(CR)₃]⁺ in dioxide, when R = Me (acetate) or OH (carboxylate). [23]


Para-normal activity: The para-selective C-H alkylation of aniline derivatives is reported. The methodology is proposed to proceed via a dual role ruthenium process: cycloruthenation at N-H, and redox radical generation. This strategy proved to access para-selective alkylations using pyrimidine and quinazoline auxiliaries.

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