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Ru(II)-catalyzed intermolecular *ortho*-C–H amidation of aromatic ketones with sulfonyl azides†‡

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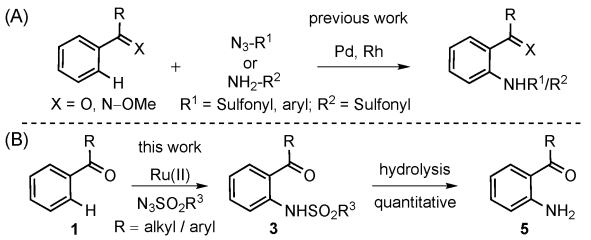
Ru(II)-catalyzed intermolecular *ortho*-C–H amidation of weakly coordinating aromatic ketones with sulfonyl azides is reported. The developed reaction protocol can be extended to various substituted aromatic ketones to afford a wide range of desired C–N bond formation products in good yields.

Following Murai's pioneering study on Ru-catalyzed C–H activation,[1] there has been significant interest in the development of transition-metal-catalyzed carbonyl-directed aryl *ortho*-C(sp^2)–H functionalization for C–C and C–X (X = halogen, O, or N) bond formation.[2] Particular attention has been paid to C–N bond formation because of the broad synthetic potential of nitrogen-bearing compounds.[3] Buchwald–Hartwig amination, for instance, allows for C–N bond induction in arenes using readily available pre-functionalized haloarenes.[4] Interestingly, direct amination of the C–H bond of arenes presents the advantages of accessing broad scenario of substrate generality and minimal waste production.[5] However, this process requires a strongly coordinating, *i.e.*, nitrogen-bearing, directing group (DG), which can be obtained from arene carbonyls/carboxylic acids through multiple synthetic manipulations.[6] Using electrophilic aminating agents, C–H amination of arenes has successfully been performed in the presence of a Pd or Rh catalyst (Scheme 1A).[7,8] The Chang group demonstrated the pyridyl and/or oxime directed amidation of arene C–H bonds with sulfonyl azides under the influence of a Rh-catalyst.[8a]

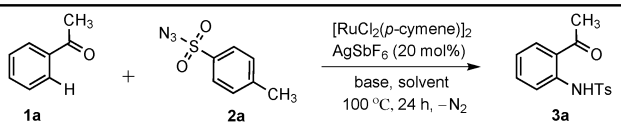
The development of novel methods for the formation of C–N bonds on readily available precursors would enhance the synthetic versatility of this strategy. For example, the direct synthesis of *ortho*-aminoaryl ketones, which are potential precursors to various biologically active molecules, from arylketones is therefore desirable.[3] An elegant approach to Pd-catalyzed carbonyl directed amidation of arene C–H bonds with sulfonamides has been reported by the Liu group.[2o]



Scheme 1 Carbonyl directed *ortho*-C–N bond formation.

However, to the best of our knowledge, the use of Ru-catalysts for the C–H amidation of arylketones is unprecedented.[9] Recently, our group demonstrated Ru-catalyzed reusable sulfoximine assisted C(aryl)–N bond formation with tosyl azides to produce anthranilic acid derivatives.[10] The preliminary results inspired us to examine the direct intermolecular *o*-C(aryl)–H amidation of weakly coordinating arylketones with tosyl azides (Scheme 1B). In this study, we focus on the use of inexpensive, easy-to-prepare and air-stable Ru(II) catalysts for direct intermolecular *o*-C–H amidation.

Table 1 Optimization of reaction conditions[a]



Entry	Base	Solvent	Yield[b] (%)
1	—	$ClCH_2CH_2Cl$	NR
2	KOAc	$ClCH_2CH_2Cl$	<5
3	$Cu(OAc)_2{\cdot}H_2O$	$ClCH_2CH_2Cl$	65
4	LiOAc	$ClCH_2CH_2Cl$	42
5	CsOAc	$ClCH_2CH_2Cl$	08
6	AgOAc	$ClCH_2CH_2Cl$	56
7	$Cu(OAc)_2{\cdot}H_2O$	Chlorobenzene	28
8	$Cu(OAc)_2{\cdot}H_2O$	$CHCl_3$	<5
9	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	<5
10	$Cu(OAc)_2{\cdot}H_2O$	Toluene	<5
11	$Cu(OAc)_2{\cdot}H_2O$	THF	08
12	**$Cu(OAc)_2{\cdot}H_2O$**[c]	**$ClCH_2CH_2Cl$**	**74**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), base (0.5 mmol). [b] Isolated yields. [c] $Cu(OAc)_2{\cdot}H_2O$ (50 mol%). NR = no reaction.

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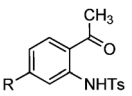
To find general conditions for the *ortho*-C(sp^2)–H amidation on aryl-ketones, reaction of acetophenone (**1a**) with tosylazide (**2a**) was conducted in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and bases in 1,2-dichloroethane (1,2-DCE) at 100 °C for 24 h (Table 1). The reaction did not proceed in the absence of base (entry 1). Interestingly, a trace amount of desired *ortho*-amidation product **3a** was noticed, when KOAc was employed in the reaction (entry 2). However, use of $Cu(OAc)_2{\cdot}H_2O$ enhanced the product formation, affording **3a** in 65% yield (entry 3). Another acetate source CsOAc was ineffective, whereas LiOAc and AgOAc furnished moderate yield of **3a** (entries 4–6). Other solvents such as chlorobenzene yielded a poor amount of **3a** (entry 7), whereas $CHCl_3$, CH_3CN, toluene and THF failed to produce even 10% of **3a** (entries 8–11). The less amount of $Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv.) did not affect the reaction efficiency, producing 74% of **3a** (entry 12).

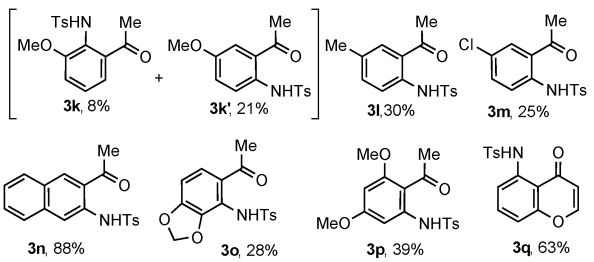
The optimized conditions in entry 12, Table 1, were screened examining the scope and functional group tolerance of this transformation. Table 2 summarizes the results of *o*-C–H amidation on arylmethyl ketones with **2a**. The *o*-C–H amidation product **3a** was isolated in 72% yield from the acetophenone (**1a**). The *para*-substituted arylmethyl ketones possessing electron-donating methyl, methoxy, i-butyl substituents delivered the corresponding *ortho*-amidation products **3b–d** in good to excellent yields. Interestingly, the OTBS protecting group was well tolerated, yielding 73% of **3e**. Halo groups (F, Cl, Br and I) were inert under the present reaction conditions, furnishing the desired products **3f–i** in good yields. The tolerance of iodo groups under the catalytic conditions is notable. The optimized conditions did not affect the ester-group, producing **3j** in 58% yield. The amidations on *meta*-substituted arylketones were found to be inferior.[2o] The regioisomeric products **3k** and **3k′** were obtained in 8% and 21% yields, respectively, from the *m*-methoxyacetophenone **1k**. Similarly, the other *meta*-substituted acetophenones **1l** and **1m** gave the corresponding less-hindered *o*-C–H amidation products **3l** (30%) and **3m** (25%), respectively. The reaction of 2-acetonaphthone (**1n**) with **2a** furnished a highly regioselective product **3n** in good yield. Notably, the hindered *o*-C–H was amidated, when 3′,4′-(methylenedioxy)acetophenone (**1o**) reacted with **2a**; the 2-NHTs substituted **3o** was produced albeit in poor yield.[2g] The *ortho*-substituted **1p** afforded **3p** in 39% yield. Pleasingly, the reaction between chromone (**1q**) and **2a** gave good amount of **3q**, leaving the conjugated double bond unaffected.

Next, we studied the *ortho*-amidation of various alkyl–aryl ketones and aryl–aryl ketones with tosyl azides (Table 3). Propyl and *n*-butyl substituted ketones, **1r** and **1s**, independently reacted with **2a** to deliver **3r** and **3s** in 85% and 73% yield, respectively. Amidation product **3t** was obtained from benzophenone in good yield. Similarly, electron-rich symmetrical 4,4′-dimethyl-benzophenone (**1u**) gave 70% of **3u**; whereas electron deficient Cl-bearing **1v** yielded **3v** in moderate yield. We next investigated the reaction of unsymmetrical diarylketones bearing an electron donating (–Me) (**1w**) and electron-withdrawing (–Br) group (**1x**) at the *para*-position in one of the aryl moieties with **2a**. The inseparable regioisomeric mixtures of the corresponding amidation products **3w**/**3w′** and **3x**/**3x′** (1.8 : 1) are obtained in moderate yields (see ESI‡).

We next turned our attention to the scope of different sulfonyl azides in the *ortho*-amidation on acetophenone (Table 4). Electron withdrawing arene-sulfonyl azides (**2b–e**), having NO_2, CF_3, F or Cl groups, successfully underwent amidation with **1a**, producing the

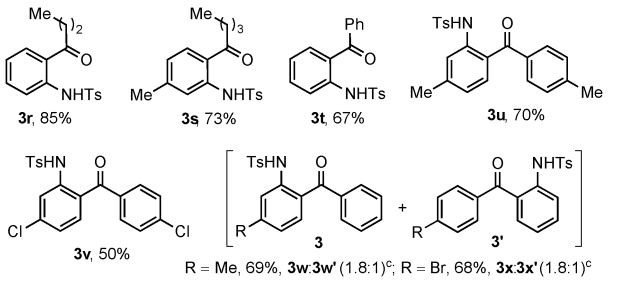
Table 2 Substrate scope of aromatic ketones[a,b]

Entry	R	Products	
1	**1a** (H)		
2	**1b** (Me)		
3	**1c** (OMe)		
4	**1d** (i-butyl)		
5	**1e** (OTBS)		
6	**1f** (F)	R = H; **3a**, 72%	R = F; **3f**, 64%
7	**1g** (Cl)	Me; **3b**, 84%	Cl; **3g**, 81%
8	**1h** (Br)	OMe; **3c**, 94%	Br; **3h**, 70%
9	**1i** (I)	i-butyl, **3d**, 83%	I; **3i**, 65%
10	**1j** (CO_2Me)	OTBS; **3e**, 73%	CO_2Me; **3j**, 58%



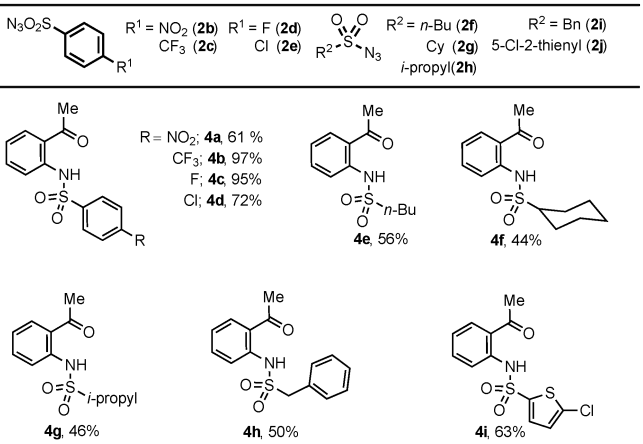
[a] Reaction conditions: **1** (1.0 mmol), azide (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (50 mol%), 1,2-DCE (2.0 mL) at 100 °C for 24 h. [b] Isolated yields.

Table 3 Substrate scope of aryl–alkyl and aryl–aryl ketones[a,b]

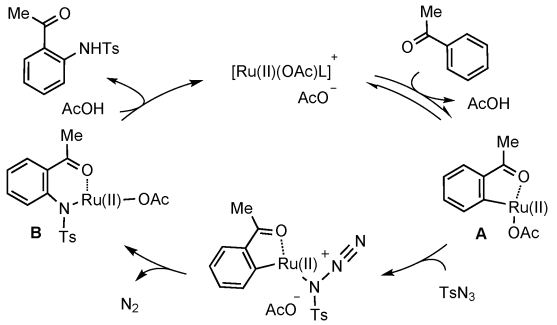


[a] Reaction conditions: **1** (1.0 mmol), azide (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (50 mol%), 1,2-DCE (2.0 mL) at 100 °C for 24 h. [b] Isolated yields. [c] Mixture of two regioisomers.

Table 4 Sulfonyl azide scope[a,b]

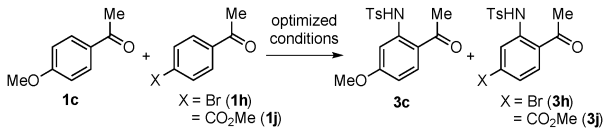


[a] Reaction conditions: **1** (1.0 mmol), azide (1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (50 mol%), 1,2-DCE (2.0 mL). [b] Isolated yields.



Scheme 2 Proposed catalytic cycle.

corresponding *ortho*-C–N bearing products **4a–d** in good to excellent yields (see ESI‡). Aliphatic sulfonyl azides **2f–i** were also viable, delivering the desired **4e–h** in moderate yields. The thienyl–sulfonyl amido bearing product **4i** was obtained in 63% yield, when 5-chlorothiophene-2-sulfonyl azide (**2j**) reacted with **1a**.



(1)

The intermolecular competitive amidation among **1c** and **1h**, **1c** and **1j** with **2a** (eqn (1)) was performed under the optimized conditions. The ratios of products **3c**/**3h** and **3c**/**3j** were found to be 1.5/1.0 and 2.5/1.0, respectively, indicating better reactivity of the electron-rich over electron-poor arenes (see ESI‡).

Although the detailed mechanism of Ru(II)-catalyzed C–H amidation of arenes is yet to be established, the proposed mechanism is outlined in Scheme 2.[11] The combination of $[RuCl_2(p\text{-cymene})]_2$, base, and $AgSbF_6$ generates the active Ru(II)-catalyst. The coordination of carbonyl oxygen to the coordinatively unsaturated Ru-catalyst triggers activation of the *o*-C–H bond and delivers the metallacycle intermediate **A**;[6e] the deuterium scrambling experiment supports the reversible cleavage of C–H bonds (see ESI‡). Coordination of azides to **A** followed by migratory insertion of sulfonamido moieties with evolution of N_2 gas leads to the intermediate **B**. Finally, protonolysis of **B** provides the desired product and generates the active ruthenium-complex for the next catalytic cycle.

In summary, we have developed a ruthenium-catalyzed direct aryl *o*-C–H amidation on the readily available aryl–alkyl and aryl–aryl ketones with sulfonyl azides. The reaction proceeds with the broad scope of arylketones in good yields. A wide range of sulfonyl azides were successfully installed on arylketones.

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