CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201301025

Ruthenium-Catalyzed Direct C–H Amidation of Arenes Including Weakly Coordinating Aromatic Ketones

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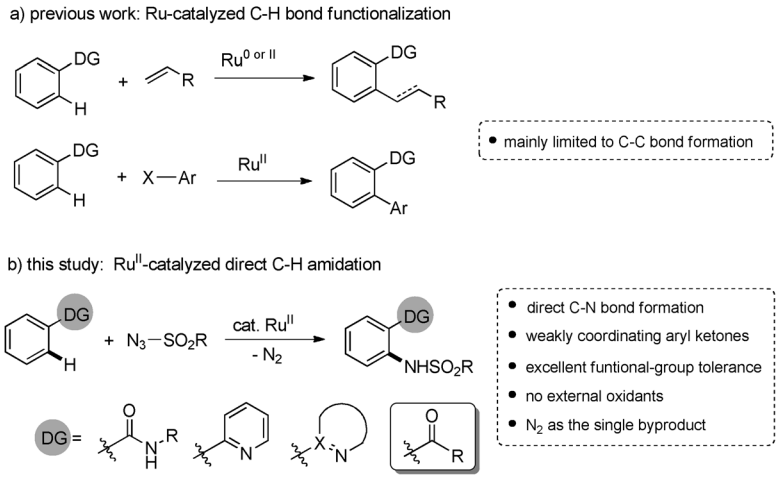
Highly efficient and selective formation of C–N bonds is one of the most important research topics in organic synthesis mainly due to the fact that numerous amine-containing molecules are bioactive, finding their utilities in medicinal and agrochemical chemistry as well as in organic synthesis and materials chemistry.[1] Although metal-mediated amination of aryl (pseudo)halides has been well developed as the most reliable and practical method for the C–N bond formation,[2] the requirement of prefunctionalized haloarene reactants has led chemists to search for alternative approaches. As a consequence, an extensive study has been devoted to metal-mediated direct C–H amination of (hetero)-arenes.[3] While direct reaction of parent amines with arenes is most desirable with respect to atom economy (two hydrogen atoms are the byproducts), external oxidants are required to quench the side products under suitable oxidative conditions.[4] On the other hand, to avoid the use of oxidants, preactivated amino precursors, such as halogenated amines, have been examined as a reagent to react with arenes.[5] However, there are two main limitations in this approach: 1) an additional procedure is needed to prepare the haloamine reactants and 2) hydrogen halides are generated as byproducts in amination reactions and, therefore, external bases are usually employed to quench these side products.

Ruthenium complexes have been widely employed as one of the most efficient and selective catalysts for the C–H bond activation.[6] Since the milestone work of Murai,[7] a large number of C–H activation reactions have been developed on the basis of ruthenium(0) or ruthenium(II) systems.[8] In particular, recent efforts to utilize the unique catalytic activity of $[Ru(arene)Cl_2]_2$ complexes have resulted in significant advances in the direct C–H bond functionalizations (Scheme 1a).[9] Despite these achievements, however, the ruthenium-catalyzed C–H bond activation strategy has been practiced almost exclusively for the introduction of alkyl, vinyl, or aryl groups.[6b,8d] In fact, intermolecular direct C–H amination of arenes mediated by ruthenium species still remains largely unexplored.[10,11]



Scheme 1. Ru-catalyzed direct C–H bond functionalizations.

Along with our continuous efforts on the development of highly efficient direct amination reactions,[12] we recently reported a new approach of rhodium-catalyzed direct sp^2 C–H amination by using azides as the amino source, thus releasing molecular nitrogen as a single byproduct.[13] The developed procedure was successfully applied to the amination of various arene substrates without requiring external oxidants. Herein, we describe inexpensive ruthenium-catalyzed direct C–H amidation of arenes by using sulfonyl azides (Scheme 1b).[14] Importantly, a new type of substrate that has weak coordinating ability can now be amidated under the new ruthenium catalyst system, thereby greatly expanding the synthetic and practical utility of our approach.

We first explored ruthenium catalyst systems in a reaction of *N-tert*-butylbenzamide (**1a**) with *para*-toluenesulfonyl azide (**2a**) under various conditions (Table 1). Whereas

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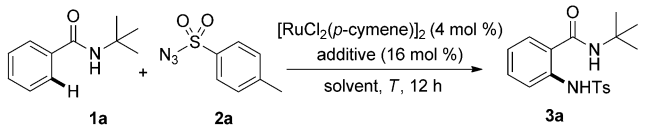
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201301025.

Table 1. Optimization studies of the Ru-catalyzed amidation.[a]



1a 2a 3a

Entry	Additive	Solvent	T [°C]	Yield [%][d]
1	–	$ClCH_2CH_2Cl$	80	n.r.
2	$AgPF_6$	$ClCH_2CH_2Cl$	80	5
3	$AgBF_4$	$ClCH_2CH_2Cl$	80	23
4	AgOTf	$ClCH_2CH_2Cl$	80	15
5	$NaPF_6$	$ClCH_2CH_2Cl$	80	n.r.
6	$AgSbF_6$	$ClCH_2CH_2Cl$	80	40
7	$AgNTf_2$	$ClCH_2CH_2Cl$	80	50
8[b]	**$AgNTf_2$**	**$ClCH_2CH_2Cl$**	**80**	**89**
9[b]	$AgNTf_2$	$ClCH_2CH_2Cl$	50	11
10[b]	$AgNTf_2$	Toluene	80	12
11[b]	$AgNTf_2$	*tert*-amylOH	80	47
12[b]	$AgNTf_2$	1,4-dioxane	80	70
13[b,c]	$AgNTf_2$	$ClCH_2CH_2Cl$	80	11

[a] Conditions: **1a** (0.2 mmol), **2a** (1.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (4 mol %), and additive (16 mol %) in solvent (0.5 mL) for 12 h at the indicated temperature. [b] **1a** (2 equiv) and **2a** (0.2 mmol) under otherwise identical conditions for 12 h. [c] $[Ru(benzene)Cl_2]_2$ (4 mol %) was used as the Ru catalyst. [d] Yield was determined by ^{1}H NMR spectroscopy by using an internal standard.

ruthenium precursors other than $[RuCl_2(p\text{-cymene})]_2$ or its analogues were inactive, the nature of additives, which convert the dimeric ruthenium(II) complexes to their corresponding cationic species, turned out to be most important.

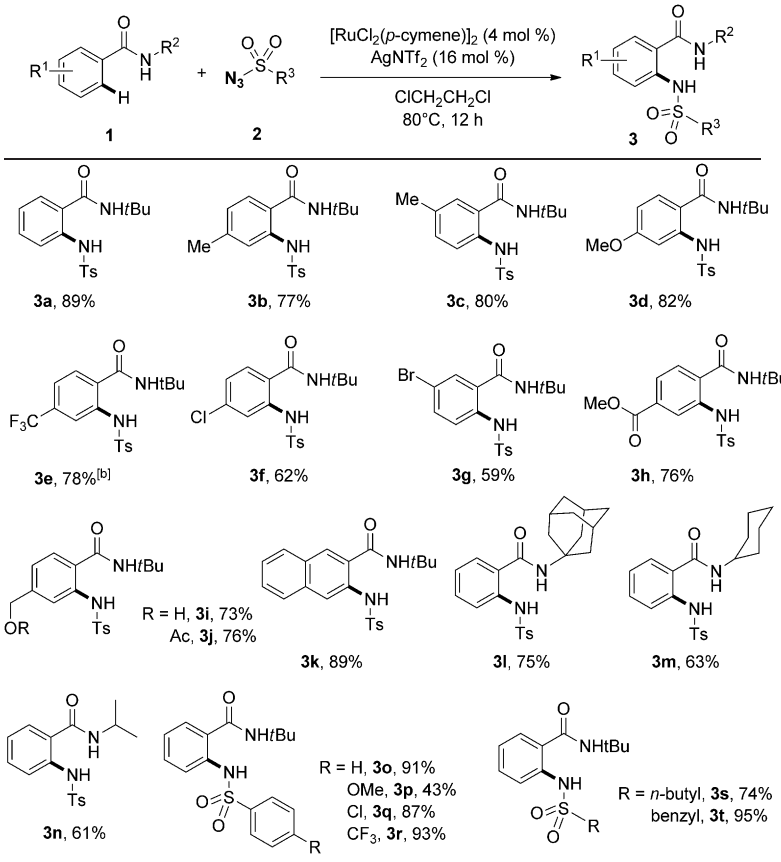
Among several silver salts screened, $AgSbF_6$ and $AgNTf_2$ (4 equiv to Ru catalyst) were especially effective (Table 1, entries 6–7) albeit the latter additive provided slightly higher efficiency. It was also found that when an azide was employed as a limiting reactant, product yield was significantly increased (entry 8). While the reaction was best performed at 80 °C in 1,2-dichloroethane, lower efficiency was the result either at lower temperatures or in different solvents (entries 9–12). Interestingly, an analogous ruthenium species $[Ru(benzene)Cl_2]_2$ displayed much inferior reactivity (entry 13).

The optimized amidation conditions were next applied to a range of benzamides in reaction with sulfonyl azides (Table 2). The position and electronic variation of substituents in benzamides little influenced the reaction efficiency (**3b–f**). Importantly, functional-group tolerance was excellent under the present conditions as can be demonstrated by substrates bearing bromo, ester, free hydroxyl, and acetate groups (**3g**, **3h**, **3i**, and **3j**, respectively). *N*-*tert*-Butyl-2-naphthamide was exclusively amidated at the 3-position in high yield (**3k**). It was also observed that the *N*-alkyl substitutents of benzamides were highly flexible to include adamantyl, cyclohexyl, and isopropyl (**3l–n**) in addition to a *tert*-butyl group. Finally, the scope of sulfonyl azides was also very broad: both arene and alkane variants were amidated into benzamide in equal efficiency with high yields (**3o–r** and **3s–t**, respectively). It needs to be mentioned that diamidated compounds were not generated in any detectable amounts by H NMR spectroscopy (<5 %) under the most optimal conditions. On the other hand, aryl azides, which were successfully utilized in the rhodium-catalyzed direct C–H aminidation of arenes,[13b] were ineffective under the present ruthenium catalyst system.

Encouraged by the successful results of the direct amidation of benzamides, we next tried to explore a new type of substrate with weak coordinating ability.[15] In particular, aryl ketones were selected to be tested since amidated products, 2-aminoaryl ketones, have a variety of synthetic utilities (vide infra). We were delighted to see that acetophenone, indeed, was readily amidated by an in situ generated cationic ruthenium catalyst with the help of acetate additive in this case (Table 3).[6b,16] In sharp contrast, our previous rhodium catalyst system[13] was not operative for this amidation of acetophenone. Although Liu et al. recently reported the Pd-catalyzed amidation of aryl ketones by using sulfonamides, the scope was rather limited to substrates bearing mainly bulky alkyl moieties to give satisfactory yields.[4 h]

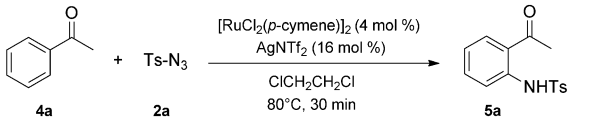
A wide range of aryl ketones were subsequently subjected to the above optimal conditions (Table 4). As in the case of aromatic ketones, the amidation took place smoothly regardless of the position and electronic properties of substitu-

Table 2. Scope of benzamide substrates.[a]



[a] Conditions: **1** (2 equiv), **2** (0.2 mmol). Isolated yields are given. [b] Run for 48 h.

Table 3. Direct amidation of acetophenone.[a]

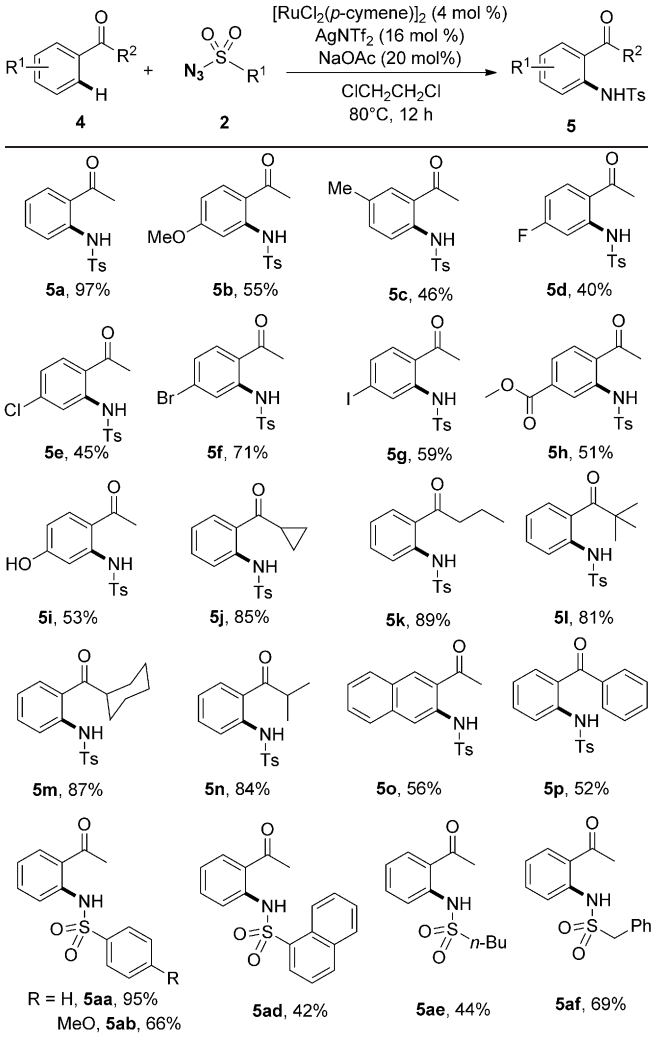


4a 2a 5a

Additive ([mol%])	Yield [%][b]
no additive	5
CsOPiv (20)	n.r.
KOAc (20)	60
NaOAc (20)	70

[a] Conditions: **4a** (2 equiv) and **2a** (0.2 mmol). [b] ^{1}H NMR spectroscopy.

Table 4. Scope of aryl ketone substrates.[a]

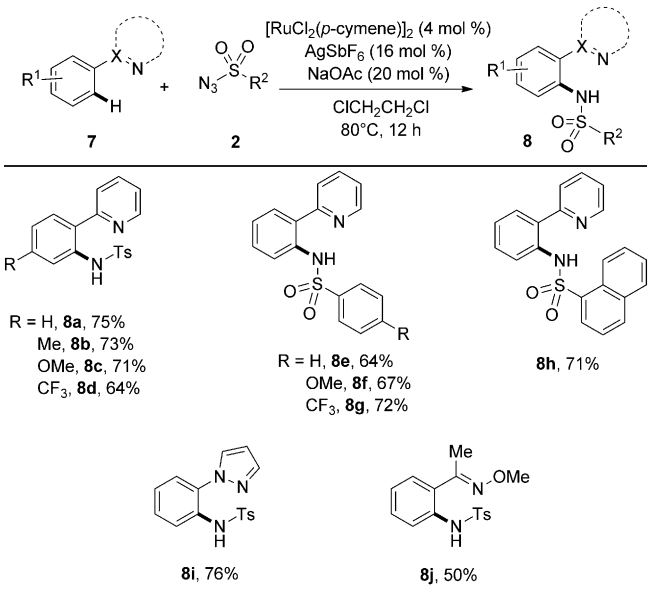


[a] Conditions: **4** (2 equiv) and **2** (0.2 mmol). Isolated yields are given.

ents on substrates (**5a–f**). In addition, the conditions were compatible with the various organic functional groups examined (e.g. **5g–i**). Derivatives of alkyl aryl ketones or benzophenone were readily amidated under the present conditions (**5j–o** and **5p**, respectively). As expected, all variants of sulfonyl azides were smoothly introduced at the *ortho* position of acetophenone in moderate to good yields (**5aa–af**). It should be noted that the reaction could be scaled up without difficulty on a gram quantity (see the Supporting Information for details).

Direct sp^2 C–H amidation of arenes bearing strong coordinating nitrogen groups was briefly investigated under the current ruthenium system (Table 5). We were pleased to observe that representative directing groups, such as 2-pyridyl, pyrazol, and ketoxime moieties all facilitated the desired amidation in the presence of $AgSbF_6$ salt and acetate additive.

Table 5. Preliminary scope of substrates bearing heterocyclic directing groups.[a]



[a] Conditions: **7** (2 equiv) and **2** (0.2 mmol). Isolated yields are given.

It was interesting to note that amidation proceeds with significantly different initial rates depending on substrates employed. Quite surprisingly, the reaction of weakly coordinating acetophenone took place much faster than benzamides and 2-phenylpyridine, which displayed similar reactivity to each other (Figure 1). Although the exact reason for this observation is not clear at the present stage, it is assumed that the relative ease of the rate-limiting C–H activation step is reflected in this rate difference.

To gain a mechanistic insight into our Ru-catalyzed amidation reaction, a series of preliminary studies were carried out. A deuterium scrambling test revealed that C–H bond activation is irreversible (Scheme 2a). A significant degree of primary kinetic isotopic effects was observed with both *N-tert*-butylbenzamide and aceotophenone substrates (Scheme 2b and c), which implied that the C–H bond cleavage is involved in the rate-limiting step.[17] The electronic effects of substituents on the reaction rate was tested to reveal that aryl ketones bearing electron-donating groups displayed faster initial rates than electron-deficient substrates. For ex-

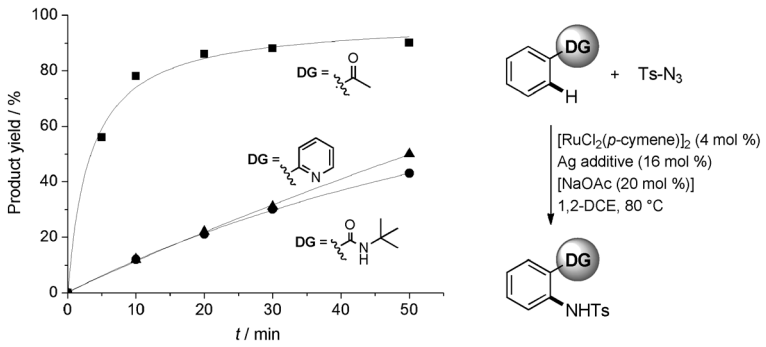
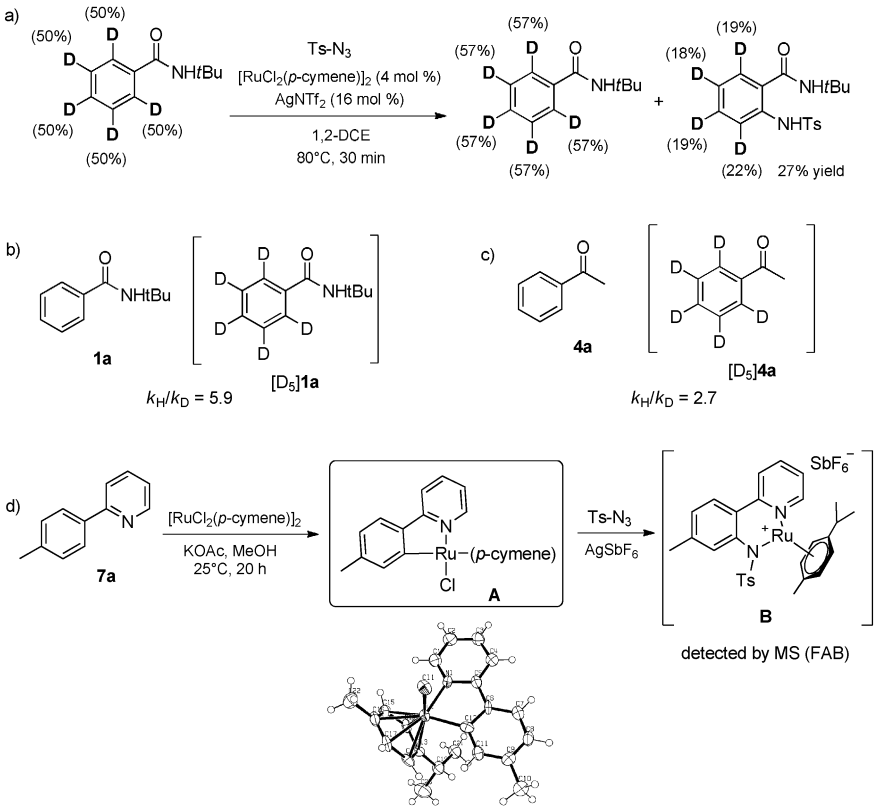


Figure 1. Reaction profile of amidation among three different types of substrates under the present Ru-catalyst system.

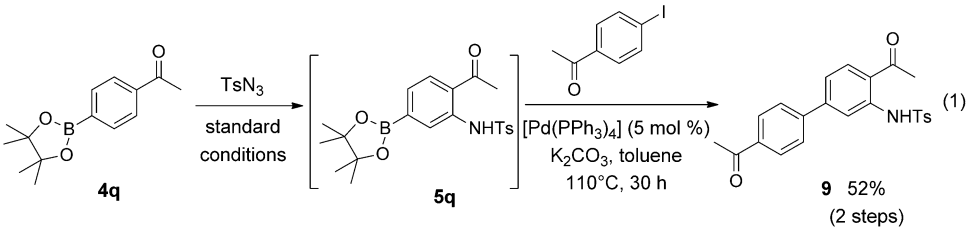


Scheme 2. Preliminary mechanistic studies.

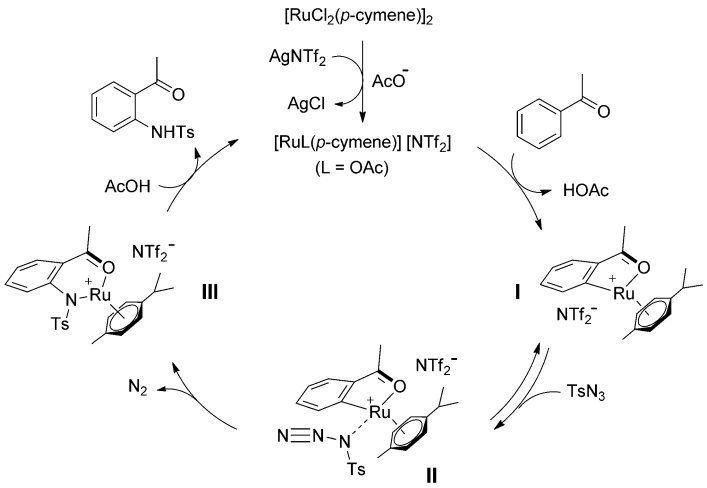
ample, 4-methoxyacetophenone was amidated about four-times faster than acetophenone, which was in turn faster than 4-chloroacetophenone by about two times (see the Supporting Information for details). A ruthenacycle species **A** was isolated and characterized by X-ray crystallographic analysis (Scheme 2d). When **A** was treated with sulfonyl azide under the reaction conditions, the corresponding amido insertion metal species **B** was detected by mass spectroscopy.

Based on the above mechanistic data and precedent reports,[13,16b,18] a plausible mechanistic pathway is depicted in Scheme 3 with acetophenone as a model substrate.[19] Silver salt is believed to convert the neutral ruthenium precursor to its cationic species.[16b] As implied by the above described electronic effects on the initial rates, the C–H bond activation is postulated to proceed by an electrophilic aromatic metalation pathway leading to the ruthenacycle species **I**.[20] A reversible coordination of azide to the cationic metal center will be followed by an amido insertion to release a nitrogen molecule giving rise to **III**, which is eventually protonated to afford the desired amidated product.

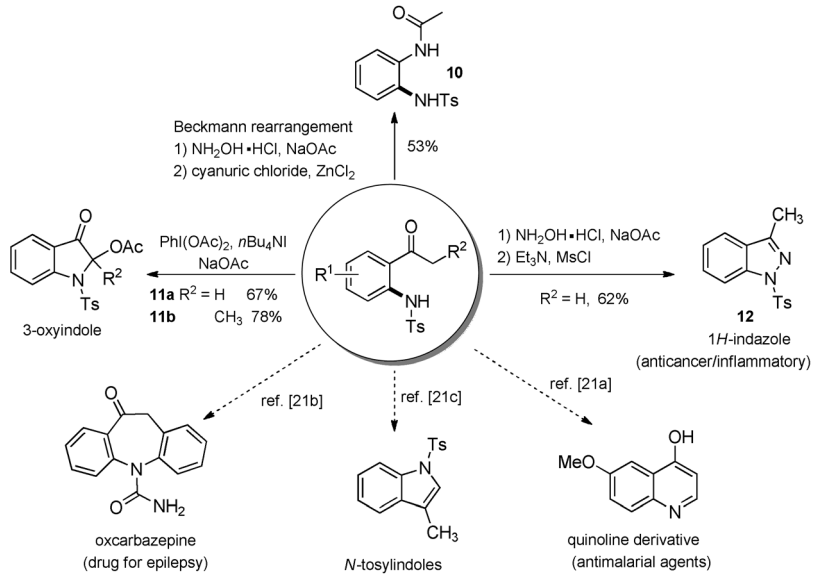
As a synthetic application, acetophenone bearing a boronate substituent (**4q**) was amidated under the present Ru-catalyzed conditions to afford **5q**, which was in situ coupled with 4-iodoacetophenone by a Pd catalyst system to provide **9** in satisfactory yield [Eq. (1)].



It is also noteworthy that synthetic utility of *ortho*-amido aryl ketone products is significant, and a wide range of bioactive heterocycles could be synthesized by simple conventional methods (Scheme 4).[21] In fact, synthetic procedures are known for the preparation of oxcarbazepines, indazoles, (oxy)indoles, and quinoline derivatives by starting from a common precursor, *ortho*-amido aryl ketones, and some examples are demonstrated herein.



Scheme 3. Proposed reaction pathway.



Scheme 4. Synthetic utility of amidated products.

In summary, we have presented the inexpensive ruthenium-catalyzed direct sp^2 C–H amidation of arenes by using sulfonyl azides as the nitrogen source. While a wide range of substrates were readily amidated, compounds bearing weak coordinating groups were also reacted with excellent efficiency and selectivity. Indeed, the introduction of an amido unit at the *ortho*-position of aryl ketones was unprecedentedly facile, which cannot be achieved with other catalytic systems, such as rhodium or palladium. Synthetic utility of the thus obtained products is enormous serving as a common synthetic building unit for the preparation of a wide range of biologically active heterocycles.

Experimental Section

Representative procedure: Acetophenone (**4a**, 0.4 mmol), *p*-toluenesulfonyl azide (**2a**, 0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (4.9 mg, 4 mol%), $AgNTf_2$ (12.5 mg, 16 mol%), NaOAc (3.3 mg, 20 mol%), and 1,2-dichloroethane (0.5 mL) were added to a screw-capped vial equipped with a spinvane triangular-shaped Teflon stirbar. The reaction mixture was stirred in a preheated oil bath at 80°C for 12 h and then cooled to room temperature, filtered through a pad of Celite, and washed with ethyl acetate (10 mL×3). The filtrate was concentrated under reduced pressure and the residue was purified by chromatography on silica gel (*n*-hexane/EtOAc 3:1) to give the desired product **5a** (56.1 mg, 97%).

Acknowledgements

This research was supported by the Institute of Basic Science (IBS).

Keywords: amination · catalysis · C–H activation · ruthenium · sulfonyl azides

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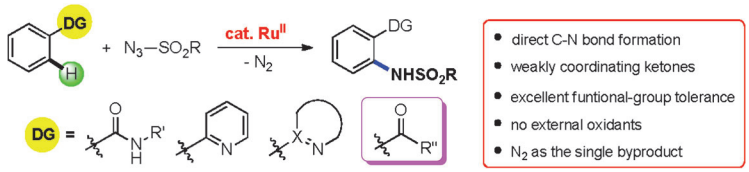
Received: March 18, 2013
Published online: ■■ ▮▮, 0000



C–H activation: The ruthenium-catalyzed direct sp^2 C–H amidation of arenes by using sulfonyl azides as the amino source is presented (see scheme). A wide range of substrates were readily amidated including arenes bearing weakly coordinating groups. Synthetic utility of the thus obtained products was demonstrated in the preparation of biologically active heterocycles.

Synthetic Methods

*J. Kim, J. Kim, S. Chang**. . ▮▮▮▮–▮▮▮▮

Ruthenium-Catalyzed Direct C–H Amidation of Arenes Including Weakly Coordinating Aromatic Ketones

