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α-Halo carbonyls enable *meta* selective primary, secondary and tertiary C–H alkylations by ruthenium catalysis†

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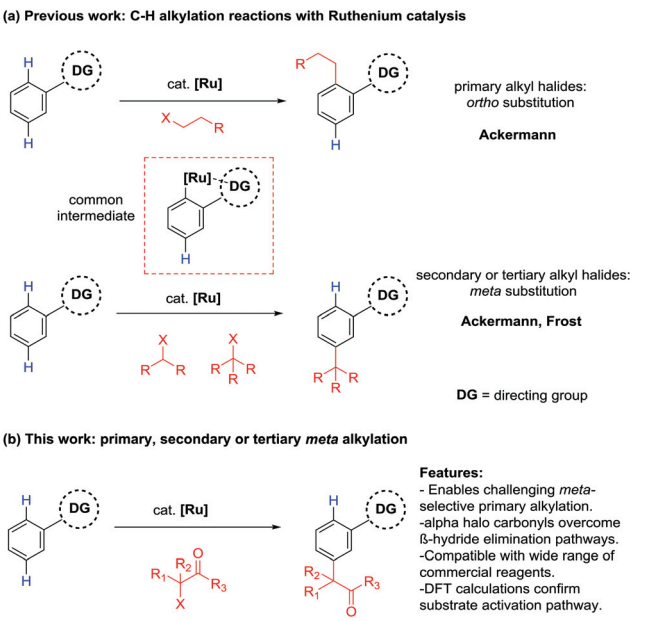
A catalytic *meta* selective C–H alkylation of arenes is described using a wide range of α-halo carbonyls as coupling partners. Previously unreported primary alkylations with high *meta* selectivity have been enabled by this methodology whereas using straight chain alkyl halides affords *ortho* substituted products. Mechanistic analysis reveals an activation pathway whereby cyclometalation with a ruthenium(II) complex activates the substrate molecule and is responsible for the *meta* selectivity observed. A distinct second activation of the coupling partner allows site selective reaction between both components.

Introduction

The direct functionalization of C–H bonds is an attractive methodology for the atom economic and streamlined synthesis of organic molecules. However, given the relatively low reactivity of C–H bonds and their ubiquity in organic molecules, intrinsic challenges arise when developing new methodologies with adequate reactivity and selectivity. There are however a number of strategies to overcome these challenges and research into this area has received great attention in the last decade.[1,2] One of the prevailing methods is the directing group approach. This method utilizes existing functionality within a molecule to coordinate a transition metal catalyst and position it in the vicinity of a C–H bond. This can lead to the formation of a metallacycle which is sufficiently reactive to undergo subsequent functionalization. In the field of aromatic sp^2 C–H functionalization, this strategy has enabled a wide range of functionality to be introduced to the *ortho* position of arenes, utilizing a diverse range of directing groups and transition metal catalysts.[3–9] Key to the success of this strategy is the relatively facile formation and conformational stability of the intermediate 5 or 6 membered metallacycles associated with *ortho* C–H functionalization. However, generating the corresponding metallacycles for more remote C–H bonds such as the *meta* C–H bond becomes increasingly challenging as ring size increases and conformational stability decreases. Because of this, a number of alternative strategies have been devised (Scheme 1).[10,11]

In a conceptually similar approach, a range of extended templates containing coordinating pyridine or nitrile groups have been developed, overcoming issues of conformational stability by forming particularly stable metallacycles.[12–24]



Scheme 1 Ruthenium catalyzed alkylation of arenes.

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Transient directing groups can also be introduced using carboxylic acids[25–29] or norbornene,[30–35] effectively installing a temporary directing group to the *ortho* position, which can undergo a subsequent *ortho* C–H functionalization. Utilizing non-covalent interactions between a directing group and a substrate can also lead to *meta* selective reactions.[36,37] In an alternative approach, ruthenium catalysis can be employed for the direct *meta* sulfonation,[38,39] secondary[40,41] and tertiary[41–43] alkylations, bromination[44–46] and nitration[47] of arenes. These *meta* selective transformations owe their selectivity to a mechanism involving a directing group assisted *ortho* cyclometalation, which activates the position *para* to the newly formed C–Ru bond. Recent studies have also revealed that addition of the coupling partners to the activated substrate are likely to be radical processes whereby a distinct single electron redox cycle could facilitate the generation of the radical species.[39,40,42,43,47]

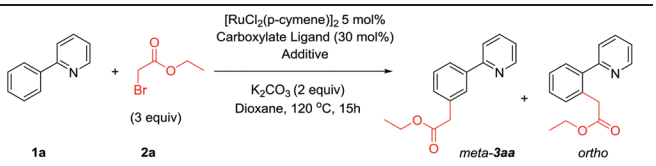
As part of our ongoing research into direct *meta* selective C–H functionalization reactions, we reported the use of α-halo carbonyls as coupling partners for the installation of quaternary carbon centers.[42] A range of these reagents are commercially available with the ability to be further modified and have recently been shown to enable synthetically useful mono- and di-fluoromethylations.[48,49] We therefore saw their potential as versatile reagents capable of installing other useful functionality to the *meta* position and enabling previously unprecedented *meta* selective primary alkylations with ruthenium catalysis, which is currently limited to direct *ortho* alkylations.[50,51] Herein we wish to report the use of α-halo carbonyl reagents to enable useful *meta* selective primary, secondary and tertiary alkylation reactions. A triaryl phosphine source was necessary to achieve *meta* selective primary alkylations and mechanistic and computational analysis show that initial cyclometalation with a ruthenium complex is responsible for the *meta* selectivity observed.

Results and discussion

Optimization

At the outset of our investigation we were interested to achieve *meta* selective primary alkylations as current ruthenium catalyzed *meta* selective methodologies are limited to secondary and tertiary alkylations.[40,42,43] Given our previous work where reaction with a tertiary α-halo carbonyl could readily furnish *meta* substituted products,[42] we believed that ethyl bromoacetate **2a** would be a suitably activated coupling partner to achieve this. We initially began our investigation using conditions known in the field, a ruthenium(II) precatalyst with carboxylate ligands.[52–54] However, these resulted in low combined yields of inseparable regioisomers (Table 1, entries 1–4). We previously proposed a dual role of ruthenium in tertiary alkylation reactions; activation of the substrate by cyclometalation, and a single electron redox catalyst to generate an alkyl radical. This proposition was independently supported by the Ackermann group in analogous tertiary alkylation reactions,[43] and recently by the Zhao group where ruthenium and ferrocene co-catalysis enabled *meta* selective benzylations.[55] We therefore envisaged a co-catalytic system whereby an additional catalyst could be employed to activate primary alkyl halide coupling partners. A number of copper systems were first employed given their natural abundance and precedence to form alkyl radicals in single electron processes[56–59] however no products were observed (entries 6–8). Similarly, photocatalytic ruthenium complexes were also ineffective, providing no benefit over the monocatalytic system (entries 9 and 10). However, the addition of $Pd(PPh_3)_4$ significantly improved reactions yields, with 10 mol% loading resulting in near complete selectivity to the *meta*-substituted product (entry 12). Other palladium sources were less effective however the use of $NiCl_2(PPh_3)_2$ led to reactions with high *meta* selectivity (entry 17). During the preparation of this manuscript, work simultaneously published by the Ackermann[48] and Wang[49] groups demonstrated the use of additional triarylphosphine ligands[48] or $Pd(PPh_3)_4$[49] respectively to enable ruthenium catalyzed mono- and di-fluoromethylations. In our system, the addition of free PPh_3 also led to reactions with comparable reaction yields and high *meta*-selectivity suggesting that the previously added metal-phosphine complexes were simply sources of free PPh_3 (entry 21). Other phosphine sources gave little additional

Table 1 Optimization of *meta* primary alkylation



Entry	Ligand	Additive	Yield[a] (%)	*m* : *o*[b]
1	No ligand	—	21	2.5 : 1
2	KOAc	—	24	2 : 1
3	MesCOOH	—	26	2.3 : 1
4	AdCOOH	—	15	2 : 1
6	MesCOOH	CuCl (20 mol%), 1,10-Phen (20 mol%)	0	—
7	MesCOOH	CuCl (20 mol%) PMETA (1 eq.)	0	—
8	MesCOOH	Cu_2O (10 mol%) 1,10-Phen (12 mol%)	0	—
9[c]	MesCOOH	$Ru(bpy)_3Cl_2$	21	1 : 1
10[c]	MesCOOH	$Ru(Phen)_3Cl_2$	19	0.6 : 1
11	MesCOOH	$Pd(PPh_3)_4$ (5 mol%)	47	3.3 : 1
12	**MesCOOH**	**$Pd(PPh_3)_4$ (10 mol%)**	**58**	**20 : 1**
13	MesCOOH	$Pd_2(dba)_3$ (5 mol%)	17	2.5 : 1
14	MesCOOH	$Pd(OAc)_2$ (10 mol%)	17	1.5 : 1
15	MesCOOH	$PdCl_2(PPh_3)_2$ (10 mol%)	46	10 : 1
16	MesCOOH	$Pd(PPh_3)_4$ (15 mol%)	55	19 : 1
17	MesCOOH	$NiCl_2(PPh_3)_2$	38	9 : 1
18	MesCOOH	$NiCl_2(PCy_3)_2$	5	1 : 1
19	MesCOOH	$NiCl_2(DME)$	0	—
20	MesCOOH	PPh_3 (10 mol%)	51	19 : 1
21	**MesCOOH**	**PPh_3 (20 mol%)**	**57**	**20 : 1**
22	MesCOOH	PPh_3 (30 mol%)	**55**	**19 : 1**
23	MesCOOH	PCy_3 (20 mol%)	0	—
24	MesCOOH	P(4-fluorophenyl)$_3$	38	15 : 1
25	MesCOOH	PPh_3 (no Ru)	0	—

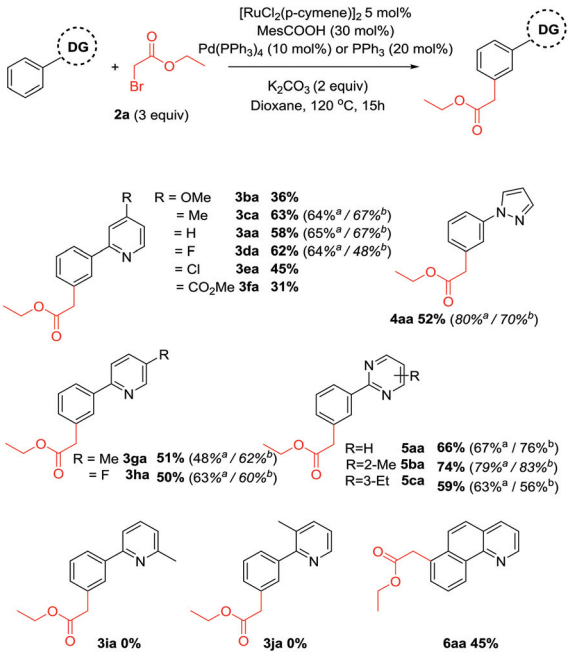
[a] Combined yield for both regioisomers. [b] *meta* : *ortho* ratio calculated by ^{1}H NMR. [c] Irradiated with blue LEDs.

benefit over PPh_3 or were ineffective (entries 23 and 24). Crucially, when no ruthenium complex was employed, no alkylated products were formed (entry 25).

Scope and limitations

With optimized conditions in hand, we aimed to explore the substrate scope with respect to the directing group (Scheme 2). In all cases, near complete selectivity (>20 : 1) to the *meta* substituted product was observed. Substitution on the pyridine ring was generally well tolerated although significantly increasing or decreasing electron density had a negative effect on reaction yields. Pyrazole and a range of substituted pyrimidines were also effective directing groups affording the *meta* alkylated products in good yields. Substitution at the 3 or the 6 position of the pyridine ring completely shut down reactivity, likely due to hindering the ability of the substrate to form a planar cyclometalated complex. Meanwhile conformationally locked benzoquinoline afforded exclusively alkylated product **6aa**. X-Ray analysis could unequivocally confirm this regioselectivity (Fig. 1) and supports the proposition that substitution occurs at the position *para* to the C–Ru bond formed following cyclometalation.

Next, substitution on the aryl component was considered (Scheme 3). Whereas unsubstituted substrates afforded nearly exclusively the *meta* substituted products, some regioisomeric products were formed when the electronic properties of the aromatic ring were altered. Generally, electron donating groups at the *para* position yielded either exclusively the *meta* product or high selectivity towards this product in modest



Scheme 2 Directing group scope on unsubstituted arenes Numbers in bold indicate isolated yield when $Pd(PPh_3)_4$ was used. [a] Reaction conversion by ^1H NMR when $Pd(PPh_3)_4$ (10 mol%) was used. [b] Reaction conversion by ^1H NMR when PPh_3 (20 mol%) was used.

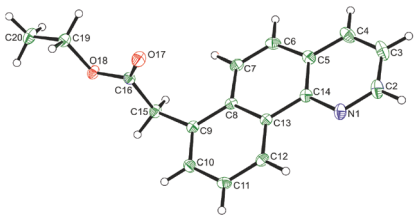
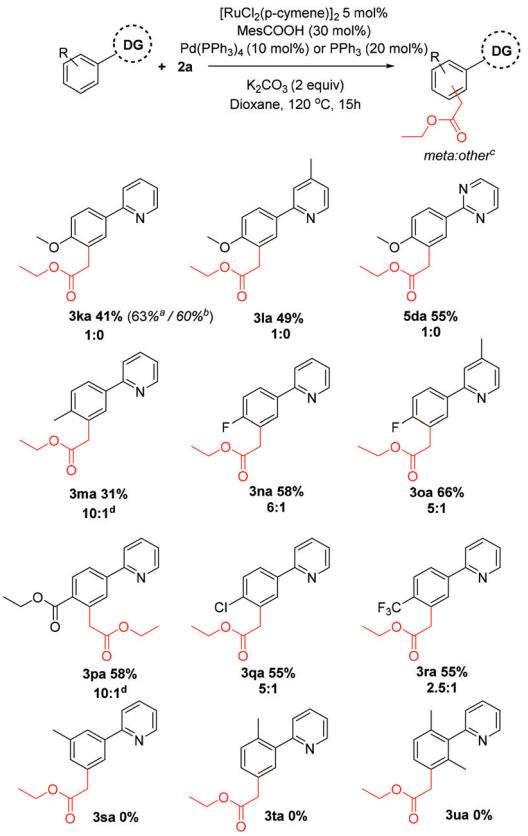


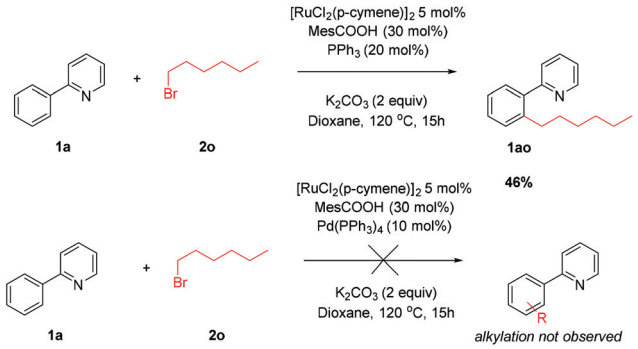
Fig. 1 X-Ray crystal structure of compound **6aa**. Ellipsoids are depicted at 30% probability.[60]



Scheme 3 Scope of substituted arenes. [a] Reaction conversion by ^1H NMR when $Pd(PPh_3)_4$ (10 mol%) was used. [b] Reaction conversion by ^1H NMR when PPh_3 (20 mol%) was used. [c] Yields quoted are combined yields of both regioisomers when $Pd(PPh_3)_4$ was used. [d] Minor isomer could be assigned as *ortho* substituted product.

yields. In contrast, electron withdrawing groups yielded a higher proportion of regioisomeric by-products. Dimethylated substrate **3u** afforded none of the *meta* alkylated product **3ua**, likely due to its inability to form a cyclometalated complex. Similarly, incorporating methyl substituents at the *ortho* or *meta* position also afforded no products, despite being effective substrates in other ruthenium catalyzed *meta* alkylations.[40,43]

The privileged reactivity of α-halo carbonyls was highlighted when reaction with straight-chain alkyl bromide **2o** resulted in no *meta* alkylated products (Scheme 4) and led to *ortho*



Scheme 4 Reaction with unactivated alkyl halide **2o**.

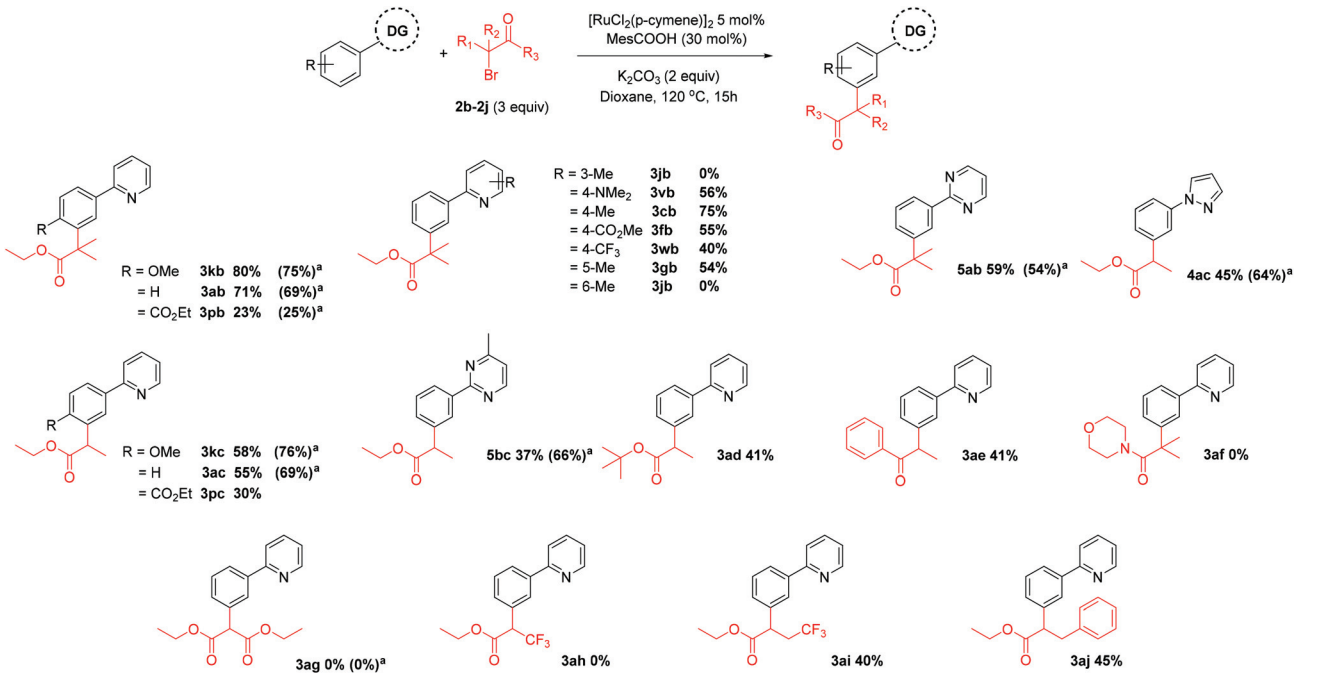
substituted product **1ao** in agreement with other work in the field.[50,51] No disubstituted products were isolated. The use of $Pd(PPh_3)_4$ led to no alkylated products and could be due to undesirable oxidative addition/β-hydride elimination pathways.

Next, we saw the potential for other α-halo carbonyls to be used to install other useful functionality at the *meta* position (Scheme 5). When tertiary α-bromo carbonyl reagents were used, the addition of PPh_3 did not improve the yield of the corresponding *meta* substituted products. However, the use of PPh_3 with secondary α-bromo carbonyl reagents improved the yield somewhat. Thus, a range of secondary and tertiary alkylated products could be achieved using a $[RuCl_2(p\text{-cymene})]_2$ precatalyst with carboxylate (MesCOOH) ligand.[40,42,43] In agreement with the reactions carried out in Scheme 2, changing the electronics on pyridine ring generally had a detrimental effect on reaction yields with a 4-Me substituent again proving to be the most effective directing group. We have previously proposed that the key to this type of reactivity when tertiary α-halo carbonyls are employed, is the facile generation of an alkyl radical.[42] Captodative stabilization by the electron donating geminal dimethyl substituent along with the electron withdrawing effect of the ester could allow facile homolytic cleavage of the C–Br bond. Thus, coupling partners with solely electron withdrawing groups bound to the α-carbon did not result in alkylated products (**3ag**, **3ah**) whereas the corresponding coupling partners with short alkyl chains introduced could furnish the *meta* substituted products (**3ai**). α-Halo ketones could also be effectively coupled (**3ae**) however α-halo amides were ineffective (**3af**), again highlighting the importance of captodative stabilization in the coupling partner.

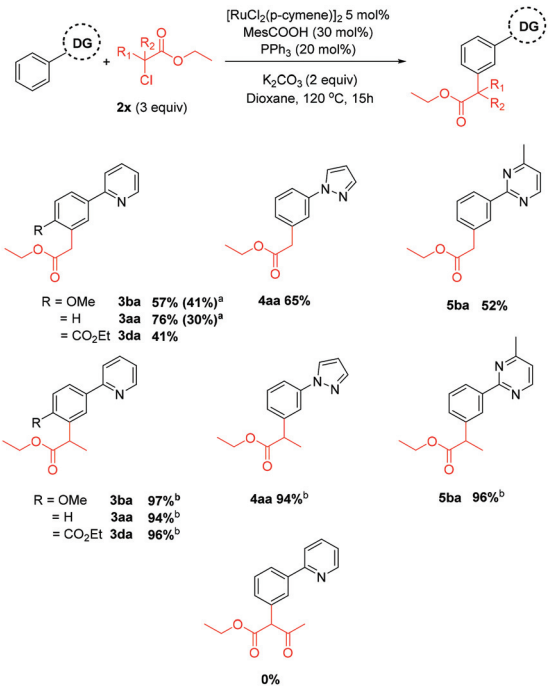
Next, we investigated the effect of the halide leaving group (Scheme 6). To our surprise, α-chloro carbonyl coupling partners displayed improved performance and this was significant when secondary coupling partners were used, affording the *meta* substituted products in near quantitative yield. Again, substrates bearing only electron withdrawing groups were ineffective, and support a radical mechanism in these cases. The corresponding α-iodo carbonyl coupling partner was less effective, indicating an order of reactivity of Cl > Br > I, however the reason for this remains unclear.

Mechanistic considerations

We previously proposed a dual metallic radical based mechanism for *meta* alkylation reactions involving initial cyclometalation, which activates the position *para* to the newly installed C–Ru bond for site selective addition.[42] Recently, we also showed that substitution happens at the *para* position of the



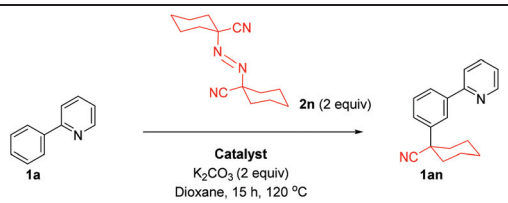
Scheme 5 Scope of α-bromo carbonyl coupling reagents. All numbers indicate isolated yields. [a] Reaction with PPh_3 additive (20 mol%).



Scheme 6 Reactions using alkyl halide coupling partners. [a] Reaction with corresponding α-iodo carbonyl. [b] Quantitative conversion of starting material observed.

newly formed C–Ru bond in stoichiometric reactions with cyclometalated complexes in analogous *meta* sulfonation reactions.[39] We were therefore interested to discover the manner in which the alkyl halide coupling partners reacted with the activated arene. In our previous work with *meta* selective tertiary alkylation reactions, we proposed a second distinct single electron redox cycle that can generate a tertiary alkyl radical, which can add to the cyclometalated complex in a site selective manner.[42] To investigate this further, a series of experiments were conducted using radical coupling partner 1,1′-azobis (cyclohexanecarbonitrile) (ABCN, **2n**) (Table 2).

Table 2 Reactions with ABCN

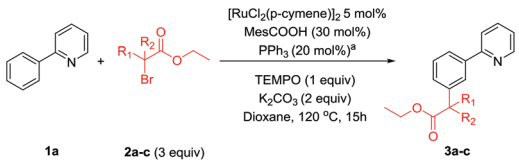


Entry	Catalyst	Yield (%)
1	No catalyst	0%
2	$[Ru(OMes)_2(p\text{-cymene})]$ (10 mol%)	9%
3	$[Ru(OMes)_2(p\text{-cymene})]$ (50 mol%)	26%
4	PPh_3 (20 mol%)[a]	0%
5	$[Ru(OMes)_2(p\text{-cymene})]$(10 mol%) + PPh_3 (20 mol%)	8%

[a] No ruthenium source added.

Thermal generation of a tertiary radical through loss of nitrogen resulted in no conversion to the *meta* product when no ruthenium complex was used however when 10 mol% preformed complex $[Ru(OMes)_2(p\text{-cymene})]$ was employed, *meta* alkylated product **1an** was formed in a 9% yield showing that ruthenium is essential for the activation of the substrate molecule. Increasing the catalyst loading increased the yield some-

Table 3 Reactions with TEMPO



Coupling partner	Yield %
2a	41
2a[b]	0
2b	0
2c	0

2a ($R_1 = R_2 = H$), **2b** ($R_1 = H$, $R_2 = Me$) **2c** ($R_1 = R_2 = Me$). [a] Not added for reaction with **2c**. [b] 3 equivalents of TEMPO used.

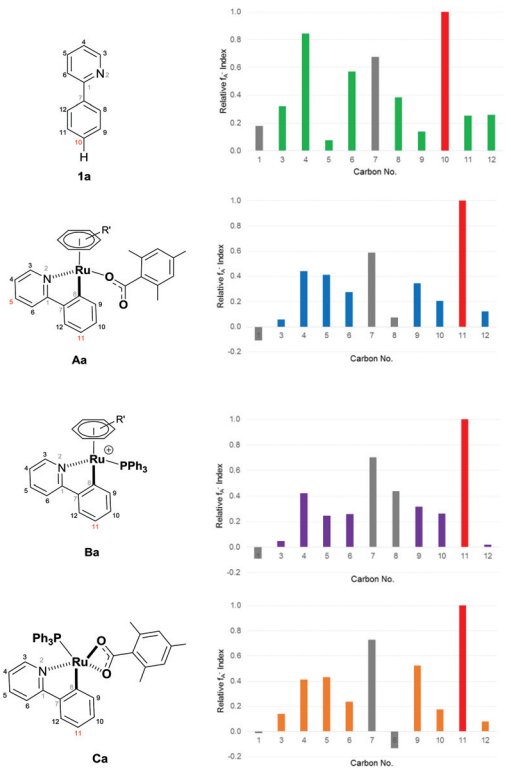


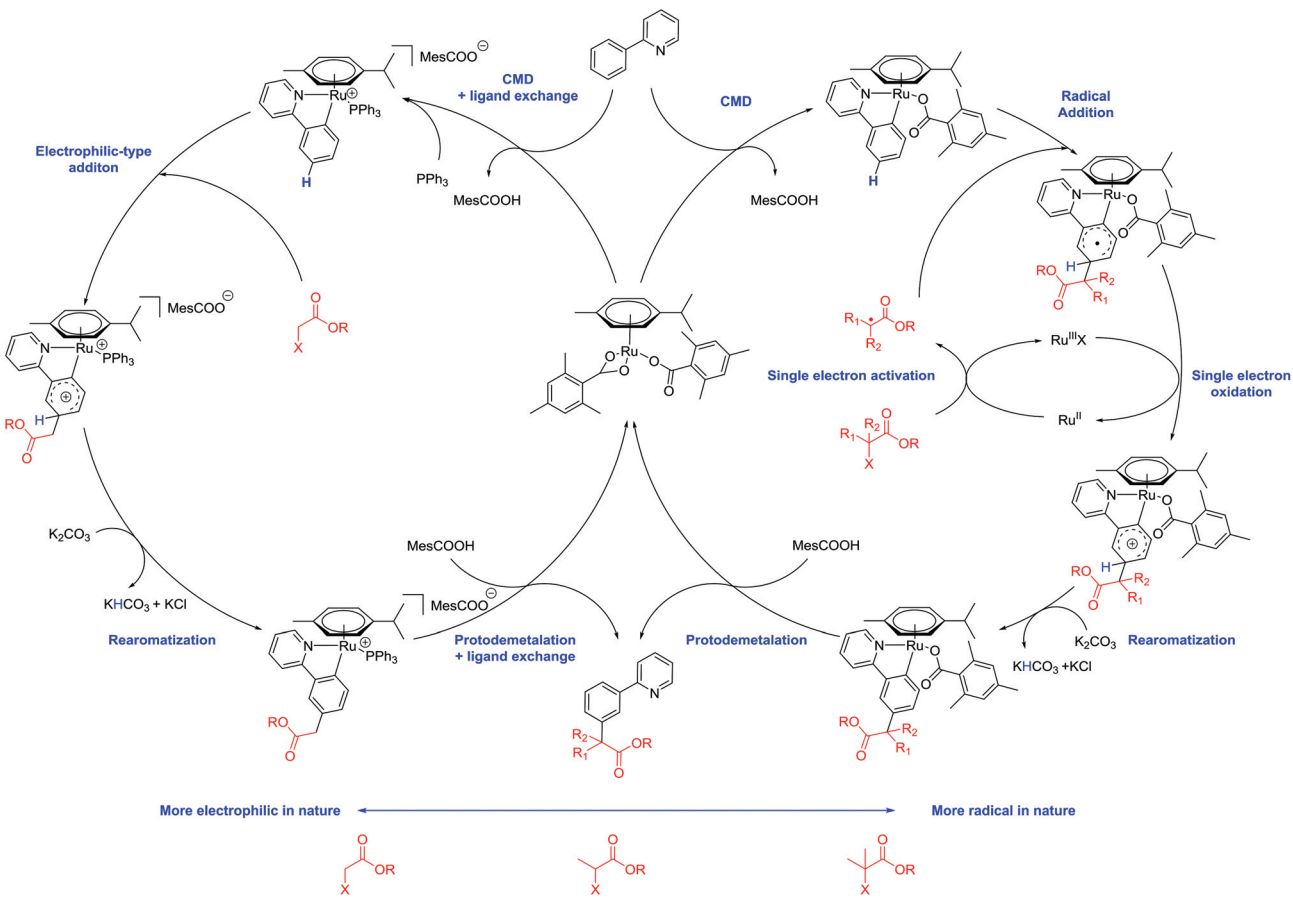
Fig. 2 Relative nucleophilicity Fukui indices (f_A^-) calculated for computed substrates **1a** and the corresponding cyclometalated complexes. Calculations were performed at the BP86/6-31G** & SDD(Ru) level of theory. Fukui indices were calculated with NBO total atomic charges from the optimized neutral structure. The most reactive C–H position is highlighted in red.

what showing that this is a stoichiometric process. These results support the proposition that cyclometalation activates the position *para* to the C–Ru bond and external activation of the coupling partner and generation of a tertiary alkyl radical can then result in addition to this complex.

We were then interested to determine whether primary α-halo carbonyl **2a** reacted in the same manner as the corresponding secondary and tertiary coupling partners. Reactions with radical scavenger TEMPO were less adversely affected than when the corresponding secondary or tertiary coupling partners (**2a** and **2b**) were used but yielded no *meta* products when 3 equivalents were used (Table 3). However, this does not conclusively imply a radical mechanism as unlike the secondary or tertiary α-halo carbonyl coupling partners that were shown to be effective in Scheme 4 or the thermally generated tertiary radical formed from ABCN, the radical formed from homolytic cleavage of the C–Br bond in **2a** would not benefit from any captodative stabilization.

Furthermore, we have shown theoretically that electrophilic mechanisms are also plausible for cyclometalated ruthenium complexes (Fig. 2 and ESI†). We have applied computational methods to model the electronic properties of the cyclometalated intermediates based on the work of Ritter and co-workers.[61] This approach accurately predicts reaction regioselectivity using relative nucleophilic Fukui indices calculated from carbon NBO values and has been applied to 2-phenylpyridine (**1a**) and other cyclometalated ruthenium complexes.[62] The relative Fukui indices in Fig. 2 show that if the organic substrate alone was the active species, then reactivity would most likely occur at C10; *para* to the pyridine ring due to increased electron density at this position. However, the regioselectivity of the substrate is altered after cyclometalation (**Aa**), with the most electron rich carbon site for functionalization now indicating addition at C11; the C–H position *para* to the new Ru–C bond. Cyclometalated complexes containing a phosphine ligand (**Ba** and **Ca**) also display similar electronic properties and could serve the additional purpose of blocking the coordination sphere of the ruthenium metal which could otherwise lead to *ortho* substituted products *via* an oxidative addition/reductive elimination pathway. The precise role of the phosphine nevertheless remains unclear and could also be involved in the activation of the α-halo carbonyl coupling partner.

Based on our most recent mechanistic observations and on previous work conducted by ourselves[42] and others[40,43] in the field, we propose the following mechanism for *meta*-selective alkylations with primary, secondary and tertiary α-halo carbonyls (Scheme 7). Reaction of a substrate molecule with a ruthenium carboxylate complex results in a cyclometalated complex



Scheme 7 Plausible catalytic cycles.

activated at the position *para* to the C–Ru bond. Reaction of this complex with secondary or tertiary radicals externally generated by a single electron Ru(II)/Ru(III)X process then leads to the formation of a cyclometalated arene radical. Single electron oxidation, rearomatization and protodemetalation then leads to the *meta* substituted products. Primary α-halo carbonyl radicals on the other hand could either undergo either a single electron, or electrophilic addition onto the cyclometalated complex. More detailed mechanistic studies are necessary to accurately determine this process and are currently underway.

Conclusions

In summary, we have reported the use of α-halo carbonyls as versatile reagents for the direct *meta* functionalization of arenes. The procedure is operationally simple and has enabled a range of primary, secondary and tertiary alkylations with the capacity for further synthetic elaborations. A phosphine source was crucial for the installation of primary alkyl groups allowing primary α-halo carbonyls to be coupled selectively to the *meta* position and was also beneficial for secondary coupling partners. Conversely, straight chain alkyl halides afforded solely *ortho* substituted products. α-Chloro carbonyls displayed the highest reactivity affording *meta* substituted products quantitatively in some cases. Experimental and computational mechanistic analysis highlight a dual activation pathway whereby cyclometalation with ruthenium activates the substrate molecule at the position *para* to the C–Ru bond and is responsible for the *meta* selectivity observed. Synergistic activation of the α-halo carbonyls then enables site selective alkylation with net *meta* selectivity.

Acknowledgements

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