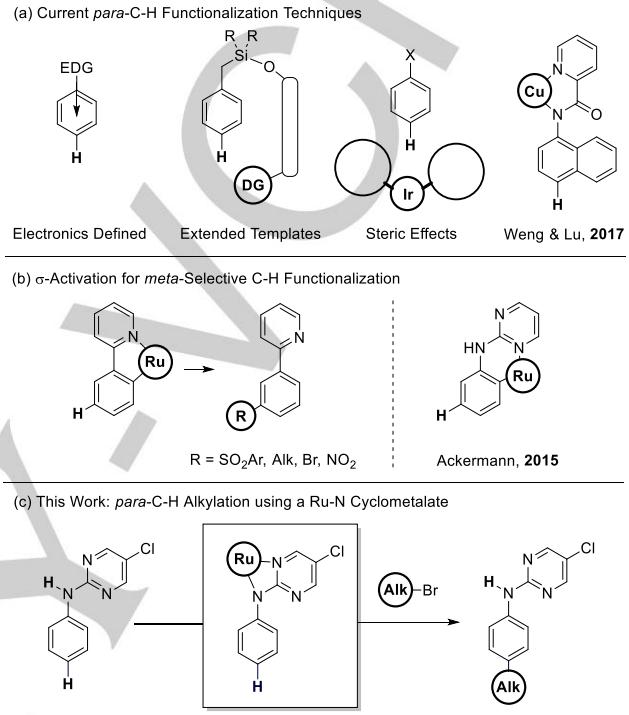
Ruthenium-Catalyzed *para*-Selective C-H Alkylation of Aniline Derivatives

Jamie A. Leitch,[a] Claire L. McMullin,[a] Andrew J. Paterson,[a] Mary F. Mahon,[a] Yunas Bhonoah,[b] and Christopher G. Frost.*[a]

Abstract: The *para*-selective C-H alkylation of aniline derivatives furnished with a pyrimidine 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 metalation (as opposed to C-H metalation in *meta*-selective processes) and form a redox active ruthenium species, to enable site selective radical addition at the *para* position.

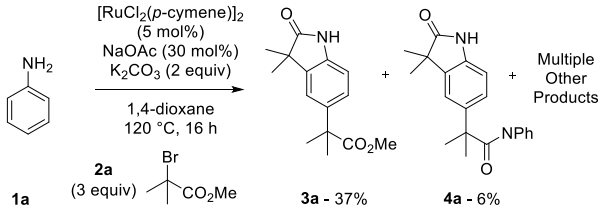
Transition-metal catalyzed C-H functionalization has evolved into a widespread and effective technique to derivate (hetero)arenes and especially biologically relevant motifs.[1] The innate hurdle in C-H functionalization is the differentiation of electronically and sterically similar C-H bonds in an 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; templated directing 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] Nicewicz,[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 pyrimidine directing groups to enable *meta*-selective alkylations (Scheme 1b).



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

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 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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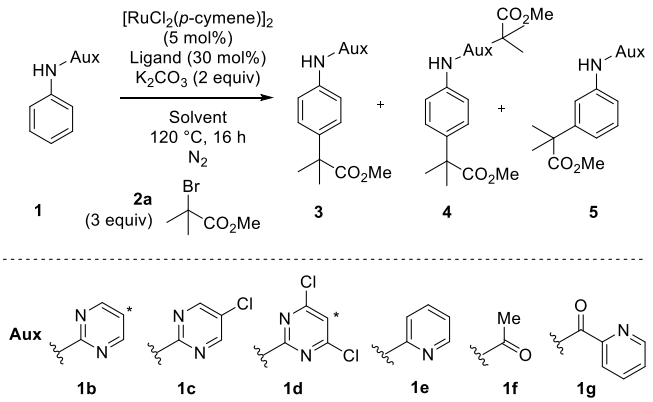
position, amongst multiple other products. No C-H alkylation products were observed in the absence of ruthenium catalyst or in the presence of radical scavenger TEMPO. This suggests a redox catalyst is formed *in situ* enabling radical arene functionalization. Encouraged by this, we endeavored to promote 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

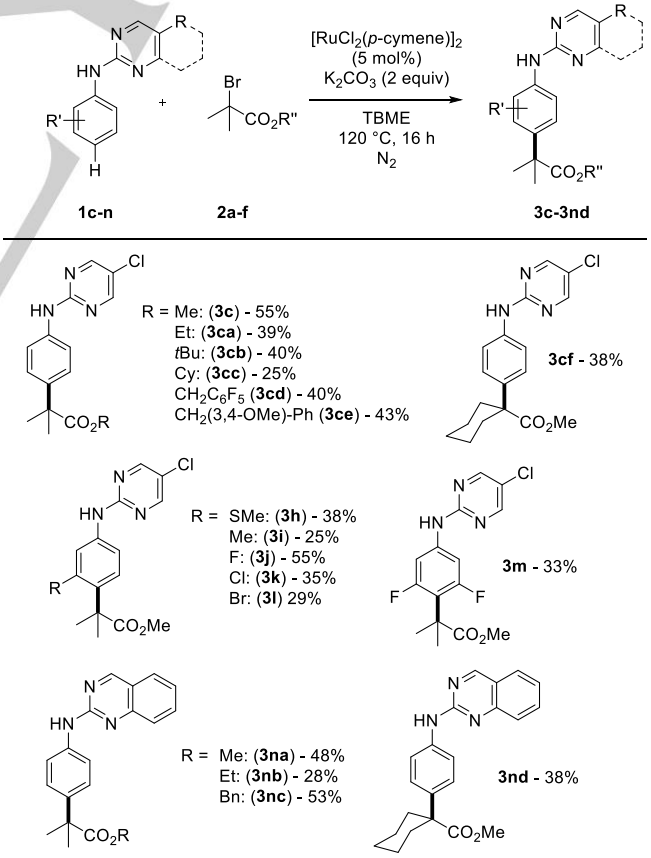


Entry [a]	Aux	Ligand	Solvent	**3** %[b]	**4** %[b]	**5** %[b]
1	**1b**	NaOAc	1,4-dioxane	35	6[c]	-
2	**1c**	NaOAc	1,4-dioxane	39	-	-
3	**1d**	NaOAc	1,4-dioxane	16	10[c]	-
4	**1e**	NaOAc	1,4-dioxane	-	-	-
5	**1f**	NaOAc	1,4-dioxane	-	-	-
6	**1g**	NaOAc	1,4-dioxane	-	-	-
7	**1c**	NaOAc	PhMe	56	-	-
8	**1c**	NaOAc	DCE	56	-	-
9	**1c**	NaOAc	TBME	81	-	-
10	**1c**	$MesCO_2H$	TBME	77	-	-
11	**1c**	Piv-Val-OH	TBME	70	-	-
12	**1c**	DMEDA	TBME	85	-	-
13	**1c**	**-**	**TBME**	**86 (55)**[d]	**-**	**-**
14[e]	**1c**	-	TBME	55	-	38
15[f]	**1c**	-	TBME	71		
16[g]	**1c**	-	TBME	-	-	-

Aux = auxiliary [a] Standard Conditions: aniline derivative (0.25 mmol), methyl α-bromoisobutyrate (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol), ligand (0.075 mmol), K_2CO_3 (0.5 mmol), solvent (1 mL) under a N_2 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).[6d],[19] 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 pyridoyl 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).

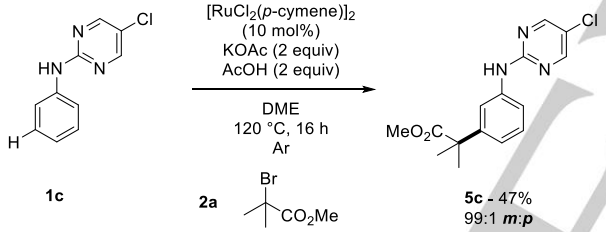
With suitable conditions in hand to access *para*-substituted structures, we applied this methodology to a range of coupling partners and substituted arenes (Scheme 3).[20]



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**-**3ce**). 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**).

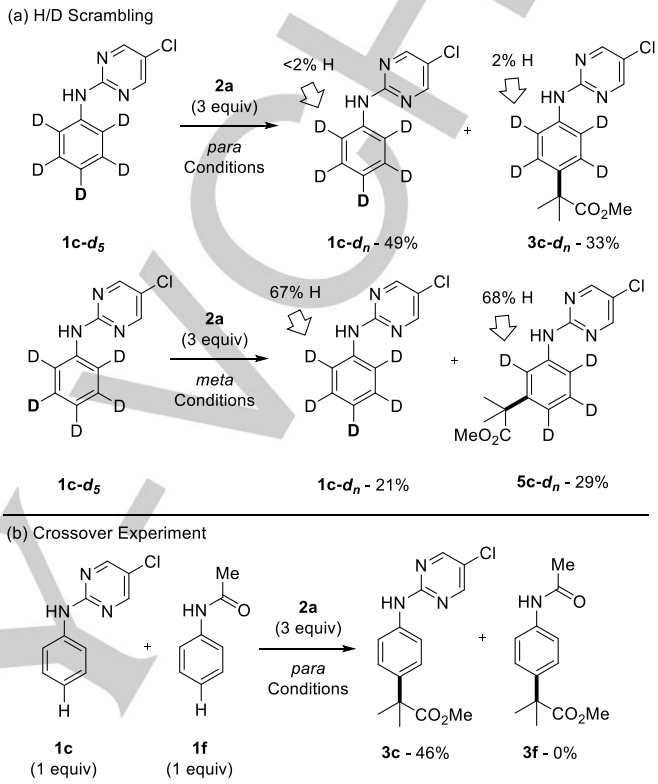
We anticipated that under certain conditions, the regioselectivity of functionalization could be switched to a *meta*-selective protocol using identical an starting material and coupling partner (Scheme 4).[21] With carboxylate assistance as well as a change of solvent from 1,4-dioxane to DME, the *meta*-selective 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_2CO_3) could favor an N-H cyclometalation to form *para*-substituted products, whereas acetate bases (KOAc) 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.[6f] 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 σ-activation/redox pathway analogous to previous *meta*-selective methodology,[6] 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 ESI for discussion).[22] 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.

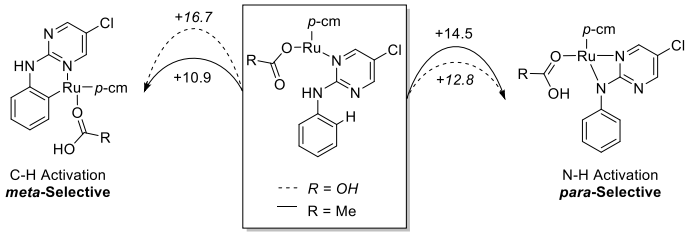


Figure 1: Summary of DFT calculated free energies (kcal mol^{-1}) relative to the most stable intermediate, for the competing C-H and N-H activations of **1c** at [Ru(*p*-cymene)(O_2CR)]$^+$ in dioxane, when R = Me (acetate) or OH (carbonate).[22]

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

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

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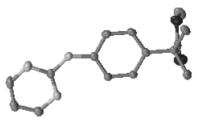
[19] Crystallographic data for **3b**. Crystal Data for $C_{15}H_{17}N_3O_2$ (**3b**): M =271.32 g mol^{-1}, triclinic, space group P-1 (no. 2), a = 6.0353(3), b = 7.4947(3), c = 16.2821(8) Å, α = 98.032(4), β = 90.419(4), γ = 111.856(4)°, U = 675.43(6) Å^3, Z = 2, T = 150 K, μ(Cu$K\alpha$) = 0.736 mm^{-1}, D_{calc} = 1.334 g cm^{-3}, 5703 reflections measured (10.998° ≤ 2Θ ≤ 146.772°), 2713 unique (R_{int} = 0.0251 which were used in all calculations. The final R1 was 0.0389 (I > 2σ(I)) and wR2 was 0.1047 (all data). Crystallographic data for 3 have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 1555867. Copies of these data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).



[20] Unreactive and low yielding coupling partners are given in the ESI..

[21] Under Ackermann's conditions from references 6b or 6d only *para*-substituted products were formed.

[22] Full details and references for computational methods can be found in the ESI.

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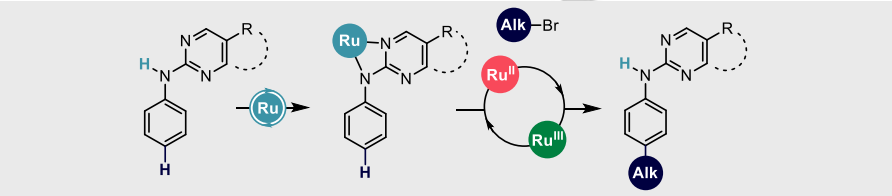

***Para*-normal activity**: The *para*-selective C-H alkylation of aniline derivatives is reported. The methodology is proposed to proceed *via* a dual role ruthenium process: cycloruthenation at N-H, and redox radical generation. This strategy proved to access *para*-selective alkylations using pyrimidine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

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1-4.

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