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meta-Selective C−H Bond Alkylation with Secondary Alkyl Halides

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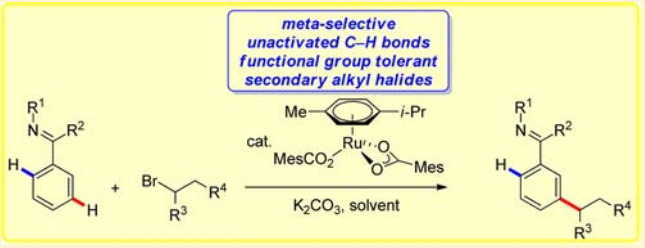
Supporting Information

ABSTRACT: Ruthenium catalysts enabled C−H bond functionalizations on arenes with challenging secondary alkyl halides. Particularly, ruthenium(II) biscarboxylate complexes proved to be the key to success for direct alkylations with excellent levels of unusual meta-selectivity. The direct alkylations occurred under mild reaction conditions with ample scope and tolerated valuable functional groups. Detailed mechanistic studies were performed, including various competition experiments as well as reactions with isotopically labeled substrates. These studies provided strong support for an initial reversible cyclometalation. The cycloruthenation thereby activates the arene for a subsequent remote electrophilic-type substitution with the secondary alkyl halides. Independently prepared cycloruthenated complexes were found to be catalytically active provided that a carboxylate ligand was present, thereby highlighting the key importance of carboxylate assistance for effective meta-selective C−H bond alkylations.



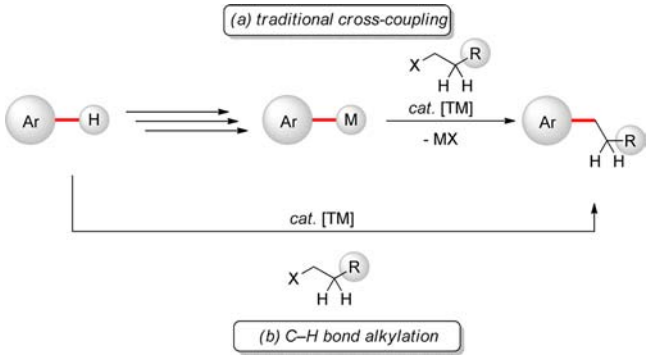
INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions are among the most important tools for the selective assembly of substituted arenes.[1−4] Thus, catalytic coupling reactions between aryl halides and aromatic organometallic reagents have found numerous applications in *inter alia* natural product synthesis, medicinal chemistry, and material sciences. In contrast to the widely utilized $C(sp^2)-C(sp^2)$ bond forming processes, the corresponding transformations of unactivated alkyl halides are less developed, with considerable recent progress being accomplished by the research groups of Fu,[5] Hu,[6] Kambe,[7] Knochel,[8] and Nakamura,[9] among others.[10] Particularly, secondary alkyl halides have proven to be extremely challenging substrates, because these alkyl halides are more sterically demanding and electron-rich, thereby rendering the elementary step of oxidative addition rather difficult.[11] More importantly, the formed metal alkyl intermediates have a strong tendency to undergo β-hydride elimination reactions, overall leading to undesired β-eliminations of the organic electrophiles.[11,12]

Generally, transition-metal-catalyzed cross-coupling reactions rely on the use of prefunctionalized nucleophilic substrates (Scheme 1a).[2,4] The preparation of the prerequisite organometallic—or main-group element—reagents unfortunately involves time-consuming reaction steps that generate undesired waste. A significantly more atom- and step-economical approach is, hence, represented by the direct use of ubiquitous C−H bonds as latent functional groups (Scheme 1b).[13]

In recent years, remarkable progress was accomplished in metal-catalyzed direct arylations and alkenylations,[13,14] whereas catalyzed C−H bond functionalizations with unactivated, β-hydrogen containing alkyl halides under nonacidic reaction conditions are scarce.[15,16] Yet, remarkable recent advances are constituted by ortho-selective palladium-, nickel-, copper-, and

Scheme 1. Traditional Cross-Coupling versus Direct C−H Bond Alkylation



cobalt-catalyzed direct alkylations as reported by Yu,[17] Daugulis,[18,19] Hu,[20,21] Miura/Satoh,[22−24] Nakamura/Yoshikai,[25−27] and others.[15,28] We, on the contrary, recently devised reaction conditions for versatile ruthenium(II)-catalyzed direct alkylations of arenes with primary alkyl[29,30] and benzyl[31] halides.[15]

One of the major challenges in developing methods for synthetically useful C−H bond functionalizations is represented by achieving site-selectivity in intermolecular transformations. Heteroarenes are electronically biased, and can, hence, be functionalized in the α-, β- or γ-position to the heteroatom with high levels of regiocontrol, exploiting the heteroatoms as intramolecular directing groups.[32] On the contrary, controlling the site-selectivity of intermolecular direct C−H bond

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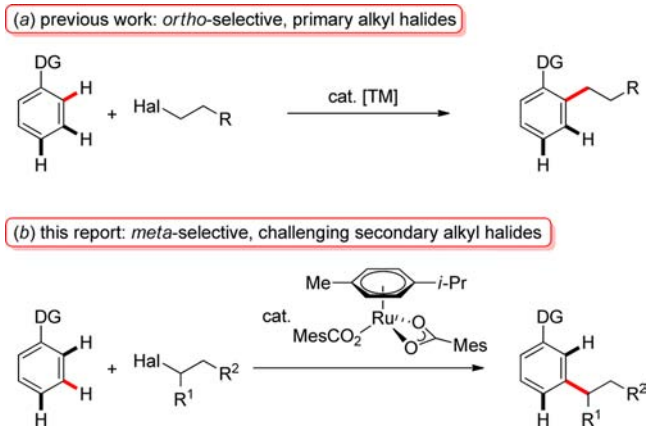
functionalization of monosubstituted unactivated arenes is considerably more difficult, and was almost exclusively accomplished in an ortho-selective fashion by means of chelation assistance.[33] Thus, only few C−H bond activation-based C−C bond forming reactions are thus far available that provide access to meta-disubstituted[34] arenes.[35−37] In pioneering studies, Yu elegantly devised palladium-catalyzed oxidative alkenylations with excellent levels of meta-selectivity.[38−40] Furthermore, two-step alkylations of arenes were very recently accomplished by Hartwig through sterically controlled iridium-catalyzed direct borylations,[41] while copper-catalyzed meta-selective direct arylations proved viable with select aromatic substrates.[42,43] Intriguingly, Frost disclosed ruthenium-catalyzed meta-selective sulfonations through rate-determining C−H bond metalation employing sulfonyl chlorides.[44] In contrast, metal-catalyzed meta-selective C−H bond alkylations under nonacidic reaction conditions have unfortunately as of yet proven elusive, irrespective of the nature of the transition metal catalyst.

Recently, we introduced carboxylates as key cocatalytic additives for robust and reliable ruthenium(II)-catalyzed C−H bond arylations,[45−48] which also proved instrumental for the development of ruthenium-catalyzed oxidative alkenylations[49] and alkyne annulations.[50,51] Ruthenium(II) carboxylate catalysts further enabled direct C−H bond alkylations with primary alkyl halides, which occurred exclusively at the ortho-position (Scheme 2a).[29,30]

Scheme 2. ortho-Selective C−H Bond Functionalization versus meta-Selective Direct Alkylation



Within our research program on sustainable C−H bond functionalizations for organic synthesis,[52] we now devised unprecedented direct C−H bond alkylations of arenes with unactivated secondary alkyl halides under nonacidic reaction conditions (Scheme 2b). Herein, we wish to disclose the development and scope of this first highly meta-selective direct C−H bond alkylation, along with detailed mechanistic studies that provide strong support for an initial remote ortho-C−H activation with subsequent meta-functionalization (Figure 1).

RESULTS AND DISCUSSION

Optimization. At the outset of our studies, we tested the effect of the stoichiometric base and the cocatalytic additive on the desired direct alkylation with secondary alkyl halide **2a** (Table 1). Preliminary experiments indicated that 1,4-dioxane proved to be optimal among a variety of solvents (NMP, *m*-xylene, PhMe, *n*-hexane, PivOH, *t*-AmOH, MeOH, MeCN,

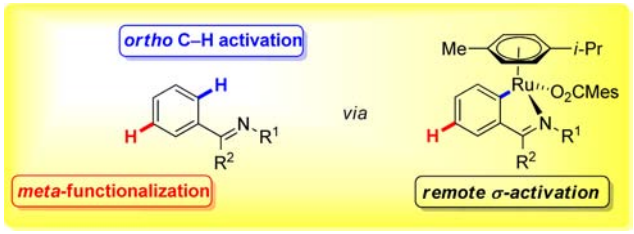
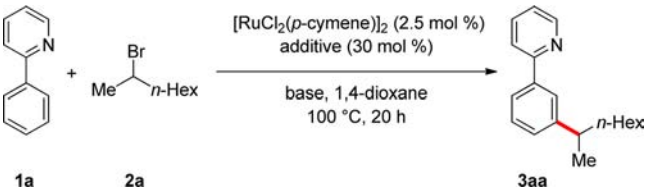


Figure 1. meta-Functionalization through remote ortho-C−H bond activation.

Table 1. Optimization of meta-Selective C−H Bond Alkylation[a]



entry	additive	base	yield (%)
1	–	K_2CO_3	–
2	–	KOAc	19
3	–	CsOAc	45
4	–	KOPiv	34
5	F_3CCO_2H	K_2CO_3	–
6	F_3CSO_3H	K_2CO_3	35
7	1-$AdCO_2H$	K_2CO_3	56
8	$PhCO_2H$	K_2CO_3	38
9	2,2′-$(C_6H_4CO_2H)_2$	K_2CO_3	31
10	$PhCH_2CH_2CO_2H$	K_2CO_3	34
11	2-$MeOC_6H_4CO_2H$	K_2CO_3	46
12	4-$MeOC_6H_4CO_2H$	K_2CO_3	52
13	4-$(F_3C)C_6H_4CO_2H$	K_2CO_3	55
14	2-$(Ph_2P)C_6H_4CO_2H$	K_2CO_3	–
15	**$MesCO_2H$**	**K_2CO_3**	**60**
16	$MesCO_2H$	–	–

[a]Reaction conditions: **1a** (0.50 mmol), **2a** (1.50 mmol), base (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), additive (30 mol %), 1,4-dioxane (2.0 mL), 20 h, 100 °C.

diglyme).[53] Low conversions of the arene **1a** were unfortunately observed in the absence of cocatalytic additives (entries 1−4). Likewise, the use of trifluoroacetic acid or trifluorosulfonic acid led to unsatisfactory results (entries 5 and 6). Conversely, particularly sterically hindered 1-$AdCO_2H$ generated a highly active ruthenium(II) catalyst, which interestingly led to C−H bond functionalization at the meta-position of substrate **1a**.[54] Among various carboxylic acids (entries 8−15), MesCO2H was found to be ideal both with respect to selectivity and catalytic efficacy (entries 15 and 16). This reactivity pattern can be rationalized in terms of steric interactions and relative solubilities of the corresponding potassium salts.

Subsequently, we evaluated the effect exerted by the substituents at the pyridine moiety onto the performance of the ruthenium-catalyzed meta-selective C−H bond functionalization (Scheme 3). Pyridines bearing substituents in the 4- or 5-position did not furnish improved yields of the desired products **3**, while substrates displaying an electron-donating group in the 3-position gave results comparable to the one observed with the parent unsubstituted compound **1a**.

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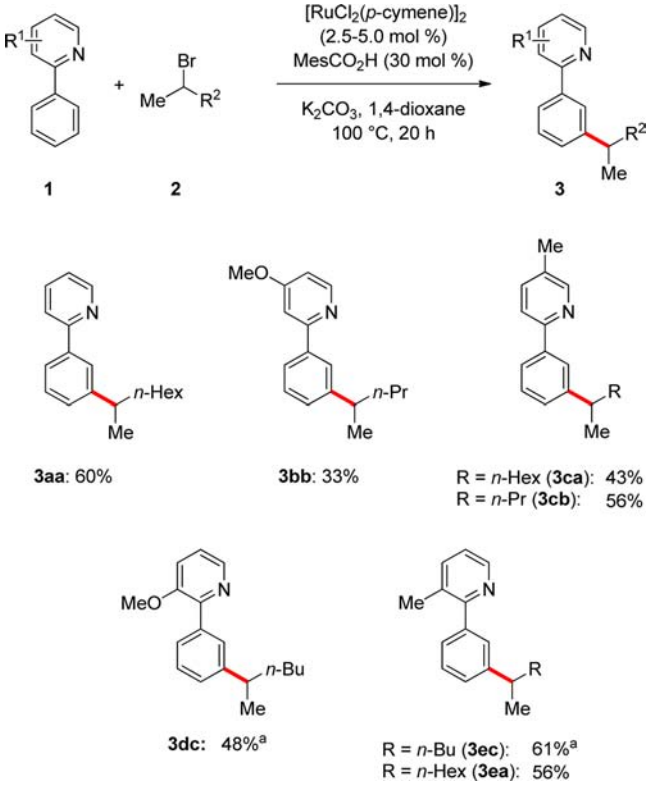
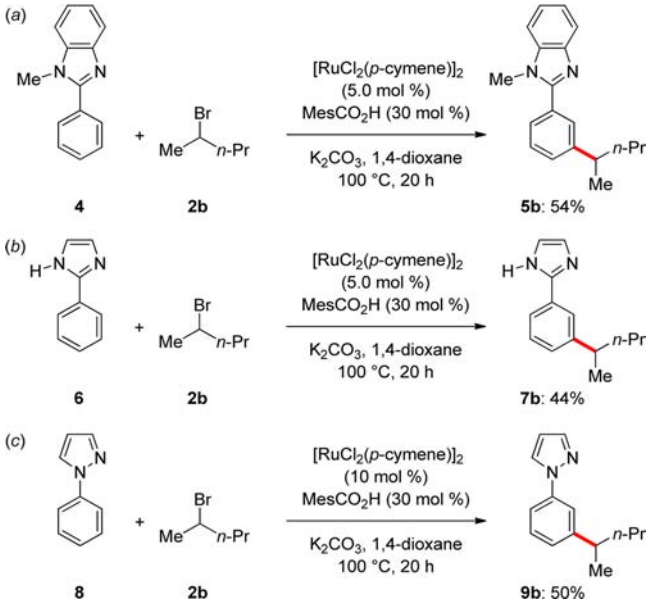
Scheme 3. Variation of the Pyridine Substitution Pattern



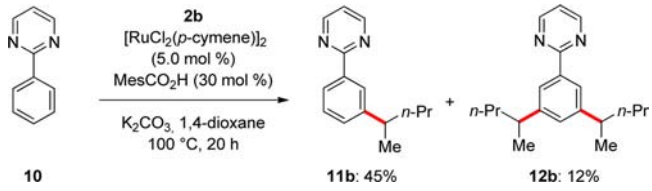
[a]The corresponding di-meta-alkylated products were also isolated (see the Supporting Information).

Scheme 4. Azole-Substituted Arenes as Substrates

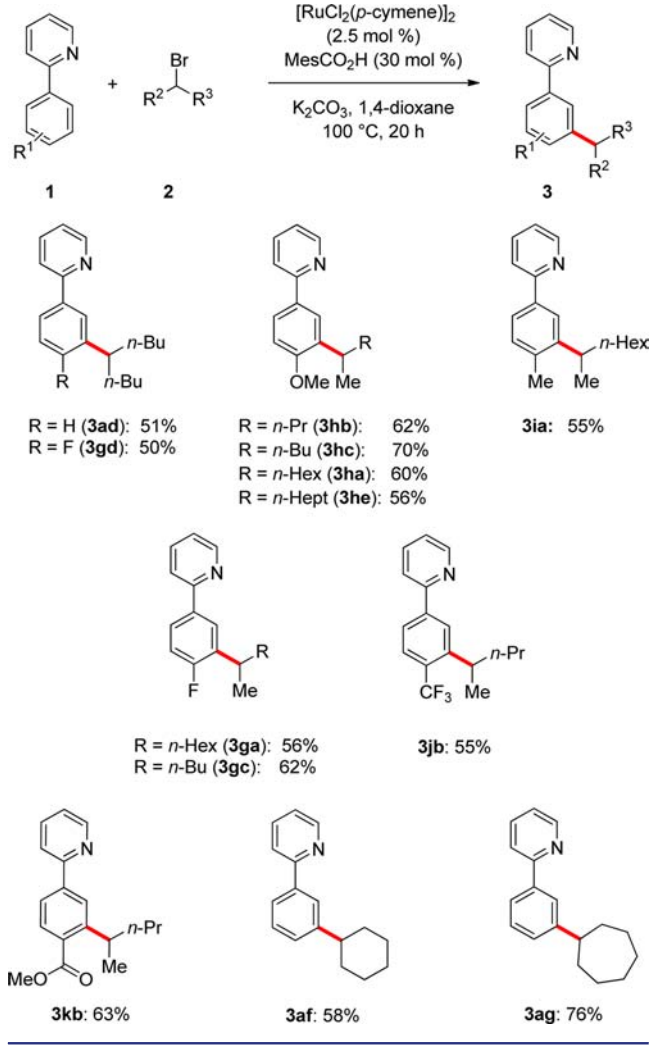


Thereafter, we tested different Lewis-basic directing groups for the direct alkylation with secondary alkyl bromide **2b** (Scheme 4). It is noteworthy that the catalytic system comprising $[RuCl_2(p\text{-cymene})]_2$ and $MesCO_2H$ was not restricted to pyridine-substituted arenes **1**. Indeed, direct C−H bond alkylations also proceeded meta-selectively with synthetically useful pyrazolyl-, imidazolyl-, and benzimidazolyl-substituted arenes **4**, **6**, and **8**, even when displaying a reactive free *NH*-moiety (Scheme 4b). It is noteworthy that the direct functionalization of substrate **6** solely furnished the mono-meta-substituted product **7b**, highlighting the excellent chemo- and site-selectivity of the optimized catalytic system.

Scheme 5. meta-Selective Direct Alkylation with Pyrimidine Derivative 10



Scheme 6. Scope of Ruthenium-Catalyzed Direct meta-C−H Bond Alkylation



Contrarily, the less electron-rich pyrimidine derivative **10** delivered both the mono- as well as the di-meta-substituted products **11b** and **12b** (Scheme 5).

Scope and Limitations. Having identified the pyridyl-substituent as the most effective and most chemo-selective directing group, we subsequently explored the scope and limitations of the meta-selective arene alkylation using secondary alkyl halides **2** (Scheme 6). The in situ generated ruthenium(II) biscarboxylate catalyst was found to be broadly applicable, as illustrated by the efficient conversion of various secondary alkyl

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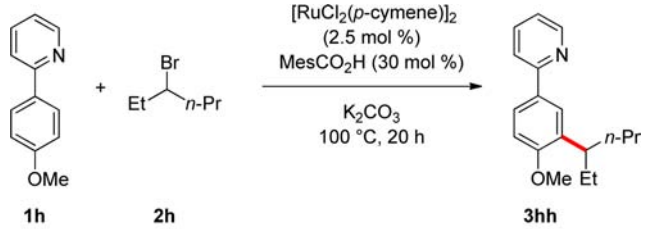
halides **2**, even when being more sterically congested. Arenes **1** bearing either electron-donating or electron-withdrawing substituents in the para-position selectively delivered the meta-substituted products **3**.[54] Furthermore, the optimized catalyst displayed a synthetically useful chemo-selectivity. Indeed, the ruthenium(II) biscarboxylate proved tolerant of electrophilic functional groups, such as a valuable ester substituent, and allowed for the conversion of cyclic secondary alkyl halides as well.

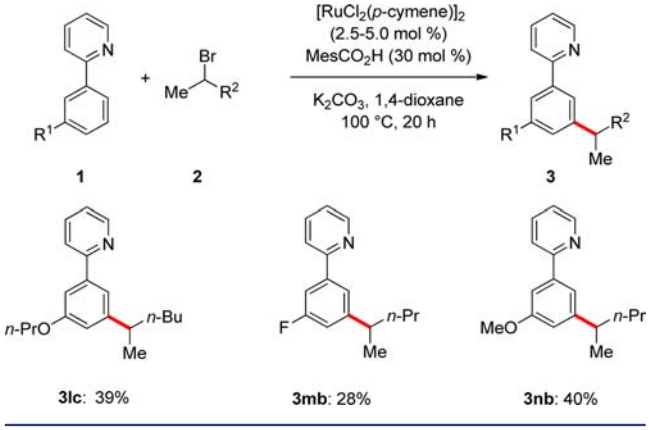
The remarkably high chemo-selectivity of the ruthenium(II) catalyst was further highlighted by meta-selective C−H bond alkylations performed in water as a nonflammable and nontoxic reaction medium[55,56] as well as by high yielding direct alkylations in the absence of solvents (Scheme 7).

Scheme 7. Solvent Effect on Direct meta-Alkylation



Arenes **1l−n** displaying meta-substituents also furnished site-selectively the meta-alkylated products (Scheme 8), but were

Scheme 8. meta-Alkylation with meta-Substituted Arenes

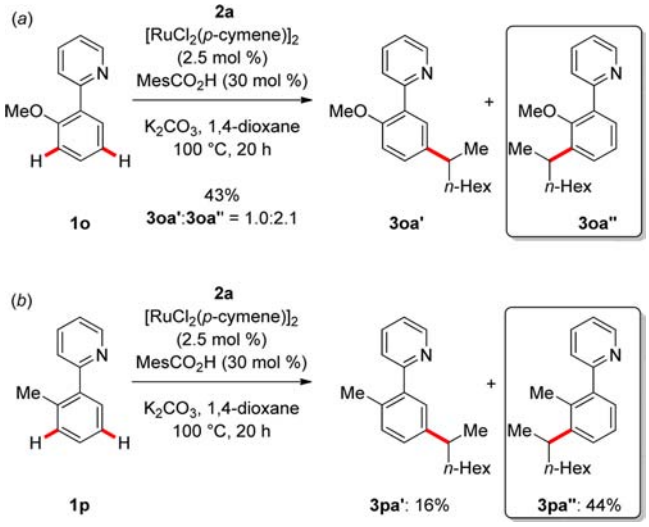


found to be considerably less reactive as compared to the corresponding para-substituted analogues (Scheme 8 versus Scheme 6). These experimental findings are particularly noteworthy, since steric interactions would suggest an inverse order of reactivity (*vide infra*).

Intramolecular competition experiments with ortho-substituted arenes **1** furnished the two corresponding products of meta-selective C−H bond functionalizations. As to the catalysts working mode, it is particularly noteworthy that the more sterically congested arenes **3oa″** and **3pa″** were counter-intuitively formed as the major products (Scheme 9).

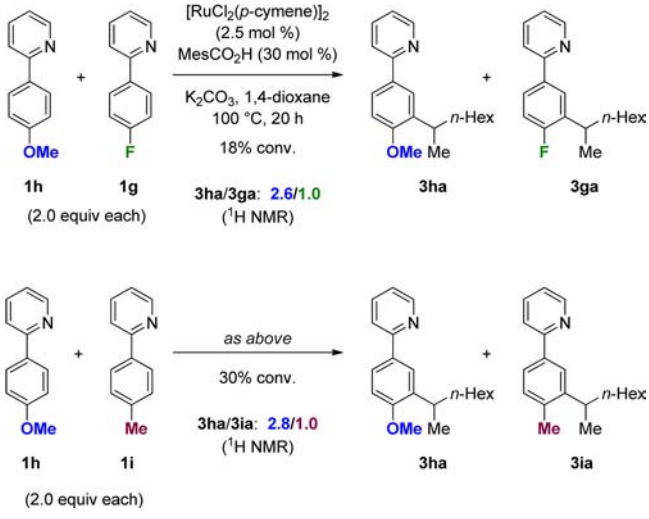
Mechanistic Studies. Given the unique meta-selectivity of our ruthenium-catalyzed direct alkylation, we performed detailed mechanistic studies to delineate its mode of action. To this end, we conducted intermolecular competition studies with differ-

Scheme 9. Intramolecular Competition Experiments with ortho-Substituted Substrates



ently substituted arenes **1** (Scheme 10), which indicated the electron-rich methoxy-substituted arene **1h** to react preferentially, thereby being suggestive of an electrophilic-type activation manifold.

Scheme 10. Intermolecular Competition Experiments



Intermolecular competition experiments between primary and secondary alkyl halides **2a** and **13a** revealed that the electrophiles were chemo-specifically transformed into the corresponding ortho- and meta-alkylated products **3aa** and **14a**, respectively (Scheme 11). These experimental findings can be rationalized with the varying steric interaction and the electrophilicities of primary and secondary alkyl halides.[57] Moreover, our experiments suggested the ortho- and the meta-alkylation to proceed with comparable catalytic efficacies.

The direct meta-alkylation with enantiomerically enriched substrate (*S*)-**2a**[58] clearly showed that a racemization of the chiral organic electrophile occurred under the reaction conditions (Scheme 12), which bears considerable potential for the future development of enantiodivergent[5] C−H bond functionalizations.

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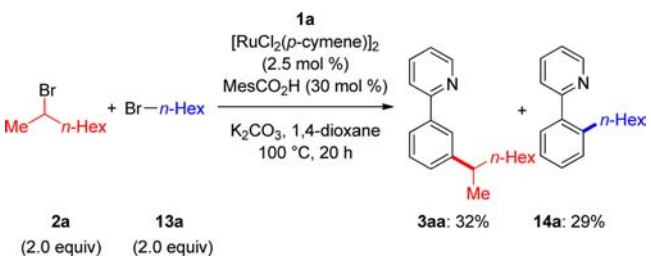
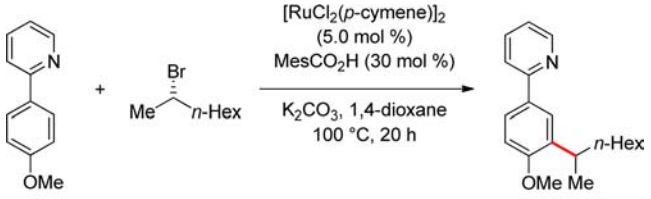
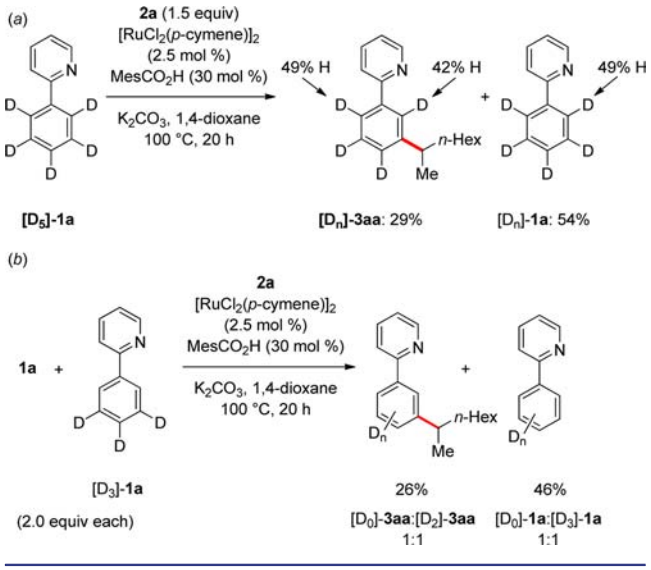
Scheme 11. Intermolecular Competition Experiments between Primary and Secondary Alkyl Halides 2a and 13a



Scheme 12. Direct meta-Alkylation with Substrate (*S*)-2a



Scheme 13. Studies with Isotopically Labeled Compounds



Moreover, we conducted experiments with isotopically labeled substrates (Scheme 13). Thus, reactions performed with the arene [D5]-**1a** provided strong support for the C−H bond metalation to initially proceed in the ortho-position of the arene (Scheme 13a). Moreover, the D/H-exchange by adventitious water in the stoichiometric base and the additive $MesCO_2H$ indicated the ortho-C−H bond metalation to be reversible in nature. Subsequently, we performed experiments with the partially deuterated starting material [D3]-**1a**, which was prepared by carboxylate-assisted ruthenium(II)-catalyzed D/H-exchange[46e] on compound [D5]-**1a** in H_2O. These studies were suggestive of the meta-C−H bond cleavage not to be kinetically relevant (Scheme 13b). This observation can be rationalized in terms of a S_EAr-type alkylative substitution in the meta-position. This electrophilic substitution is facilitated by the strong activation as well as the ortho-/para-directing effect induced by the Ru−C(sp^2) σ-bond.[59−61]

The initial formation of the cyclometalated complexes as key intermediates directly explains the reduced efficacies of the direct alkylation with meta-substituted arenes (Scheme 8) due to the considerable steric interactions between the C-3 substituent and the ruthenium fragment in the ortho-position (Figure 2a).

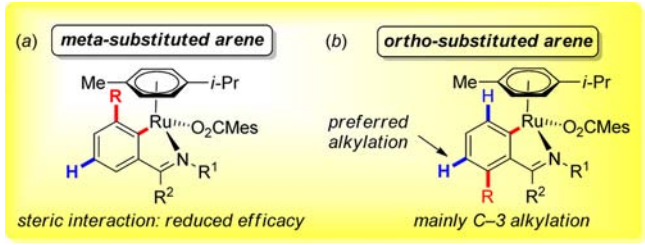
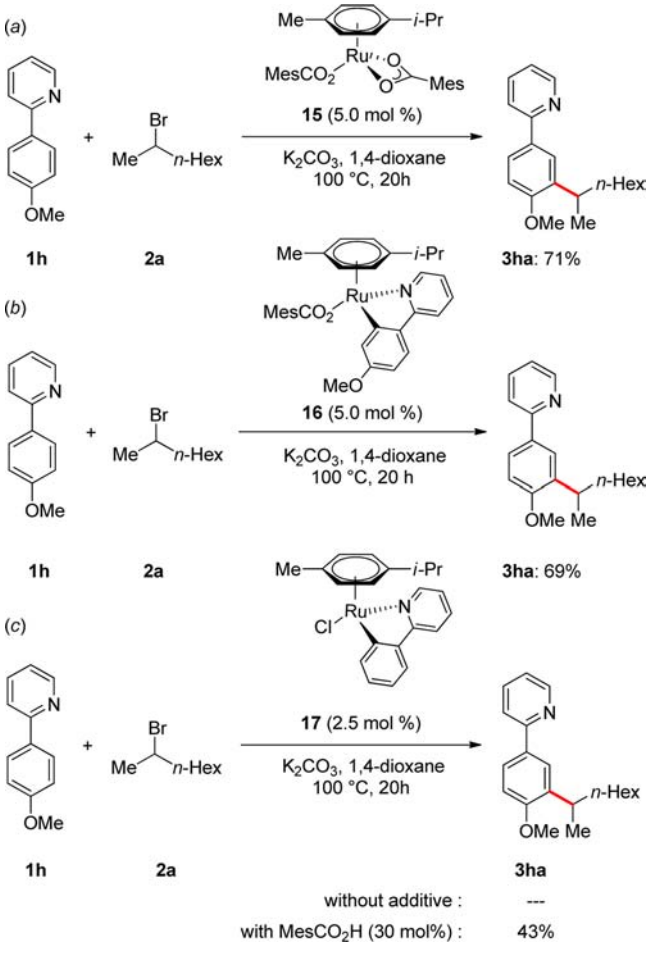


Figure 2. Sterically controlled reactivity and selectivity with meta- and ortho-substituted substrates.

Scheme 14. Well-defined Ruthenium(II) Complexes as the Catalysts



Moreover, the *a priori* unexpected formation of the more sterically hindered C-3 alkylated products observed in the direct alkylations of ortho-substituted arenes is thus governed through a steric shielding by the bulky ruthenium moiety (Figure 2b).

Since our mechanistic studies indicated cycloruthenated complexes to be key intermediates, we consequently became intrigued by probing the reactivity of well-characterized ruthenium(II) complexes, first evaluating ruthenium(II) biscarboxylate **15**[29] (Scheme 14). Thus, the isolated complex **15** selectively delivered the meta-alkylation product **3ha** in a high isolated yield. Likewise, the independently prepared cyclo-

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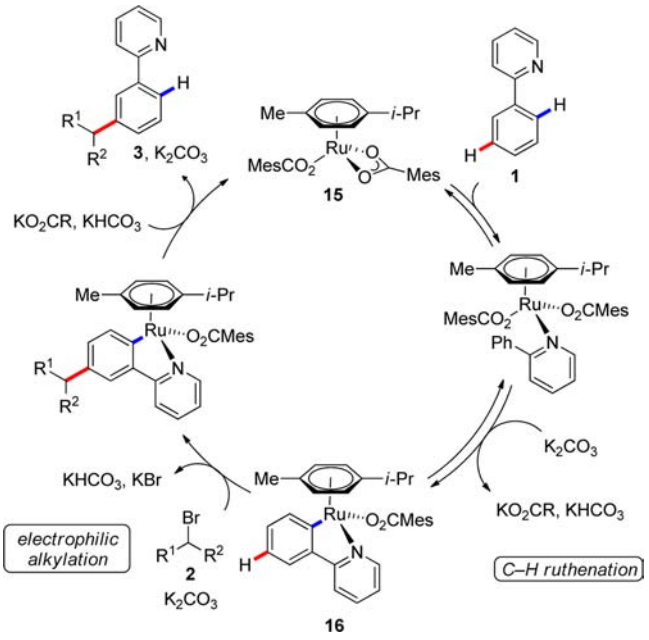
Scheme 15. Proposed Catalytic Cycle



metalated complex **16** bearing a carboxylate ligand was found to be catalytically competent (Scheme 14b). In stark contrast, the corresponding chloro-ruthenacycle **17** did not furnish product **3ha**. In this case, the catalytic activity could, however, be restored by adding cocatalytic amounts of the carboxylic acid $MesCO_2H$ (Scheme 14c), clearly highlighting the key importance of carboxylate assistance.[47]

On the basis of our mechanistic studies, we propose the catalytic cycle to involve an initial reversible formation of the cyclometalated complex **16** (Scheme 15). This cyclometalation activates the aromatic substrates **1** for a S_EAr-type alkylation with the secondary alkyl halides **2** through the strong directing group effect of the Ru−C(sp^2) σ-bond,[61] thus leading to a functionalization in the para- or ortho-position of the Ru−C(sp^2) bond.[62] Finally, proto-demetalation provides the desired meta-substituted product **3** and regenerates the catalytically active species **15**.

CONCLUSIONS

In summary, we have reported on the first metal-catalyzed meta-selective direct alkylation reaction of arenes with secondary alkyl halides under nonacidic reaction conditions. Thus, ruthenium(II) biscarboxylates enabled C−H bond alkylations on various arenes with ample scope. Detailed mechanistic studies were supportive of an initial reversible cycloruthenation. This cyclometalation increases the reactivity of the arenes to undergo an electrophilic-type substitution. The strong directing group effect of the Ru−C(sp^2) σ-bond thereby overall allows for an efficient and site-selective meta-alkylation. Experiments with independently prepared, well-defined ruthena(II)cycles clearly highlighted their key importance as crucial intermediates, and provided strong evidence for carboxylate assistance.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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