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Ruthenium-catalysed *meta*-selective C_{Ar}–H bond alkylation *via* a deaminative strategy†

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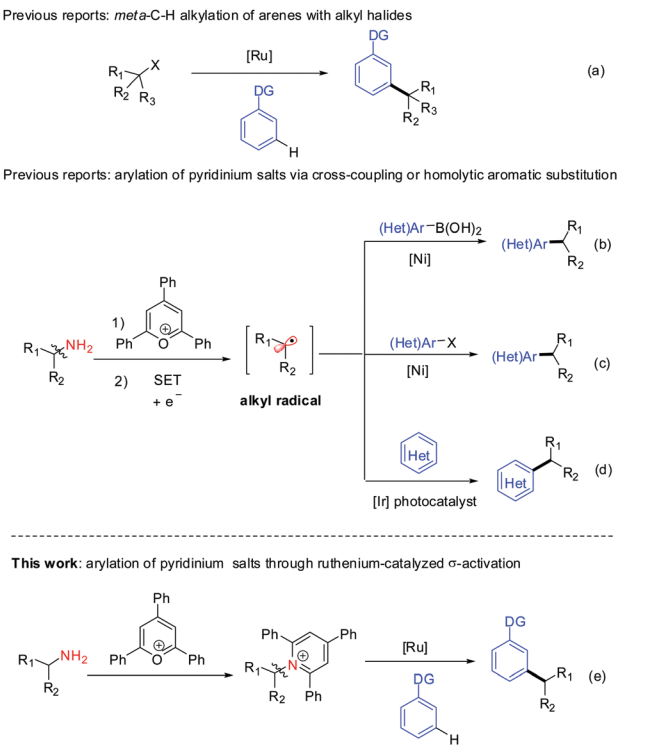
The use of aliphatic amines as alkylating reagents in organic synthesis *via* C–N bond activation remains underdeveloped. We herein describe a novel ruthenium-catalysed and directing-group assisted protocol for the synthesis of *meta*-alkylated arenes *via* dual C–H and C–N activation. Bench-stable and easily handled redox-active Katritzky pyridinium salts derived from abundant amines and amino acid species were used as alkyl radical precursors. This catalytic reaction could accommodate a broad range of functional groups and provide access to various *meta*-alkylated products.

The conversion of C–H bonds into C–C and C–heteroatom bonds is an efficient and powerful approach for rapid generation of complex molecules from simpler ones.[1] However, the control of site selectivity in molecules that contain diverse C–H bonds with electronic and steric similarity remains a critical challenge in organic synthesis.[2] Directing-group-assisted transition-metal catalysis has been identified as an effective strategy toward proximity-driven *ortho*-selective C–H functionalization,[3] which is well established. In contrast, methods for remote *meta*-selective C–H activation remain underdeveloped.[4–6] The ruthenium-catalyzed σ-activation strategy, representatively developed by Ackermann, Frost and others in recent years,[7–13] has proven valuable for radical-type *meta*-selective C–H functionalization through an *ortho*/*para* fashion, thus enabling access to the alkylated,[8,9] acylated,[10] sulfonated,[11] brominated,[12] and nitrated[13] products. Note that tertiary and secondary alkyl halides could act as the efficient alkyl radical precursors for the *meta*-selective C–H alkylation (Scheme 1a)[8] but the reaction of unactivated primary alkyl halides *via* ruthenium catalysis led to the *ortho*-C–H alkylation.[8b,14] Despite these significant advances in the field, the development of new methods for *meta*-C–H alkylation *via* ruthenium catalysis to meet various demands is still required.

The generation of alkyl radicals from naturally abundant and inexpensive feedstocks is highly important for synthetic chemistry. Although aliphatic amines are widely found in synthetic chemicals and bioactive molecules, their utilizations as the alkylation reagents in organic synthesis remain underdeveloped.[15] In recent years, bench-stable Katritzky salts, readily obtained from the condensation of primary amines with 2,4,6-triphenylpyrylium in one step, have been employed as the efficient alkyl radical precursors *via* C–N bond cleavage in a



Scheme 1 Radical deaminative arylation of pyridinium salts and *meta*-C–H alkylation of arenes.

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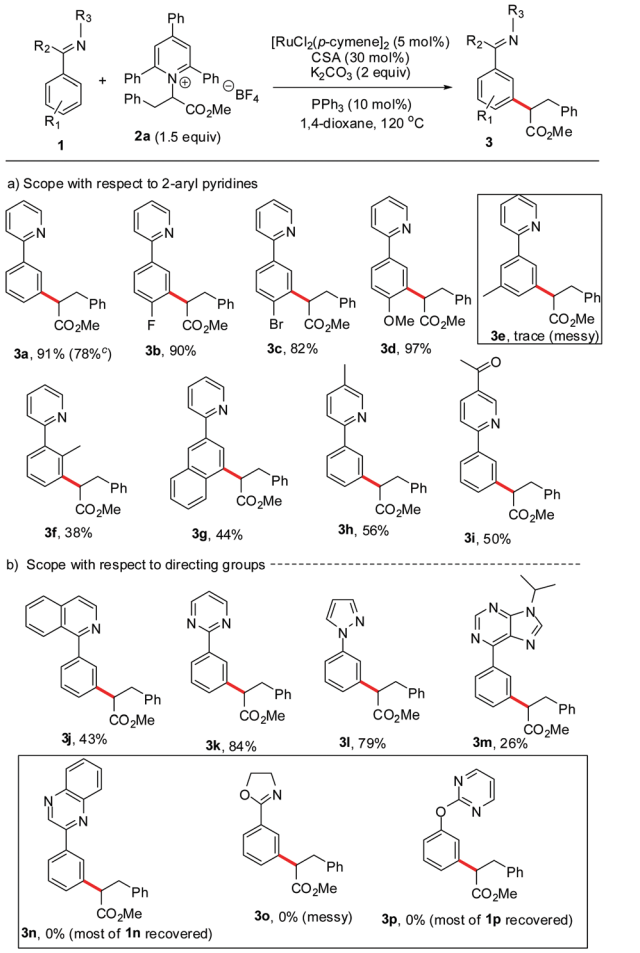
number of reactions.[16] In 2017, Watson and co-workers described that Katritzky salts could act as amine-derived alkyl electrophiles in Ni-catalyzed deaminative cross-coupling reactions with arylboronic acids (Scheme 1b).[17] This reaction proceeded with the generation of alkyl radicals through a single-electron reduction and fragmentation process. Recently, Ni-catalyzed reductive cross-coupling of aryl halides with Katritzky salts, which was independently developed by the groups of Watson,[18a] Martin,[18b] Rueping,[18c] Pan,[19] and Molander,[20] has also been applied successfully to $C(sp^3)$–C_{Ar} bond formation (Scheme 1c). Besides, Glorius's group developed a photoredox-mediated alkylation of heteroarenes with Katritzky salts *via* homolytic aromatic substitution (Scheme 1d).[21] This Minisci arylation represents another radical strategy to convert the ubiquitous NH_2 moiety.

Motivated by the advantages of alkyl amine derivatives as alkylation reagents, we wondered whether the combination of C–N bond activation and *meta*-C_{Ar}–H functionalization could be adapted to synthesis of functionalized aromatic rings. In continuation of our research effort on radical transformation of alkylpyridinium salts,[22] we herein report the first example of ruthenium-catalyzed dual activation of a C–N bond and C–H bond for *meta*-C_{Ar}–$C(sp^3)$ bond formation (Scheme 1e). This protocol allows an array of alkyl groups to be installed, providing a general method for the transformation of amino groups into various aryl moieties.

After examining various conditions with respect to Ru catalysts, inorganic bases, solvents, and ligands (see the ESI,† Table S1, entries 1–19), we were pleased to find that, with 5 mol% of $[RuCl_2(p\text{-cymene})]_2$ (10 mol% of [Ru]) as the catalyst, 2 equiv. of K_2CO_3 as the base, 30 mol% of camphorsulfonic acid (CSA) and 10 mol% of PPh_3 as the synergistic ligands, and 1,4-dioxane (0.25 M) as the solvent, the catalytic reaction readily offered the desired *meta*-alkylated product **3a** in 91% yield (Table S1, ESI,† entry 13). Variation in other commonly used Ru catalysts, such as $Ru_3(CO)_{12}$, $RuCl_3{\cdot}3H_2O$, and $RuCl_2(PPh_3)_3$, provided lower chemical yield than $[RuCl_2(p\text{-cymene})]_2$ under otherwise identical reaction conditions (Table S1, ESI,† entries 17–19). The control experiments revealed that the ruthenium catalyst and ligands were all essential for the success of the reaction (Table S1, ESI,† entries 20–22).

With the optimized reaction conditions in hand, we aimed to survey the scope and limitations of this strategy for *meta*-C_{Ar}–H alkylation with Katritzky salts. As shown in Table 1a, the reaction could accommodate a range of functional groups on the aromatic ring (**3b–d** and **3f–g**) or the chelating pyridine ring (**3h–i**) regardless of their electronic properties. Remarkably, the bromine atom is well reserved in this Ru-catalyzed reaction (**3c**). As might be expected, blocking one of the *meta*-positions on the phenyl ring led to only trace amount of alkylated product being detected in the reaction (**3e**). Note that these experimental findings (*e.g.* **3e** and **3f**) could indicate that the reaction is sensitive to the steric interactions. We next turned our attention to the investigation of different directing groups (Table 1b). We were delighted to find that the isoquinoline-, pyrimidine-, pyrazole-, and purine-containing substrates could efficiently deliver the desired products (**3j–m**). Unfortunately, under similar reaction conditions, our efforts to achieve the alkylated products **3n–p** were unsuccessful.

Table 1 Substrate scope with respect to C_{Ar}–H bonds[ab]

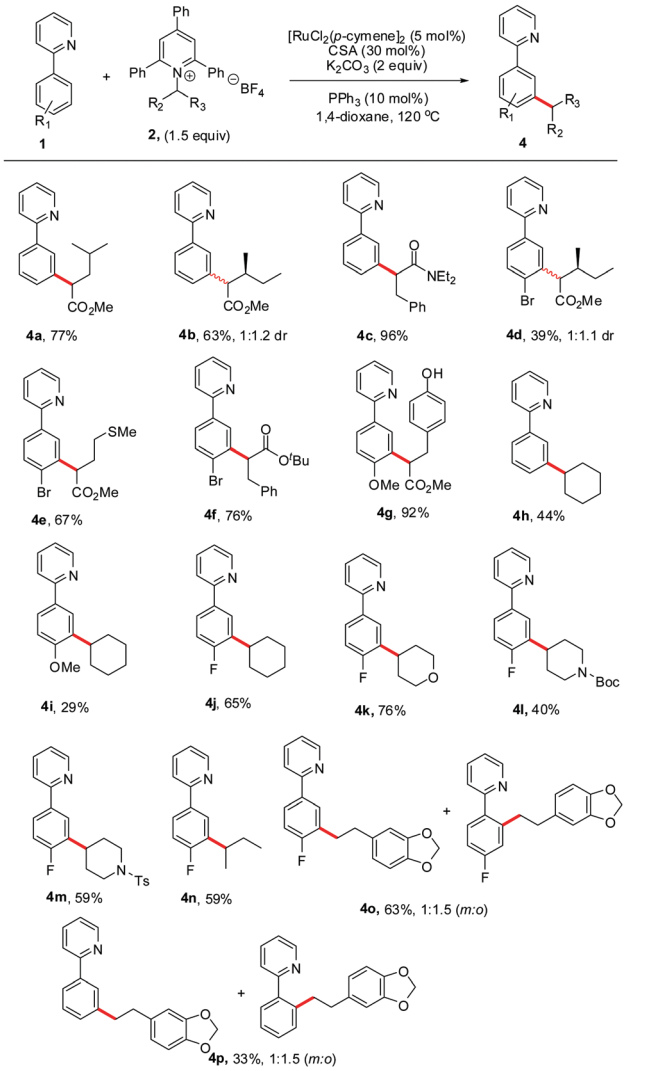


[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), CSA (camphorsulfonic acid, 30 mol%), K_2CO_3 (0.4 mmol) and PPh_3 (10 mol%) in 1,4-dioxane (0.8 mL, used without dehydration) was stirred at 120 °C (oil bath, sealed tube) for 48–72 h. [b] Isolated yields. [c] **1a** (1.2 mmol, 186 mg) and **2a** (1.8 mmol, 1.0 g).

To demonstrate the synthetic utility of this protocol, the reaction using 1.2 mmol of **1a** and 1.8 mmol (1.0 g) of **2a** was performed under the standard conditions. The reaction still proceeded smoothly, offering the desired product **3a** in 78% yield.

To explore the further practicability of this deaminative strategy, we examined the reaction of 2-arylpyridines (**1**) with various primary amine-derived redox-active Katritzky salts (**2**). As depicted in Table 2, a broad range of acyclic, cyclic and heterocyclic alkylpyridiniums were accommodated well by this Ru-catalyzed radical reaction, furnishing the desired *meta*-alkylated products in reasonable yields (**4a–p**). Note that the efficiency of the electrophilic radicals (**4a–c**) is better than that of the nucleophilic radicals (**4h** and **4p**) when using 2-phenylpyridine as the coupling partner. This protocol exhibits excellent functional group compatibility, with, for example, amides/sulfonamides (**4c** and **4l–m**), sulfides (**4e**), and unmasked hydroxyl groups (**4g**) being well tolerated. Strikingly, the reaction of unactivated primary alkyl Katritzky salts *via* the

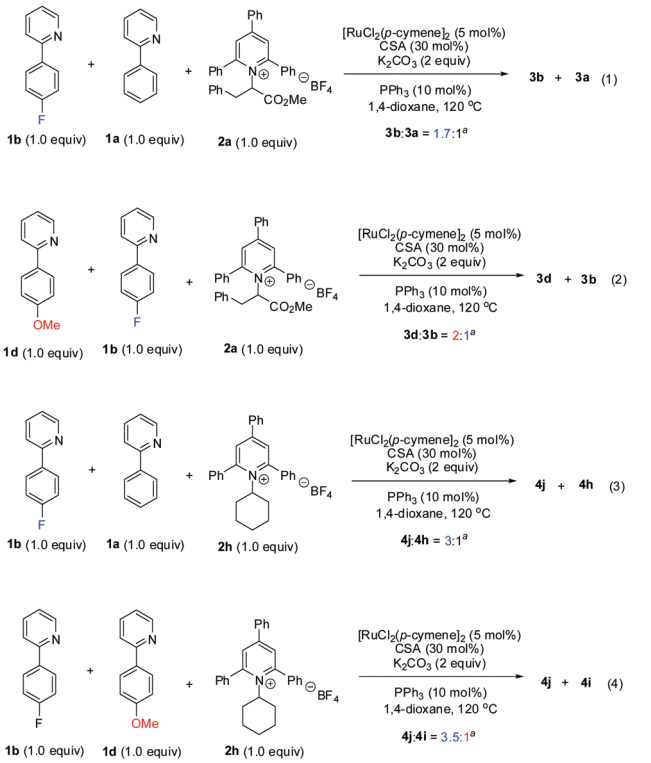
Table 2 Substrate scope of alkylpyridinium salts[ab]



[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), CSA (30 mol%), K_2CO_3 (0.4 mmol) and PPh_3 (10 mol%) in 1,4-dioxane (0.8 mL, used without dehydration) was stirred at 120 °C (oil bath, sealed tube) for 48–72 h. [b] Isolated yields. Diastereoselectivity ratio (dr) and regioisomeric ratio (*m*:*o*) determined from the ^{1}H NMR spectra.

Ru catalytic system could afford both *meta*-C–H and *ortho*-C–H alkylation products (**4o–p**), while the reaction of unactivated primary alkyl halides led to *ortho*-C–H alkylation as the exclusive reaction pattern under similar conditions.[8b,14]

To gain further understanding of the reaction mode, we performed intermolecular competition experiments between differently substituted phenylpyridines (Scheme 2). When using the Katritzky salt **2a** derived from amino acid ester as the alkylating reagent, the results revealed that electron-rich methoxy-substituted arene **1d** was the most reactive substrate (Scheme 2, eqn (1) and (2)). In contrast, the experimental data obtained from the competitive reactions of Katritzky salt **2h** demonstrated that electron-deficient arenes could be inherently more reactive than their electron-neutral or electron-rich

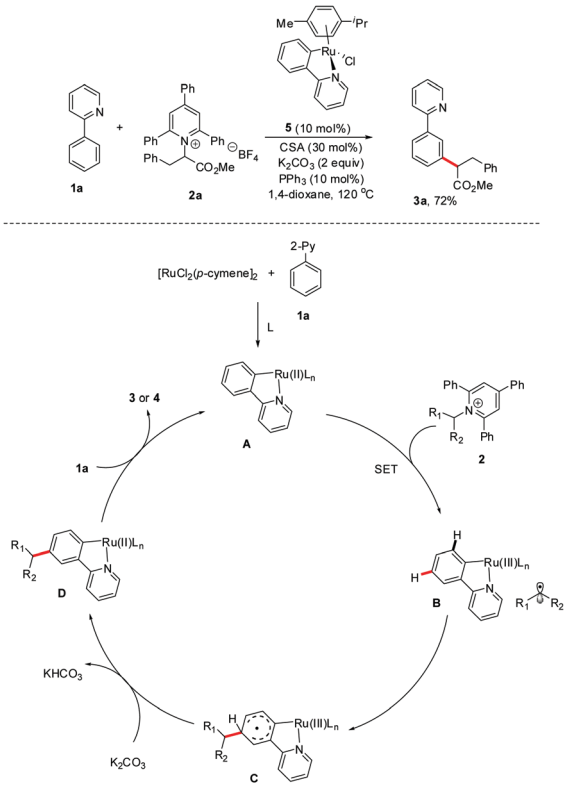


Scheme 2 Competitive experiments.

counterparts (Scheme 2, eqn (3) and (4)). Interestingly, fluorine-containing substrate **1b** is more reactive than 2-phenylpyridine (**1a**) in both cases (eqn (1) and (3)). This could be attributed to the conjugative effect of the F-atom to activate its *ortho* positions. These phenomena suggest that a simple electrophilic substitution type mechanism could be unlikely. On the other hand, with TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as a radical scavenger, the reaction did not lead to the formation of the desired product **3a** (see the ESI†). This result could support the involvement of a radical process.

Furthermore, we prepared the well-defined cyclometalated ruthenium complex **5**,[8c] which showed high catalytic activity as $[RuCl_2(p\text{-cymene})]_2$ under similar reaction conditions (Scheme 3). On the basis of the observations and previous reports,[8,9] a proposed mechanism of the catalytic transformation is depicted in Scheme 3. The *in situ* generated ruthenium(II) complex **A** undergoes single-electron transfer (SET) to Katritzky salt **2** to offer the ruthenium(III) complex **B**, as well as the corresponding alkyl radical, which attacks on the arene moiety at the activated position *para* to ruthenium, delivering the adduct species **C**. Subsequently, ligand to metal charge transfer and re-aromatization leads to the ruthenacycle **D**. Finally, ligand exchange could provide the desired *meta*-alkylated product **3** or **4** and thus regenerate the ruthenium(III) complex **A** to close the catalytic cycle.

In summary, we have described a novel method towards *meta*-decorated arenes that is based on an unprecedented ruthenium-catalyzed dual activation of C–N and C–H bonds. The readily available redox-active Katritzky pyridinium salts



Scheme 3 Control experiment and proposed mechanism.

derived from abundant amines were used as efficient radical precursors for remote C_{Ar}–H bond alkylation. The reaction works well with a range of N-containing directing groups, such as pyridine, pyrimidine, pyrazole, isoquinoline, and purine. This catalytic reaction displays an excellent functional group tolerance and could be applicable to the introduction of a variety of alkyl moieties.

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Conflicts of interest

The authors declare no competing financial interest.

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