Letter

Ketone-Assisted Ruthenium(II)-Catalyzed C–H Imidation: Access to Primary Aminoketones by Weak Coordination

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Ketone-Assisted Ruthenium(II)-Catalyzed C–H Imidation: Access to Primary Aminoketones by Weak Coordination

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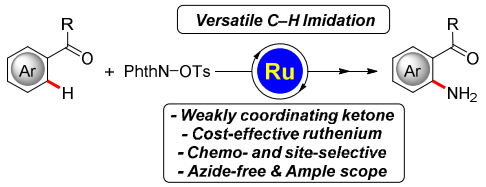
Supporting Information Placeholder

ABSTRACT: The ruthenium(II)-catalyzed intermolecular C–H imidation with weakly-coordinating ketones provided step-economical access to synthetically useful primary aminophenones. The azide-free C–H imidation strategy occurred with ample scope and excellent functional group tolerance to efficiently deliver densely substituted aminophenones.



KEYWORDS: *C–H activation • heterocycles • mechanism • nitrogenation • ruthenium*

Aminophenones are key structural motifs in natural product syntheses, medicinal chemistry, crop protection or material sciences,[1] and represent versatile intermediates in organic synthesis.[2] As a consequence, methods that allow for the efficient preparation of decorated aminophenones continue to be in high demand.[3] The development of new chemical transformations based on the catalytic functionalization of otherwise inert C–H bonds has the potential to dramatically simplify the synthesis of complex molecules.[4] For instance, transition metal-catalyzed C–H amidations have emerged as an increasingly viable alternative to the palladium-catalyzed[5] aminations of aryl halides.[6] Particularly, ruthenium(II) complexes have in recent years been identified as powerful tools for C–H nitrogenations, largely exploiting strongly coordinating directing groups that are difficult to remove[7] or modify.[8] In spite of major advances in ruthenium-catalyzed C–H nitrogenations by *inter alia* Chang,[9,10] Jiao,[11] Yu,[12] Sahoo,[13] Patureau[14a] and Ackermann,[14b] ruthenium(II)-catalyzed C–H amidations[15] with weakly coordinating[16] directing groups[17,18] continue to be scarce, and limited to azide-based chemistry.[8] Within our program on sustainable C–H functionalizations,[19] we have now developed the first azide-free ruthenium(II)-catalyzed[20] C–H nitrogenation by weak ketone coordination, on which we report herein (Figure 1). The successful use of challenging ketones illustrates the beneficial features associated with rather inexpensive ruthenium(II) catalysts. The transformative nature of our C–H activation platform provided step-economical access to primary aminophenones – key intermediates in the synthesis of various bioactive heteroarenes.

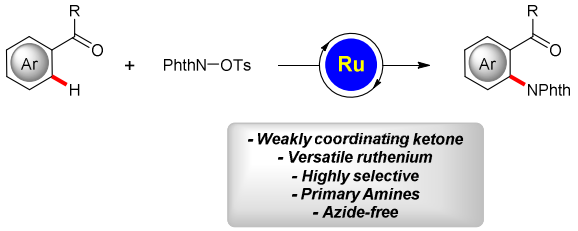
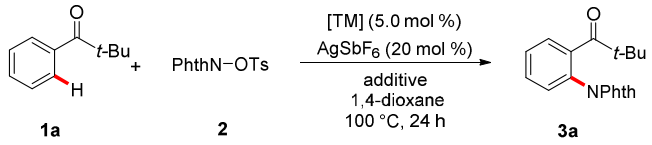


Figure 1. Azide-free C–H Imidation by weakly-coordinating ketones

At the outset of our studies, we tested various reaction parameters for the envisioned ruthenium-catalyzed C–H amidation of ketone **1a** (Table 1).[21] Among a variety of additives, copper(II) acetate proved most effective for the synthesis of product **3a** (entries 1–8). The dimeric complex $[RuCl_2(p\text{-cymene})]_2$ outperformed $[Ru_2(hp)_4Cl]$ and $[Ru_2(OAc)_4Cl]$ (entries 8–11). Typical cobalt, palladium or rhodium catalysts failed short in delivering the desired product **3a** (entries 12–14), highlighting the challenging nature of the ketone-assisted C–H nitrogenation.

Table 1. Ruthenium(II)-Catalyzed C–H Imidation[a]



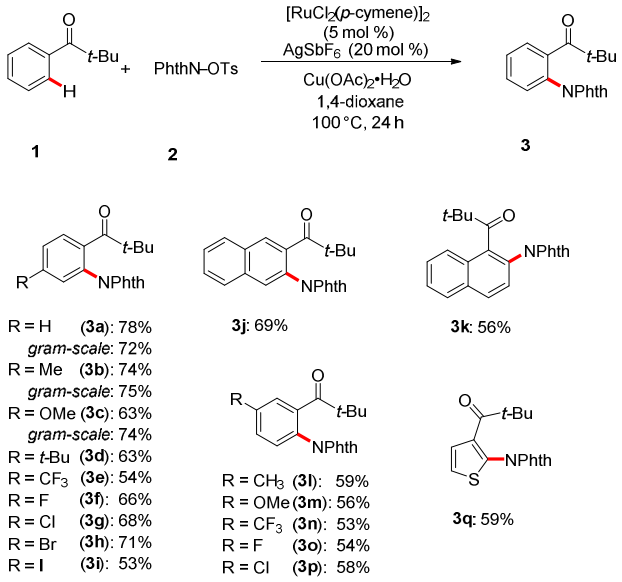
1a 2 3a

entry	catalyst	additive	**3a** [%]
1	$[RuCl_2(p\text{-cymene})]_2$	---	---
2	$[RuCl_2(p\text{-cymene})]_2$	NaOAc	14
3	$[RuCl_2(p\text{-cymene})]_2$	KOPiv	23
4	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	19
5	$[RuCl_2(p\text{-cymene})]_2$	LiOAc	21
6	$[RuCl_2(p\text{-cymene})]_2$	$Mn(OAc)_2•H_2O$	---
7	$[RuCl_2(p\text{-cymene})]_2$	$Zn(OAc)_2•H_2O$	27
8	**$[RuCl_2(p\text{-cymene})]_2$**	**$Cu(OAc)_2•H_2O$**	**78**
9	$[Ru_2(hp)_4Cl]$	$Cu(OAc)_2•H_2O$	9
10	$[Ru_2(OAc)_4Cl]$	$Cu(OAc)_2•H_2O$	23
11	---	$Cu(OAc)_2•H_2O$	---
12	$[Cp^*CoI_2(CO)]$	$Cu(OAc)_2•H_2O$	16
13	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2•H_2O$	---
14	$Pd(OAc)_2$	$Cu(OAc)_2•H_2O$	---

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5.0 mol %), $AgSbF_6$ (20 mol %), additive (0.5 equiv), 1,4-dioxane (2.0 mL), 100 °C, 24 h, yield of isolated product.

With the optimized catalytic system in hand, we tested its versatility by probing the influence of the arene substitution pattern on the C–H imidation regime. Pleasingly, a range of ketones **1** with diverse electronic properties provided the imidophenones **3** by weak ketone assistance (Scheme 1). Hence, *para*-substituted ketones **1b**–**1i** were chemo-selectively converted to the mono-imidated products **3**. The robustness of the versatile ruthenium(II) C–H activation catalyst was reflected by fully tolerating valuable functional groups, including fluoro, chloro, bromo, and iodo substituents. These features should prove instrumental for further post-synthetic diversification of the thus obtained imidophenones **3**. The C–H imidation strategy was also found amenable to the gram-scale synthesis of products **3a**–**c**. C–H imidations with naphthalene derivatives **1j** and **1k** illustrated the excellent positional selectivity of the C–H functionalization protocol, in that products **3j** and **3k** were formed as the sole products, respectively. High levels of site-selectivity were observed within intramolecular competition experiments with *meta*-substituted arenes **1l**–**1p** as well. Substitutions on the aromatic moiety of imidating reagents **2** were likewise tolerated under the optimized reaction conditions (Scheme S1 in the Supporting Information).[21] In contrast, the methyl-, *iso*-propyl- or phenyl-substituted phenones **1** thus far failed to deliver the imidated products **3**.[22] Yet, the robust ruthenium(II) catalyst was not limited to carbocyclic aromatic compounds. Indeed, the C–H imidation of thiophene **1q** proved viable as well, occurring with excellent levels of positional control.

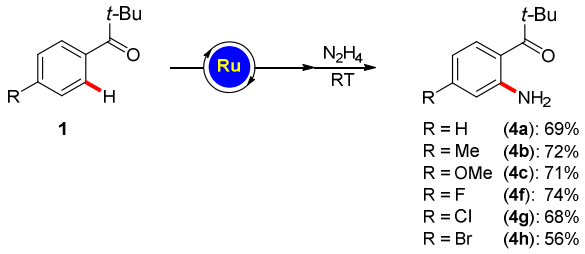
Scheme 1. Ruthenium(II)-Catalyzed C–H Imidation.



1 2 3

The synthetic utility of the ruthenium(II)-catalyzed imidation protocol was illustrated by providing efficient access to the valuable primary aminophenones **4** with synthetically useful overall yields ranging from 56 to 74% for the two-step procedure (Scheme 2).

Scheme 2. Facile Access to Primary Aminophenones 4.[21]



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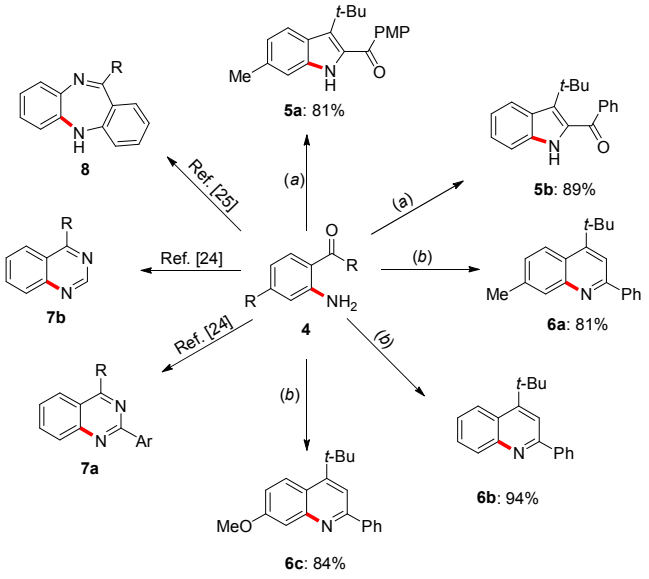
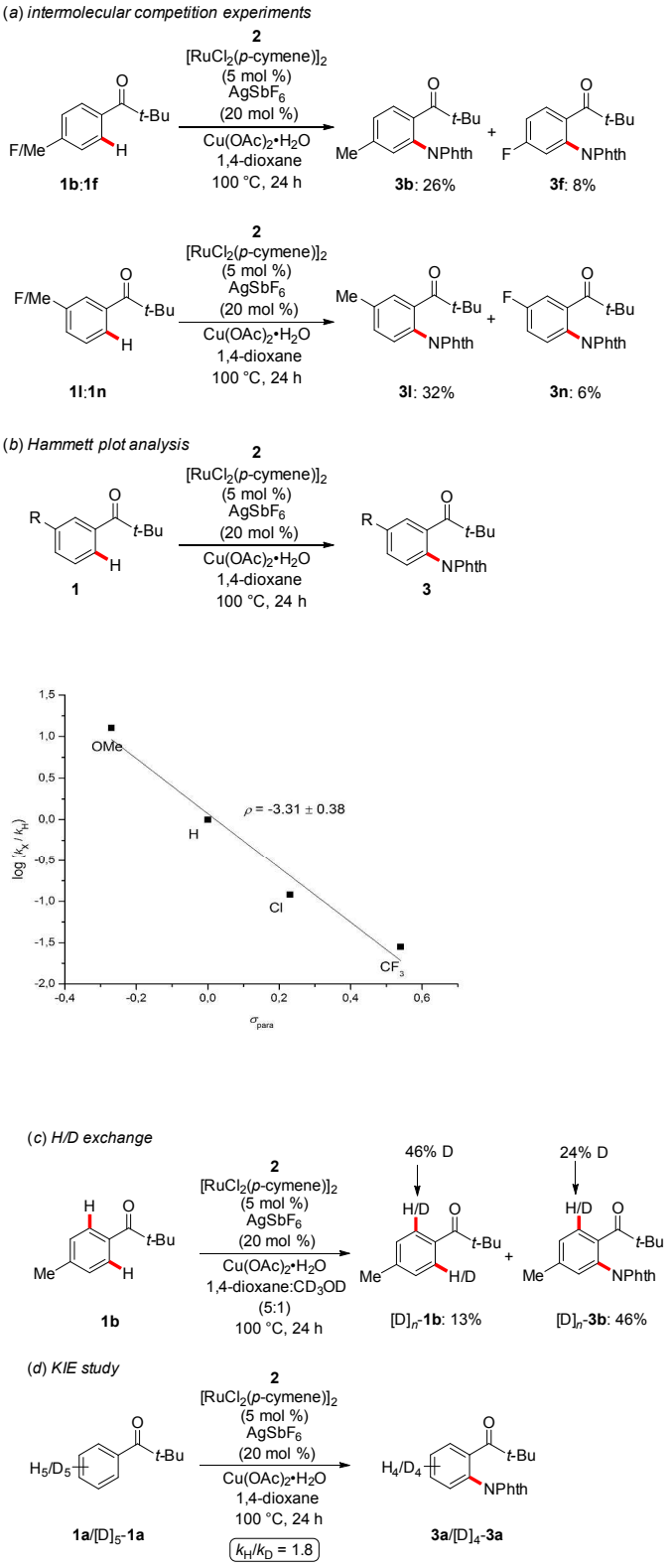
The unique value of our C–H activation approach was showcased by the chemo-divergent access to a wealth of bioactive heterocyles, such as indoles **5**,[23] quinolines **6**,[24] quinazolines **7**,[25] and diazepines **8**,[26] in a step-economical fashion (Scheme 3).

Scheme 3. Diversification of products 4. (*a*) 4, $ArCOCH_2Br$, DMF, 100 °C, 16 h. (*b*) 4, ArC≡CH, $InCl_3$ (20 mol %), CH_3CN, 90 °C, 24 h.[21]



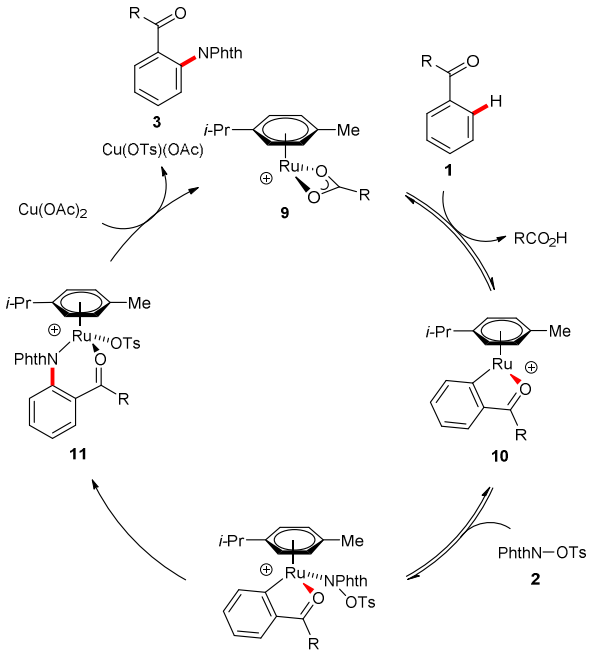
In consideration of the unique selectivity features displayed by the ketone-assisted ruthenium(II)-catalyzed C–H imidation, we performed mechanistic studies to delineate the catalyst's mode of action. To this end, intermolecular competition experiments between differently substituted arenes **1** indicated that electron-rich arenes **1** reacted preferentially (Scheme 4a), which was further illustrated by a Hammett value of ρ = -3.3 (Scheme 4b).[21] This observation can be rationalized in terms of a base-assisted, intermolecular electrophilic substitution (BIES)-type C–H metalation event to be operative.[27] C–H imidations conducted in the presence of an isotopically labeled co-solvent were suggestive of a reversible H/D-exchange (Scheme 4c). A kinetic isotope effect (KIE) of $k_H/k_D \approx 1.8$ was determined by means of the initial rates for independent reactions of substrates **1a** and $[D]_5$-**1a** (Scheme 4d).

Scheme 4. Summary of Mechanistic Findings.



Based on our mechanistic findings, we propose the ruthenium(II)-catalyzed C–H nitrogenation to commence by a facile BIES-type[27] C–H ruthenation by the cationic ruthenium(II) monocarboxylate complex **9** (Scheme 5). Hence, the $Cu(OAc)_2$ serves as an effective additive for the formation of the cationic ruthenium(II) carboxylate catalyst **9**. The thus-formed cyclometalated intermediate **10** is subsequently coordinated by the imidating reagent **2**. Thereafter, the N–O cleavage delivers the cationic complex **11**, which finally regenerates the catalytically active species **9**, thereby liberating the desired product **3**. While the exact working mode of the N–O cleavage step awaits more detailed analysis, an oxidative addition[6j] pathway represents a viable alternative to an isohypsic transformation.

Scheme 5. Proposed Catalytic Cycle



In summary, we have reported on the first azide-free ruthenium(II)-catalyzed C–H amidation by weakly coordinating ketone assistance. The synthetic utility of the C–H activation protocol was reflected by giving expedient access to synthetically useful primary aminophenones, and enabling step-economical late stage diversifications. The operationally simple protocol featured high catalytic efficacy and excellent functional group tolerance, while detailed mechanistic studies were indicative of a BIES-type[27] C–H ruthenation.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR-spectra for compounds.

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Notes

The authors declare no competing financial interest.

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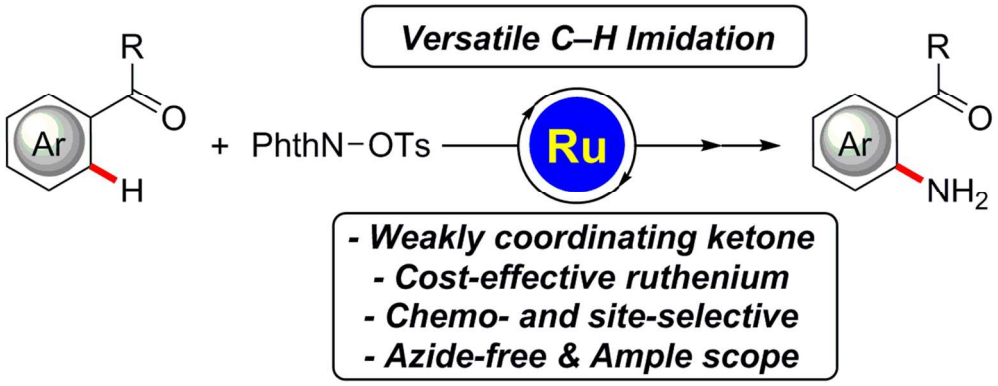

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