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# *N*-Acyl Amino Acid Ligands for Ruthenium(II)-Catalyzed *meta*-C−H *tert*-Alkylation with Removable Auxiliaries

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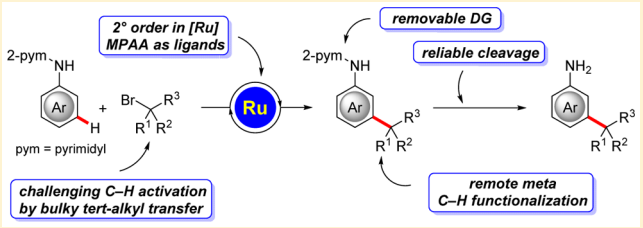
Supporting Information

**ABSTRACT:** Acylated amino acid ligands enabled ruthenium(II)-catalyzed C−H functionalizations with excellent levels of *meta*-selectivity. The outstanding catalytic activity of the ruthenium(II) complexes derived from monoprotected amino acids (MPAA) set the stage for the first ruthenium-catalyzed *meta*-functionalizations with removable directing groups. Thereby, *meta*-alkylated anilines could be accessed, which are difficult to prepare by other means of direct aniline functionalizations. The robust nature of the versatile ruthenium(II)−MPAA was reflected by challenging remote C−H transformations with tertiary alkyl halides on aniline derivatives as well as on pyridyl-, pyrimidyl-, and pyrazolyl-substituted arenes. Detailed mechanistic studies provided strong support for an initial reversible C−H ruthenation, followed by a SET-type C−Hal activation through homolytic bond cleavage. Kinetic analyses confirmed this hypothesis through an unusual second-order dependence of the reaction rate on the ruthenium catalyst concentration. Overall, this report highlights the exceptional catalytic activity of ruthenium complexes derived from acylated amino acids, which should prove instrumental for C−H activation chemistry beyond remote functionalization.




## INTRODUCTION

The direct transformation of otherwise inert C−H bonds as latent functional groups has received considerable attention, because this approach avoids the use of prefunctionalized starting materials.[1] Since the substrates of interest usually display numerous C−H bonds with close dissociation energies, controlling the positional selectivity represents the key challenge in intermolecular C−H functionalizations.[1,2] In this context, the recent years have witnessed remarkable progress through the use of Lewis-basic entities that allowed for proximity-induced C−H transformations.[3] Thus, site-selectivity ensuring entities have been identified, which set the stage for entropically favored C−H metalations by substrate precoordination to the metal catalyst.[1,3,4] Despite significant recent advances, the vast majority of chelation-assisted C−H activations provided solely access to a plethora of *ortho*-functionalized products.[1] In stark contrast, general methods for *meta*-selective C−H functionalizations continue to be scarce.[5] Notable exceptions include remote C−H transformations that exploit the inherent steric or electronic features of substrate−catalyst interactions (Figure 1a).[6] As an alternative, rationally designed templates were elegantly devised by, among others, Yu and co-workers (Figure 1b).[7] To avoid a stoichiometric template, transient covalent or secondary hydrogen-bonding interactions set very recently the stage for *meta*-selective C−H functionalizations (Figure 1c), as elegantly devised by Yu[8] and Dong.[9,10]

In contrast, ruthenium(II) complexes[11] were recently shown to facilitate *meta*-selective C−H functionalizations by means of chelation-assisted cyclometalation (Figure 1d).[12] While these reports indicated a unique strategy for remote *meta*-C−H activation, the approach was thus far significantly limited to strongly coordinating heteroaromatic pyridyl,[12b−d] pyrazolyl,[12c] imidazolyl,[12c] or pyrimidyl[12c] directing groups, which are unfortunately very difficult to remove[13] or modify. Hence, ruthenium-catalyzed *meta*-selective C−H functionalizations with removable directing groups have as of yet unfortunately proven elusive. Another notable limitation was constituted in that ruthenium(II)-catalyzed *meta*-C−H functionalizations were thus far not amenable to electron-rich arenes, such as synthetically useful anilines. In consideration of the practical importance of aniline derivatives in inter alia drug discovery, crop protection, and material sciences,[14] we set out to devise ruthenium catalysts for *meta*-selective C−H functionalizations of *N*-(pyrimidine-2-yl)anilines,[15] important structural motifs of biologically active compounds of relevance to pharmacologically active ingredients (Figure 2).[16] As a result of our efforts, we herein[17] report on a novel ligand design for ruthenium-catalyzed C−H functionalizations that allowed for the challenging *meta*-C−H activation on electron-rich aniline derivatives. Thus, monoprotected amino acids (MPAA), employed by Yu[18] for palladium-catalyzed transformations, proved to be the best in class ligands for ruthenium(II)-catalyzed remote C−H functionalizations. Notable features of our C−H activation strategy are (i) an unprecedented high catalytic activity in ruthenium-catalyzed *meta*-C−H-activation through MPAA ligand acceleration, (ii) exceptionally high

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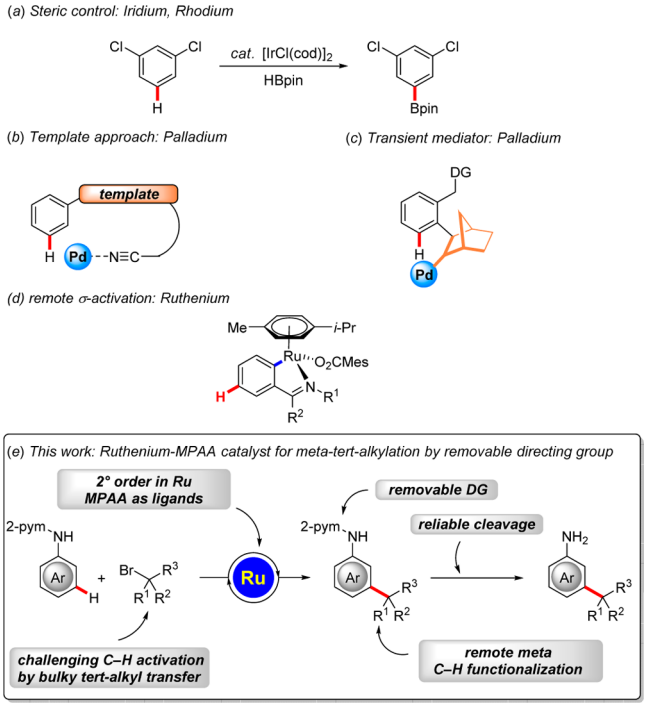



**Figure 1.** Strategies for *meta*-selective C−H functionalization. (a) Steric interactions controlling site-selectivity. (b) Template-assisted transformation. (c) Norbornene as mediator. (d) Remote $\sigma$-activation. (e) Ruthenium(II)−MPAA-catalyzed *meta*-selective alkylation with removable directing groups; pym = pyrimidyl.

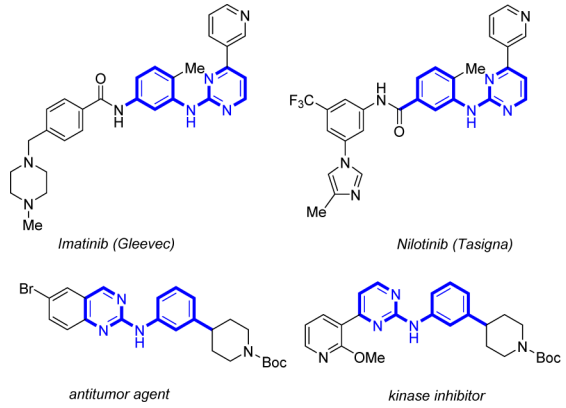


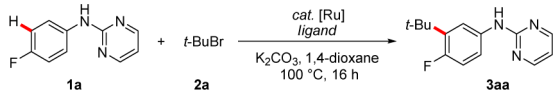

**Figure 2.** Representative bioactive *meta*-substituted *N*-(pyrimidine-2-yl)anilines.

levels of *meta*-selectivity, (iii) remote C−H functionalizations with synthetically useful removable auxiliaries, and (iv) C−H transformations with challenging tertiary alkyl halides (Figure 1e).[19] With respect to the last point, notable progress has been made in metal-catalyzed cross-coupling, including the development of nickel catalysts to promote challenging coupling reactions of unactivated tertiary alkyl halides by Fu and coworkers.[20]

## RESULTS AND DISCUSSION

**Aniline Derivatives: Optimization.** At the outset of our studies, we probed reaction conditions that we had previously optimized for the ruthenium(II)-catalyzed *meta*-alkylation of 2-phenylpyridines with secondary alkyl bromides.[12c] To our delight, the desired *meta*-alkylated product was obtained in 30% yield (Table 1, entry 1). KOAc also proved to be a competent ligand, albeit leading to a significantly lower yield (entry 2).

**Table 1. Optimization of *meta*-Selective *tert*-Alkylation**[a]



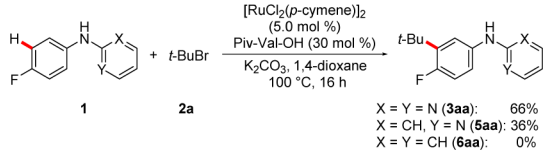

| entry | catalyst | ligand | yield (%) |
|---|---|---|---|
| 1 | $[RuCl_2(p\text{-cymene})]_2$ | $MesCO_2H$ | 30 |
| 2 | $[RuCl_2(p\text{-cymene})]_2$ | KOAc | 26 |
| 3 | $[RuCl_2(p\text{-cymene})]_2$ | | 0 |
| 4 | $[RuCl_2(p\text{-cymene})]_2$ | Piv-Phe-OH | 50 |
| 5 | $[RuCl_2(p\text{-cymene})]_2$ | Piv-Leu-OH | 58 |
| **6** | **$[RuCl_2(p\text{-cymene})]_2$** | **Piv-Val-OH** | **66** |
| 7 | $[RuCl_2(p\text{-cymene})]_2$ | H-Val-OH | 18 |
| 8 | $[RuCl_2(p\text{-cymene})]_2$ | $Boc_2$-Val-OH | 54 |
| 9 | $[RuCl_2(p\text{-cymene})]_2$ | $MeO_2C$-Val-OH | 58 |
| 10 | $[RuCl_2(p\text{-cymene})]_2$ | Boc-Val-OH | 55 |
| 11 | $[RuCl_2(p\text{-cymene})]_2$ | Ac-Val-OH | 47 |
| 12 | $[RuCl_2(p\text{-cymene})]_2$ | 1-Ad-Val-OH | 62 |
| 13 | $[RuCl_2(p\text{-cymene})]_2$ | 1-Ad-Ile-OH | 65 |
| 14 | [RuCl(Piv-Val-O)(*p*-cymene)] (**4**) | | 56 |

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), ligand (30 mol %), $K_2CO_3$ (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 16 h; yields of isolated products.

While the reaction did not occur in the absence of an additive (entry 3), a considerably improved catalytic efficacy proved viable with the MPAA Piv-Phe-OH as the ligand (entry 4). While ruthenium(II)−amino acid complexes are well established in the literature,[21] MPAAs have as of yet not been exploited for ruthenium-catalyzed C−H functionalizations. Encouraged by our initial lead, we examined differently substituted MPAA ligands. Thus, among a representative set of pivaloyl-protected amino acids, the valine derivative turned out to be optimal (entries 4−6). In contrast, the parent amino acid valine delivered the desired arene **3aa** only in an unsatisfactorily low yield, highlighting the importance of the amide moiety and its *N*-substitution pattern (entry 7). In agreement with this observation, *N*,*N*-disubstituted valine bearing the amide motif proved to be a competent ligand (entry 8). Further *N*-protected MPAAs afforded the *meta*-alkylated product **3aa** in comparable yields (entries 9−13). To unravel the nature of the in situ generated ruthenium catalyst, we independently prepared the ruthenium(II)−MPAA complex **4**. Intriguingly, the single-component ruthenium(II) species **4** was found to be catalytically active, despite the decreased ligand loading (entry 14).

Thereafter, we explored the dependence of the ruthenium(II)-catalyzed *meta*-C−H alkylation on the nature of the aniline's *N*-substitution pattern (Scheme 1). Interestingly, the switch from the pyrimidyl to the more strongly coordinating[22] pyridyl group resulted in a considerable loss in catalytic efficacy.

**Scheme 1. Effect of the *N*-Substitution Pattern**



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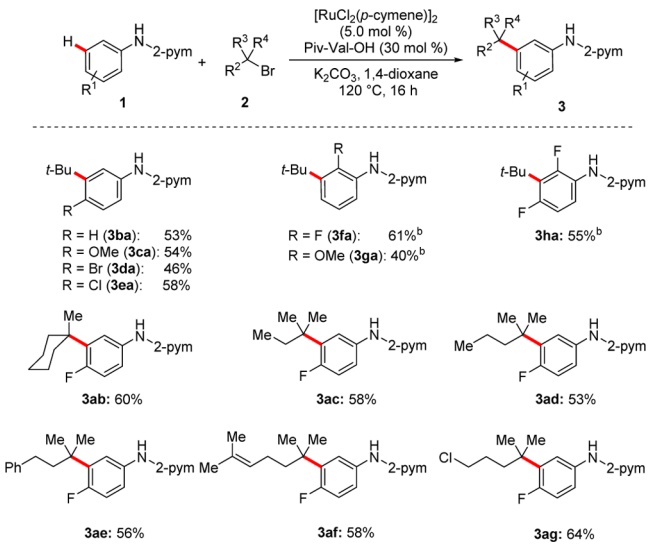
Moreover, a simple diarylaniline failed to furnish the desired product, thereby highlighting the relevance of chelation assistance.

**Scope and Limitations.** With the optimized ruthenium(II) catalytic system in hand, we explored its scope and limitations in the *meta*-selective *tert*-alkylation (Scheme 2). We were

**Scheme 2. Scope of Ruthenium(II)-Catalyzed *meta*-Alkylation of Anilines 1**[a]

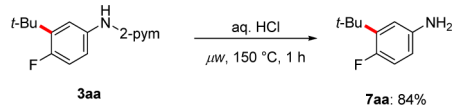



[a](a) Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), Piv-Val-OH (30 mol %), $K_2CO_3$ (1.0 mmol), 1,4-dioxane (2.0 mL), 16 h, 120 °C; yields of isolated products. (b) 1-Ad-Ile-OH (30 mol %).

pleased to observe that the ruthenium−MPAA complex was broadly applicable. Thus, electron-rich as well as functionalized arenes **1** bearing bromo or chloro substituents were efficiently converted, furnishing the desired *meta*-alkylated products **3ba**−**3ea**. Notably, the ligand Ad-Ile-OH even enabled the direct *meta*-alkylation of challenging *ortho*-substituted substrates, furnishing the *tert*-alkylated products **3fa** and **3ga** through the exclusive functionalization at the sterically more congested *meta*-C−H bond. The 2,4-disubstituted aniline **1h** was smoothly alkylated at the 3-position within an intramolecular competition, illustrating the excellent site-selectivity of the approach. Subsequently, we tested a variety of tertiary alkyl bromides **2** in the C−H transformation. Thus, cyclic tertiary bromide **2b** delivered the desired product **3ab** in 60% yield. Likewise, sterically more hindered acyclic tertiary alkyl bromides **2** also afforded the corresponding products. Aryl- and alkenyl-substituted alkyl bromides **2e** and **2f** were well tolerated, thereby providing a handle for further postsynthetic diversifications. It should be noted that the alkyl bromide **2g** displaying a primary alkyl chloride was chemo-selectively converted at the more hindered site on the alkyl halide (**3ag**). This observation clearly unraveled the relative reactivity pattern within the ruthenium(II)-catalyzed C−H alkylation process (vide infra).

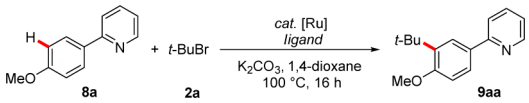
Intriguingly, the pyrimidyl group could be reliably cleaved in a traceless fashion, providing *meta*-alkylated aniline derivative **7aa** in 84% yield (Scheme 3). Thereby, our strategy offers a novel approach for the step-economical synthesis of *meta*-substituted anilines **7**, which are extremely difficult to access by other aniline functionalization methods.

**Scheme 3. Removal of the Directing Group**




**Heteroarenes: Optimization.** Given the unique catalytic efficacy of the ruthenium−MPAA complex in the C−H functionalization with aniline derivatives **3**, we became attracted by exploring its versatility with differently decorated arenes. Hence, we tested various in situ generated ruthenium(II) catalysts in the direct functionalization of pyridyl-substituted[23] arene **8a** (Table 2). The desired reaction could not be achieved

**Table 2. Optimization for *meta*-Selective *tert*-Alkylation of 2-Arylpyridine 8a**[a]




| entry | catalyst | ligand | yield (%) |
|---|---|---|---|
| 1 | $[RuCl_2(p\text{-cymene})]_2$ | | 0 |
| 2 | $[RuCl_2(p\text{-cymene})]_2$ | KOAc | 50 |
| 3 | $[RuCl_2(p\text{-cymene})]_2$ | Piv-Leu-OH | 55 |
| 4 | $[RuCl_2(p\text{-cymene})]_2$ | Piv-Gly-OH | 48 |
| 5 | $[RuCl_2(p\text{-cymene})]_2$ | Piv-Phe-OH | 53 |
| **6** | **$[RuCl_2(p\text{-cymene})]_2$** | **Piv-Val-OH** | **76** |
| 7 | $[RuCl_2(p\text{-cymene})]_2$ | H-Val-OH | 19 |
| 8 | $[RuCl_2(p\text{-cymene})]_2$ | $Boc_2$-Val-OH | 46 |
| 9 | $[RuCl_2(p\text{-cymene})]_2$ | $MeO_2C$-Val-OH | 58 |
| 10 | $[RuCl_2(p\text{-cymene})]_2$ | Boc-Val-OH | 61 |
| 11 | $[RuCl_2(p\text{-cymene})]_2$ | Ad-Val-OH | 55 |
| 12 | **[RuCl(Piv-Val-O)(*p*-cymene)] (4)** | | **80** |
| 13 | | Piv-Val-OH | 0 |

[a]Reaction conditions: **8a** (0.5 mmol), **2a** (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), ligand (30 mol %), $K_2CO_3$ (1.0 mmol), 1,4-dioxane (2 mL), 100 °C, 20 h, under $N_2$; yields of isolated products.

solely with $[RuCl_2(p\text{-cymene})]_2$ in the absence of any ligand (entry 1). Likewise, the ligand KOAc furnished only an unsatisfactorily low yield (entry 2), while Frost observed in very recent independent studies high conversions with KOAc as the stoichiometric base at an elevated reaction temperature of 120 °C.[12d] Among a set of representative amino acid derivatives, Piv-Val-OH was again found to be the ligand of choice (entries 3−11). It is noteworthy that the single-component ruthenium(II)−MPAA complex **4** delivered the product **9aa** in an improved yield of 80% at a significantly reduced ligand loading (entry 12). Finally, a control experiment confirmed that the ruthenium catalyst proved to be essential (entry 13).

**Scope and Limitations.** After having optimized the reaction conditions, we explored the generality of both the in situ formed ruthenium(II) catalytic system (Scheme 4, conditions A) as well as the single-component complex **4** (conditions B). Generally, the in situ formed and the well-defined ruthenium(II)-MPAA catalysts **4** furnished comparable results. Thus, the parent unsubstituted 2-phenylpyridine (**8b**) as well as the *para*-substituted derivatives **8a** and **8c** were efficiently converted under both reaction conditions (**9aa**−**9ca**). Phenylpyridines **8c**−**8e** bearing electron-withdrawing fluoro, acetyl, or ester groups in the *para*-position selectively delivered the corresponding *meta*-alkylated products. It is



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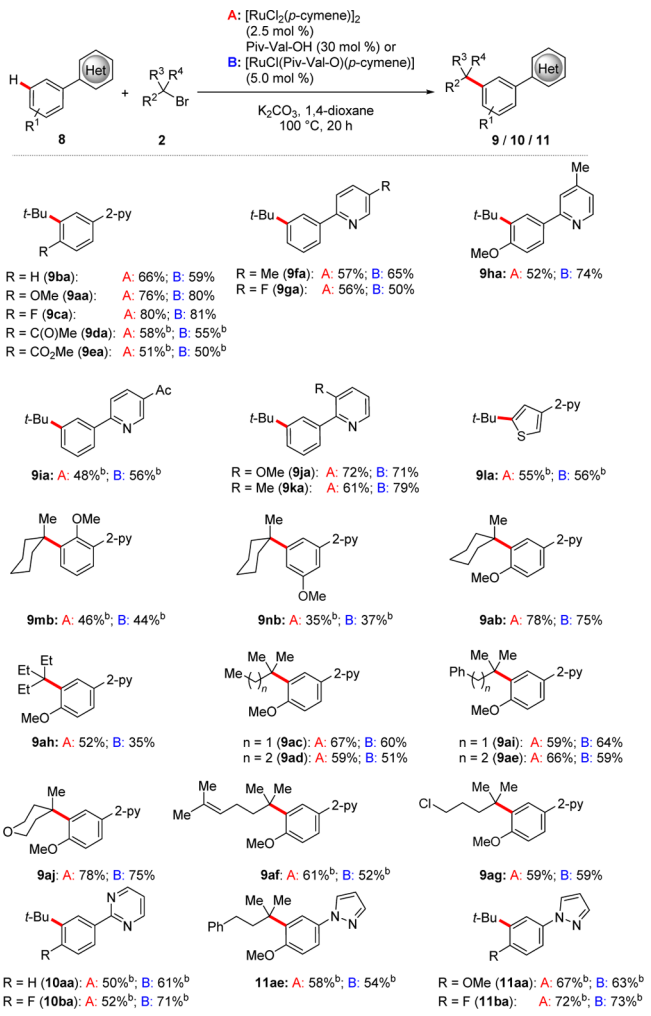
**Scheme 4. Scope of Heteroarene-Assisted *meta*-C−H *tert*-Alkylation**[a]

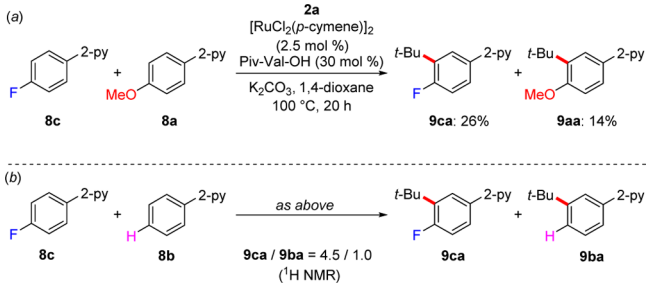



[a](a) Reaction conditions: (A) $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), Piv-Val-OH (30 mol %) or (B) [RuCl(Piv-Val-O)(*p*-cymene)] (5.0 mol %); **8** (0.5 mmol), **2** (1.5 mmol), $K_2CO_3$ (1.0 mmol), 1,4-dioxane (2.0 mL), 20 h, 100 °C under $N_2$ atm; yields of isolated products. (b) $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %) or [RuCl(Piv-Val-O)(*p*-cymene)] (**4**, 10 mol %).

noteworthy that C−H functionalizations of substrates **8a**−**8e** at the *ortho*-position of a weakly coordinating directing ether, halo, ketone, or ester in the presence of a strongly coordinating pyridine substituent are extremely difficult to achieve. Different substituents in the 3, 4, or 5 position on the pyridine moiety were well tolerated by the ruthenium(II) catalyst (**9fa**−**9ka**), with electron-donating substituents slightly improving the performance. Given the importance of heteroarenes as key motifs in various bioactive compounds,[24] we were delighted to observe that the remote C−H *tert*-alkylation of substituted thiophene **9la** proceeded with excellent positional selectivity. Likewise, *ortho*- and *para*-disubstituted arenes **8m** and **8n** underwent the site-selective *meta*-C−H alkylation with the ruthenium(II)−MPAA catalytic system. Subsequently, the robustness of the ruthenium(II) catalyst was probed with various unactivated tertiary alkyl bromides **2** under otherwise identical reaction conditions. Thus, 1-methylcyclohexyl bromide (**2b**) gave the C−H alkylated products **9ab**−**9mb**. Sterically more congested tertiary alkyl bromides **2h**, **2c**, and **2d** afforded the desired products **9** as well. Tertiary alkyl bromides **2** bearing functional groups, such as an arene, an ether, an alkene, or the chloro group, were well tolerated (**9ai**−**9ag**). Intriguingly, the *meta*-*tert*-alkylated product **9ag** was not contaminated by the *ortho*-primary[25] alkylated arene, again demonstrating the useful chemo-selectivity. The versatile ruthenium(II)−MPAA catalyst was not restricted to the strongly coordinating pyridine derivatives. Indeed, the synthetically useful pyrazole and pyrimidine groups also served as the site-selectivity ensuring entities for the C−H *meta*-alkylation, affording the corresponding *meta*-alkylated products **10aa**−**10ba** and **11ae**−**11ba**, respectively.

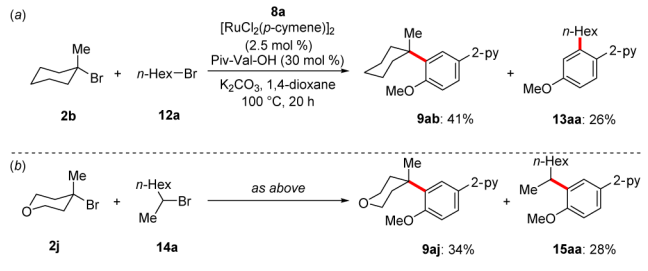
**Mechanistic Studies.** In consideration of the unique catalytic activity of the ruthenium(II)−MPAA complexes, we became intrigued by studying their mode of action. To this end, we performed intermolecular competition experiments between differently substituted phenylpyridines **8**,[26] which revealed electron-deficient arenes to be inherently more reactive than their electron-neutral or electron-rich counterparts (Scheme 5). This phenomenon renders a simple electrophilic substitution-type mechanism unlikely to be operative.

**Scheme 5. Intermolecular Competition Experiments**




Furthermore, we conducted competition experiments between tertiary alkyl halide **2a** and primary or secondary alkyl bromides **12a** and **14a**, respectively (Scheme 6).

**Scheme 6. Competition between 3°, 2°, and 1° Alkyl Halides**




Interestingly, the relative reaction rates across these different classes of electrophiles were similar. Furthermore, the positional selectivity that was observed in single-component reactions with individual electrophiles was preserved in the competition experiments. Indeed, the primary alkyl bromide furnished the *ortho*-substituted product,[25a] while the secondary and tertiary electrophiles delivered the *meta*-substitution pattern.

Subsequently, we conducted C−H functionalization with isotopically labeled compounds (Scheme 7). In the course of the *meta*-alkylation of arene $[D_5]$-**8b**, a significant D/H exchange was observed, which was solely detected in the *ortho*-position of the product $[D_n]$-**9ba** and the reisolated substrate $[D_n]$-**8b** (Scheme 7a). This result provided strong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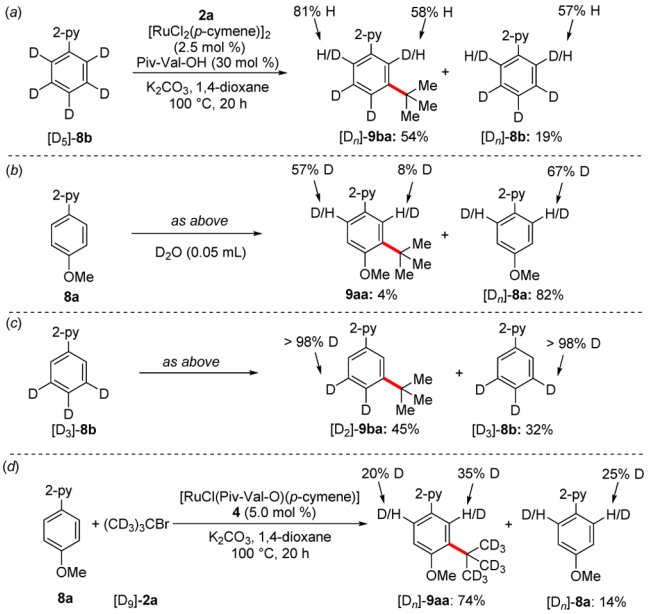
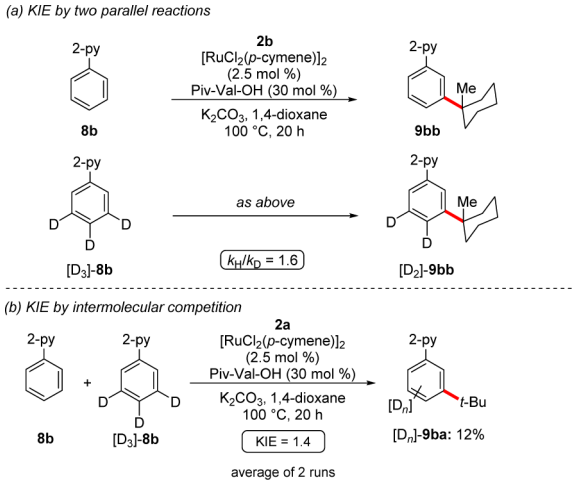
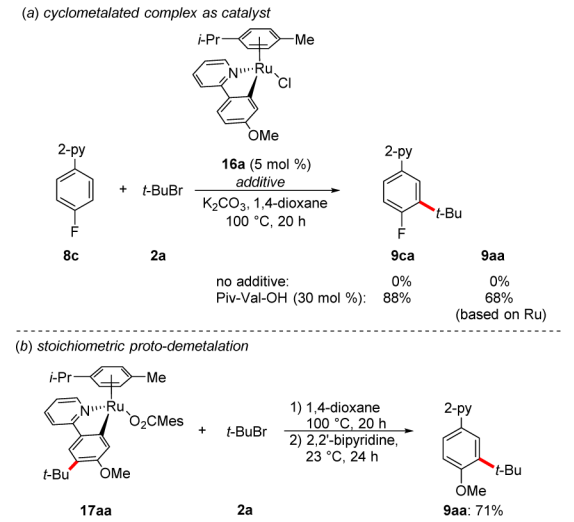
**Scheme 7. Isotopic Labeling Studies**




**Scheme 8. Kinetic Isotope Effect (KIE) Studies**




**Scheme 9. Reactions with Cyclometalated Ruthenium(II) Complexes**




support for the C−H bond metalation step to proceed by an initial *ortho*-metalation in a reversible manner. We also performed the standard *meta*-C−H alkylation in the presence of $D_2O$ (Scheme 7b). Here, a significant amount of deuterium incorporation in the *ortho*-positions of both product [$D_n$]-**9aa** and the recovered starting material [$D_n$]-**8a** was noted. To probe the mode of the *meta*-C−H cleavage and the C−C formation, substrate [$D_3$]-**8b** was subjected to the optimized reaction conditions (Scheme 7c). Careful $^1$H NMR spectroscopic analysis did not show any hydrogen incorporation in the *meta*-position, neither in the product [$D_2$]-**9ba** nor in the recovered starting material [$D_3$]-**8b**. These findings indicate the *meta*-C−H cleavage and C−C forming elementary steps likely to be irreversible in nature. It is interesting to note that the C−H alkylation with isotopically labeled alkyl bromide [$D_9$]-**2a** resulted in a H/D exchange in the *ortho*-positions of both the product [$D_n$]-**9aa** and the recovered starting material [$D_n$]-**8a** (Scheme 7d). This experiment revealed key information on the dual role of the organic electrophile **2a**, in that it not only served as the electrophilic alkylating reagent, but also as the proton source for the key elementary step of proto-demetalation.

The kinetic isotope effect (KIE) of the *meta*-C−H cleavage was investigated by means of the initial rates for independent reactions of substrates **8b** and [$D_3$]-**8b**, highlighting a KIE of $k_H/k_D \approx 1.6$ (Scheme 8). Intermolecular competition experiment between the substrates **8b** and [$D_3$]-**8b** established a KIE of 1.4 as an average of two independent runs, which could be rationalized in terms of a kinetically relevant *meta*-C−H cleavage step.[27]

Given the key importance of the cycloruthenated complexes as potential intermediates in the ruthenium(II)-catalyzed *meta*-alkylation, we subsequently performed reactions with well-defined complexes **16a** and **17aa**. Notably, the chloro-ruthenacycle **16a** was not catalytically competent. However, the presence of cocatalytic amounts of the MPAA ligand Piv-Val-OH restored the catalytic ability, affording the *meta*-alkylated **9aa** in an excellent yield (Scheme 9a).[26] These results clearly illustrate the importance of carboxylate assistance[28] for the ruthenium(II)-catalyzed C−H functionalization.[29] Moreover, the alkyl bromide *t*-BuBr (**2a**) was found to be indispensable for releasing the desired product **9aa** from the cyclometalated ruthenium(II) complex **17aa** (Scheme 9b). This observation illustrates the crucial relevance of the alkyl halides **2** for the proto-demetalation step.

Thereafter, we became interested in understanding the activation mode of the C−Br cleavage[30] as well as the nature of the *meta*-C−C forming step within the ruthenium(II)-catalyzed *meta*-alkylation with secondary and tertiary alkyl bromides. In this context, it is noteworthy that we[12c] and subsequently Frost[12d] had previously reported the detrimental effect exerted by the radical scavenger TEMPO. The independently prepared alkylpyridinium salt **18** was not a competent alkylating reagent (Scheme 10a). Moreover, the use of the alkene methylenecyclohexane (**19a**) did not afford the desired product **9ab**, which rendered a reaction sequence comprised of $\beta$-elimination and a hydroarylation[31] unlikely to be at play (Scheme 10b). Thereafter, the stereochemically well-defined *cis*- and *trans*-1-bromo-4-phenylcyclohexanes (**14b**)[32] were utilized as electrophiles in two independent C−H functionalizations. Interestingly, both reactions delivered the same diastereomeric product mixture. This epimerization can be rationalized in terms of a



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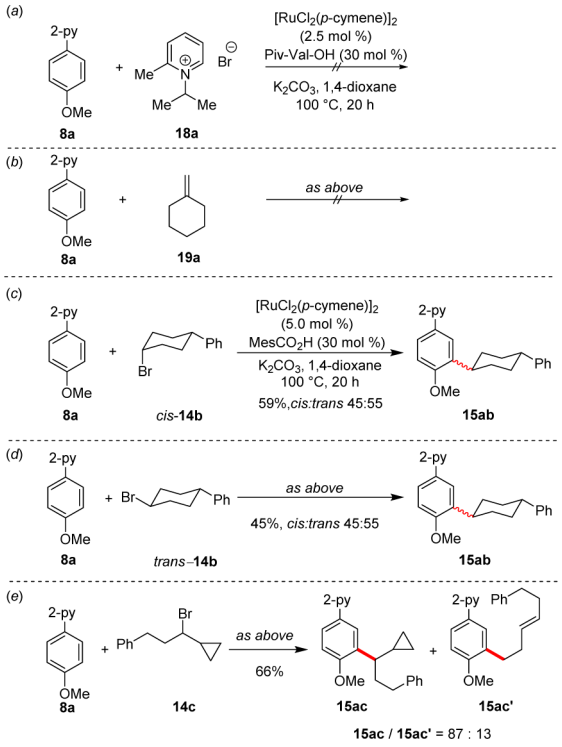
**Scheme 10. Investigation on the *meta*-C−C Formation**




homolytic C−Br cleavage. In good agreement with these observations, experiments with the radical clock (3-bromo-3-cyclopropylpropyl)benzene (**14c**) furnished the *meta*-alkylated product **15ac** with retention of the cyclopropane ring as the major product, along with 9% of the *meta*-homoallylated arene **15ac′**. Thus, a radical rebound should feature a reaction rate being close to that previously observed for the ring opening of the cyclopropylmethylene radical of $7.0 \times 10^7$ $M^{-1}$ $s^{-1}$.[32] These findings are in agreement with the inhibition of the *meta*-alkylation by the radical scavenger TEMPO, as reported by us[12c] and Frost.[12d]

Finally, we performed a detailed kinetic analysis of the ruthenium(II)-catalyzed *meta*-C−H alkylation.[26] Hence, the reaction displayed the a priori expected first-order kinetics with respect to the arene **8b**. However, our studies revealed a second-order dependence on the concentration of the ruthenium catalyst (Figure 3). This unusual kinetic profile is suggestive of a second ruthenium complex being involved in or before the rate-determining step. Given the epimerization of the stereochemically well-defined substrates **14b** (vide supra), we thus propose a second ruthenium complex to facilitate the homolytic[34] C−Br cleavage within a homobimetallic[35] catalysis regime.[36]

On the basis of our detailed mechanistic analysis, we propose the *meta*-C−H *tert*-alkylation to be initiated by the formation of the ruthenium(II)−MPAA complex **4** (Scheme 11). The catalytically active complex **4** is initially undergoing a reversible C−H ruthenation, thus leading to a H/D exchange in the *ortho*-position of the arenes **1**/**8**. Subsequently, a single-electron transfer-type activation of the alkyl halides **2** leads to intermediate **18**. The formation of the radical intermediate hence rationalizes the previously observed racemization of enantiomerically enriched secondary alkyl halides as well as the inhibition by the radical scavenger TEMPO,[12c] and provided a rational for the epimerization of the 1,4-disubstituted cyclo-

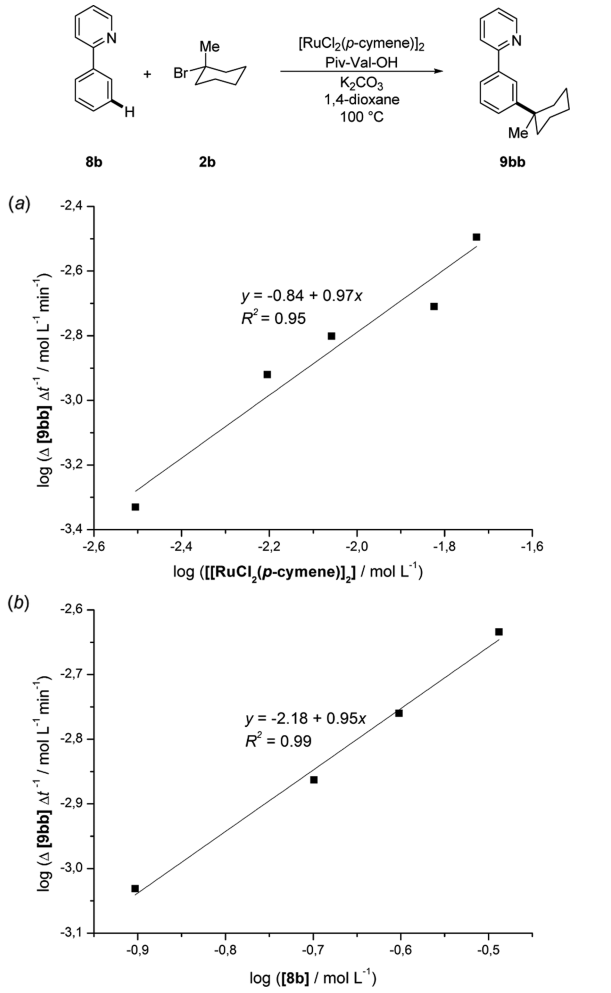
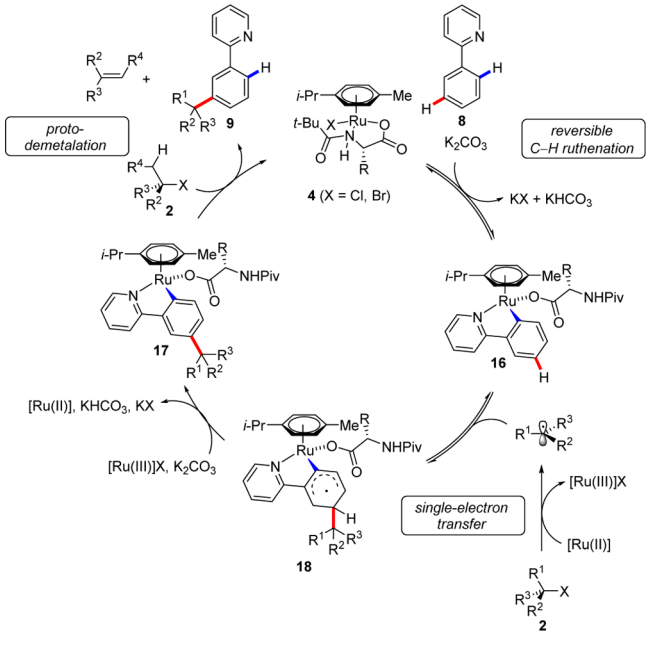



**Figure 3.** Double logarithmic plot of the initial rate versus the concentration of $[RuCl_2(p\text{-cymene})]_2$ and the concentration of 2-phenylpyridine (**8b**).

**Scheme 11. Plausible Catalytic Cycle**



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hexane derivatives as well as for the second-order dependence on the ruthenium concentration (Scheme 10c,d). Hydrogen atom abstraction delivers cyclometalated intermediate **17**, which undergoes proto-demetalation with an additional equivalent of the alkyl halide **2**. Thereby, the desired *meta*-substituted product **3**/**9** is liberated and the catalytically active complex **4** regenerated.

## CONCLUSION

In summary, we have reported on the first ruthenium(II)-catalyzed *meta*-selective C−H functionalization with synthetically useful removable directing groups. Thus, *N*-acyl amino acids were found to be the key to success for the remote C−H *tert*-alkylation, which set the stage for the first ruthenium(II)-catalyzed *meta*-functionalization of electron-rich aniline derivatives. Thereby, our removable auxiliary strategy provided a unique access to *meta*-substituted anilines, which complements traditional approaches. The power of the ruthenium(II)−MPAA-catalyzed remote C−H functionalization was reflected by efficient couplings with secondary and sterically congested tertiary alkyl halides. Detailed experimental mechanistic studies were conducted and provided strong support for an initial reversible cyclometalation by a ruthenium(II)−MPAA complex. Thereafter, a ruthenium-catalyzed homolytic C−Hal cleavage occurs, thus resulting in an unusual second-order dependence of the C−H functionalization rate on the ruthenium concentration. In more general terms, this report showcases, for the first time, the power of ruthenium−MPAA complexes for catalytic C−H functionalizations. Further, studies on the use of ruthenium−MPAA complexes in C−H functionalization are currently ongoing in our laboratories and will be reported in due course.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08435.

Experimental procedures, characterization data, and $^{1}H$ and $^{13}C$ NMR spectra for new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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