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Deaminative *meta*-C–H alkylation by ruthenium(II) catalysis†

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Precise structural modifications of amino acids are of importance to tune biological properties or modify therapeutical capabilities relevant to drug discovery. Herein, we report a ruthenium-catalyzed *meta*-C–H deaminative alkylation with easily accessible amino acid-derived Katritzky pyridinium salts. Likewise, remote C–H benzylations were accomplished with high levels of chemoselectivity and remarkable functional group tolerance. The *meta*-C–H activation approach combined with our deaminative strategy represents a rare example of selectively converting C(sp³)–N bonds into C(sp³)–C(sp²) bonds.

Introduction

The straightforward formation of modified amino acids from native amino acid precursors¹ is conceptually appealing in order to increase the step- and atom-economy associated with the preparation of orthogonally protected molecular scaffolds. Synthetic methods have in the past mainly focused on the modification of limited nucleophilic residues of amino acids, such as found in lysine, tyrosine or cysteine.² The prevalence of carboxylic acids motifs abundant in peptidic structures of aspartic acid, glutamic acid and α -carboxylic acids, renders them as ideal candidates for targeted peptide modifications. Beyond the traditional amidation and esterification, proteino-genic alkyl carboxylic acids have generally been utilized as handles for transition-metal-catalyzed decarboxylative functionalizations, either by employing activated redox-active esters³ or the direct manipulation of native peptides.⁴ C–H functionalizations of inert C–H bonds of peptides are of current topical importance for selective late-stage diversifications.⁵ However, deaminative functionalizations of amino acids as a complementary strategy for the late-stage modifications of amino acids and peptides continue to be underdeveloped (Fig. 1a). By means of activating kinetically stable C(sp³)–N bonds *via* the *in situ* formation of α -diazoesters, Wang developed the transition-metal-free deaminative coupling with boronic acids for the synthesis of α -aryl esters.⁶ Very recently, Rovis reported on a challenging photoredox-catalyzed deaminative alkylation with sterically encumbered α -primary amines.⁷ Similarly, bench-stable redox-active alkylpyridinium salts—also known as

Katritzky pyridinium salts—were utilized by Watson as deaminative reagents for elegant Suzuki–Miyaura cross-coupling reactions.⁸ Glorius concurrently found a visible-light-mediated Minisci reaction with Katritzky salts.⁹ Photo-induced deaminative borylations¹⁰ and Giese reactions¹¹ were further made possible *via* the formation of electron-donor–acceptor complex by Aggarwal. The popularity of Katritzky salts as a functional handle was likewise demonstrated by visible-light-mediated transformations, such as Mizoroki–Heck-type reactions,¹² allylations,¹³ alkynylation¹⁴ and nickel-catalyzed couplings.¹⁵

Positional selectivity is paramount to synthetically useful C–H transformations, but challenging because of the close bond dissociation energies.¹⁶ Proximity-induced *ortho*-C–H functionalization by chelation assistance¹⁷ proved powerful for late-stage diversification. In stark contrast, remote C–H functionalizations of arenes¹⁸ continue to be challenging. Especially, strategies for *meta*-C–H functionalizations¹⁹ continue to be scarce, even though major progress has been achieved by steric control, template

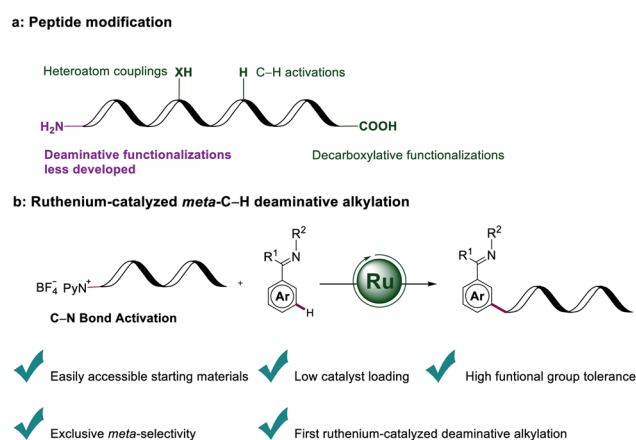


Fig. 1 (a) Peptide modification. (b) Ruthenium-catalyzed *meta*-C–H deaminative alkylation.

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assistance, transient mediators and weak hydrogen bonding.²⁰ In this context, we have now merged ruthenium-catalyzed *meta*-C–H transformations²¹ with a deaminative bond formation to disclose herein unprecedented ruthenium-catalyzed *meta*-C–H alkylations with Katritzky salt. Notable features of our findings (Fig. 1b) include (1) easily accessible and bench-stable alkylating agent for C–H functionalizations, (2) low catalyst loading, (3) high functional group tolerance, and (4) selective ruthenium-catalyzed deaminative *meta*-C–H alkylation and benzylation.

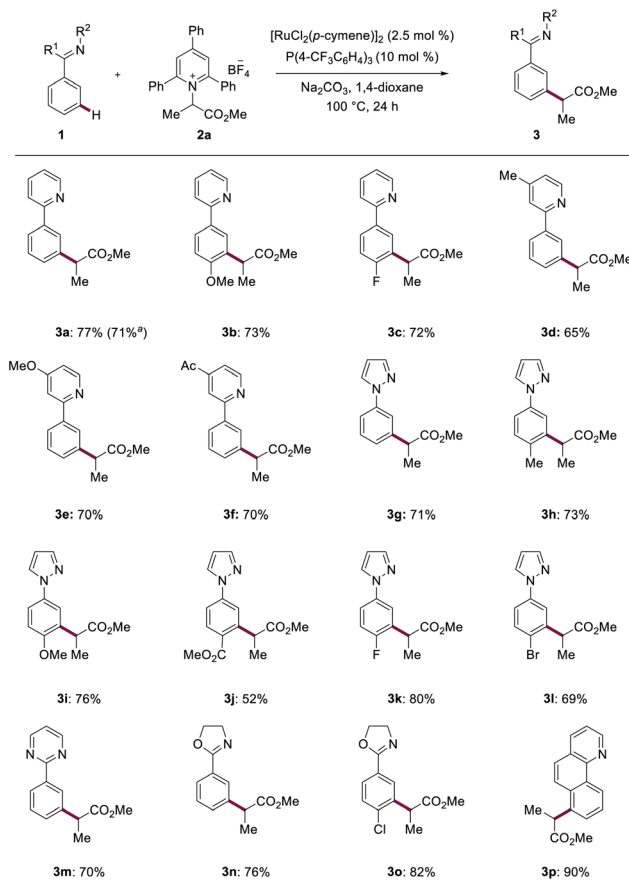
Results and discussion

Optimization of the reaction conditions

We initiated our studies by probing the secondary alkylation of arene **1a** with Katritzky salt **2a** (Table 1). Among a variety of phosphine ligands, electron-deficient P(4-CF₃C₆H₄)₃ proved to be optimal (entries 1–5). Subsequently, we tested different ruthenium catalysts, and [RuCl₂(*p*-cymene)]₂ led to the desired *meta*-alkylated product **3a** in high yield (entries 8 and 9). Control experiments verified the key role of the phosphine ligand and the ruthenium catalyst (entries 6 and 7). Notably, decreasing the amount of the catalyst and the phosphine ligand did not significantly alter the reaction performance (entry 9).

Versatility

With the optimized reaction conditions for the ruthenium-catalyzed deaminative C–H alkylation in hand, we next examined its versatility (Scheme 1). The ruthenium catalysis was not limited to pyridine guidance. Indeed, the *meta*-alkylation also allowed for the use of pyrazoles (**3g–3l**), pyrimidines (**3m**), oxazolines (**3n** and **3o**) and benzoquinoline (**3p**) as orienting



Scheme 1 Ruthenium-catalyzed *meta*-C–H alkylations with heteroarene orienting groups.^a Gram scale reaction at 1 mmol.

Table 1 Optimization for ruthenium-catalyzed deaminative alkylation^a

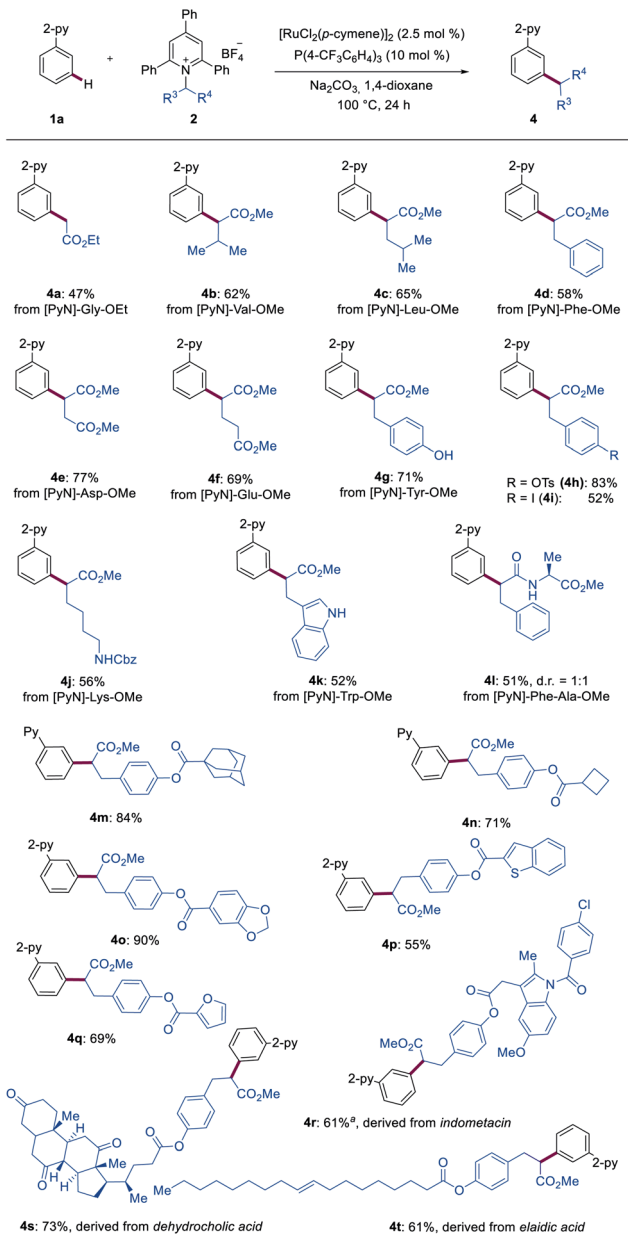
Entry	Catalyst	Ligand	Yield ^b /%
1	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	PPh ₃	37
2	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	P(4-F-C ₆ H ₄) ₃	45
3	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	P(4-MeOC ₆ H ₄) ₃	24
4	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	P(4-C ₆ H ₄ CF ₃) ₃	63
5	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	PCy ₃	7
6	[Ru(O ₂ CMe) ₂ (<i>p</i> -cymene)]	—	Trace
7	—	P(4-C ₆ H ₄ CF ₃) ₃	Trace
8	[RuCl ₂ (<i>p</i> -cymene)] ₂	P(4-C ₆ H ₄ CF ₃) ₃	79
9	[RuCl ₂ (<i>p</i> -cymene)] ₂	P(4-C ₆ H ₄ CF ₃) ₃	77 ^{c,d}

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Ru(O₂CMe)₂(*p*-cymene)]₂ (15 mol%), P(4-C₆H₄CF₃)₃ (45 mol%), Na₂CO₃ (0.4 mmol) 1,4-dioxane (2.0 mL) at 100 °C for 24 h. ^b Yield of isolated products. ^c [RuCl₂(*p*-cymene)]₂ (2.5 mol%), P(4-C₆H₄CF₃)₃ (10 mol%). ^d 2,4,6-Triphenyl pyridine was isolated in 89%.

motifs, while the functionalization of heteroarenes provided thus far less satisfactory results. A range of synthetically useful functional groups, such as halides (**3c**, **3k** and **3l**), ester (**3j**) and ketone (**3f**), were well tolerated and furnished the desired *meta*-alkylated products **3** in good to excellent yields and high levels of *meta*-selectivity.

Next, Katritzky salts **2** derived from functionalized amino acids were tested (Scheme 2). A wide range of aliphatic amino acids, including alanine, valine, leucine, and phenylalanine, could be selectively converted into the desired products **4a–4d**. Furthermore, the corresponding products **4e** and **4f** were obtained in 77% and 69% yield, respectively, when aspartic acid- and glutamic acid-derived Katritzky salts were employed. Notably, functional groups, including the free hydroxyl group in tyrosine (**4g**) and the free amino group in lysine (**4j**) as well as free NH-indole in tryptophan (**4k**), were well tolerated. Derivatives from protected tyrosine and phenylalanine containing easily transformable functional groups furnished the desired products **4h** and **4i** efficiently. Structurally more complex dipeptide-derived Katritzky salt ([P₂N]–Phe–Ala–OMe) selectively underwent the *meta*-ligation, delivering the desired product **4l**. In addition, heteroarenes (**4o–4q**) were compatible with the ruthenium catalysis. Importantly, the transformative power of our approach was harnessed for late-stage diversifications. Marketed drugs and natural product-like compounds,

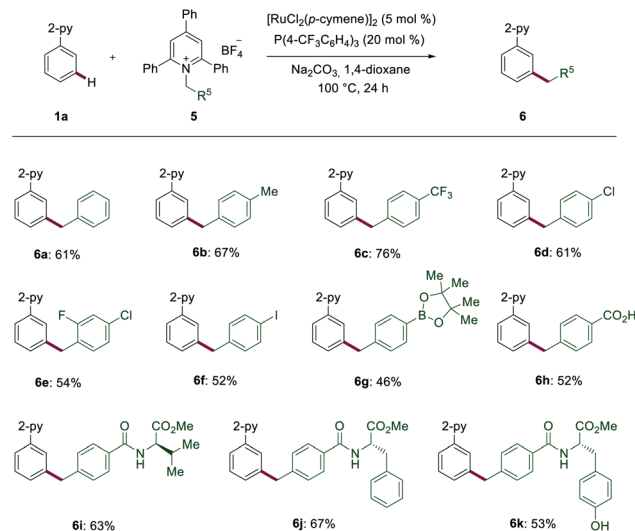




Scheme 2 Ruthenium-catalyzed *meta*-C–H secondary alkylation. ^a 5 mol% of $[RuCl_2(p\text{-cymene})]_2$ was used.

such as indomethacin (**4r**), dehydrocholic acid (**4s**) and elaidic acid (**4t**), proved to be amenable, indicating the potential for drug discovery programs.

In addition to amino acid derivatives, we also explored Katritzky salts of primary amines to achieve benzylations (Scheme 3). Electron-donating and electron-withdrawing benzyl groups, such as products **6b** and **6c** were well obtained. Halogen-containing substrates also resulted in good yields of the corresponding *meta*-benzylated products **6d–6f**. Notably, highly labile functional groups, such as Bpin (**6g**), also proved to be applicable. Katritzky salts bearing a free acid chemo-selectively led to the desired product **6h**. Products **6i–6k** were obtained in a synthetically useful yield and with high levels of chemo-selectivity from the amino acids-derived Katritzky salts.



Scheme 3 Scope of ruthenium-catalyzed *meta*-C–H benzylations.

Mechanistic studies

In order to elucidate the reaction mechanism of the ruthenium(II)-catalyzed *meta*-C–H transformations, we subsequently conducted mechanistic studies. Competition experiments highlighted that electron-rich substrates are inherently less reactive than the electron-deficient counterparts. Katritzky salts with electron-withdrawing groups turned out to be more effective for the *meta*-transformation (see ESI[†]). Reactions with isotopically labelled co-solvent CD_3OD provided strong support for facile reversible C–H activation at the *ortho*-position (Fig. 2). Given this exclusive *meta*-selectivity, we were inspired to identify key intermediates. First, the ruthenium complexes **7** and **8** were synthesized and isolated. When catalytic amounts of complex **7** were utilized, the product **3a** was obtained in 23% (Fig. 3a). Instead, ruthenium–phosphine catalyst **8** displayed a significantly improved performance (Fig. 3b).

Subsequently, experiments with the typical radical trapping reagent TEMPO led to an inhibition of reactivity (see ESI[†]). A radical clock experiment with allyl-containing Katritzky salt afforded the corresponding ring closure product observed by ESI-MS spectrometry (see ESI[†]), being supportive of a radical pathway being operative.

On the basis of our mechanistic findings, a plausible reaction mechanism for the ruthenium-catalyzed *meta*-C–H alkylation is put forward in Scheme 4, which commences by a chelation-assisted C–H ruthenation and dissociation of *p*-cymene ligand, forming ruthenacycle **I**.²² Single-electron transfer (SET) from the ruthenium(II) complex **I** to the Katritzky salt **2**

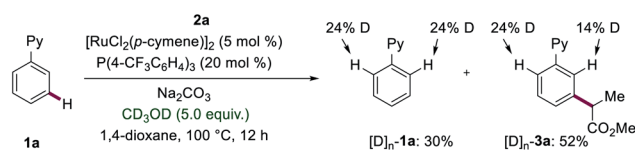


Fig. 2 H/D exchange experiment.



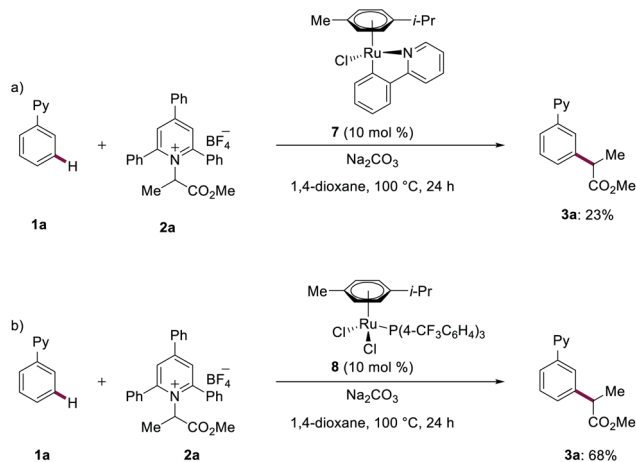
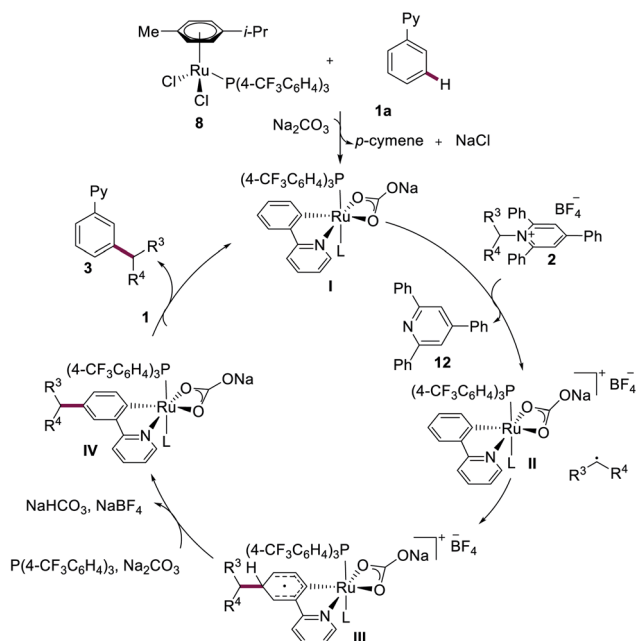


Fig. 3 Reactions with isolated complexes 7 and 8.



Scheme 4 Proposed mechanism.

delivers the ruthenium(III) intermediate **II**, along with isolated triphenylpyridine (**12**) (see ESI[†]). The newly formed secondary alkyl radical attacks the aromatic motif at the position *para* to the C–Ru bond, generating the triplet ruthenium intermediate **III**. Rearomatization then leads to the formation of ruthenacycle **IV**. Finally, proto-demetalation and ligand exchange affords the desired *meta*-functionalized product **3** and regenerates ruthenium(II) complex **I**.

Conclusion

In summary, we have reported on ruthenium-catalyzed *meta*-selective C–H secondary alkylations and benzylations with easily accessible pyridinium salts. The ruthenium catalysis featured excellent chemo- and position-selectivities as well as

a broad functional group tolerance. Importantly, the deaminative strategy set the stage for late-stage diversification of bioactive molecules and marketed drugs by deaminative transformations of amino acids and peptides.

Author contributions

L. A. and Y. H. conceived the project. W. W. performed the experiments, analyzed and interpreted the experimental data. W. W. and A. Z. drafted the paper. All of the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

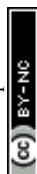
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