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Expedient C−H Amidations of Heteroaryl Arenes Catalyzed by Versatile Ruthenium(II) Catalysts

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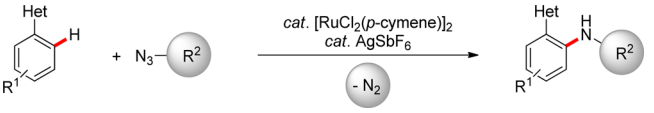
ABSTRACT



Heteroaryl-substituted arenes and heteroarenes were efficiently amidated through ruthenium-catalyzed C−H bond functionalizations with a variety of sulfonyl azides. Particularly, cationic ruthenium(II) complexes proved to be most effective and allowed nitrogenations of electron-rich and electron-deficient arenes with ample substrate scope.

Transition-metal-catalyzed C−H bond functionalizations are attractive tools for improving the atom- and step-economy of organic syntheses.[1] In recent years, ruthenium(II) complexes have been identified as powerful catalysts for the direct transformation of otherwise unreactive C−H bonds into C−C bonds.[2] On the contrary, ruthenium(II)-catalyzed C(sp^2)−heteroatom bond forming processes continue to be scarce. Given the recent success in ruthenium-catalyzed direct arene oxygenations,[3] along with the practical importance of substituted anilines in medicinal chemistry, crop protection and material sciences,[4] we became intrigued by devising ruthenium-catalyzed[5,6] intermolecular C−N bond forming arene functionalizations. A very recent independent report from Sahoo[7] on functionalizations of amides prompted us to disclose herein our results on the development of versatile ruthenium(II) catalysts for expedient amidations of heteroaryl arenes with sulfonyl azides.

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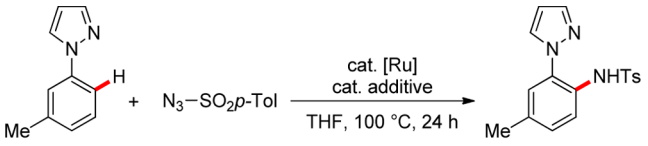
10.1021/ol401321q

Table 1. Optimization of C−H Amidation of Pyrazole **1a**[a]

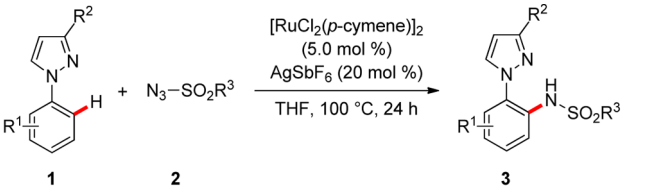


1a **2a** **3a**

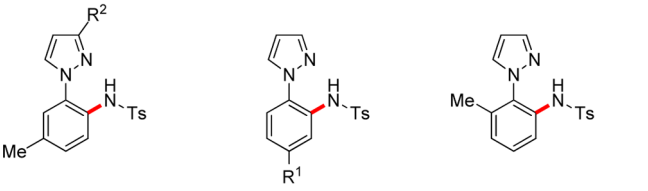
entry	[Ru] (mol %)	additive	yield (%)
1	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	–	–
2	–	$AgSbF_6$	–
3	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	KO_2CMes	8
4	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	KPF_6	–
5	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	$AgAl(OCF_3)_4$	21
6	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	$AgBF_4$	37
7	$[RuCl_2(p\text{-cymene})]_2$ (5.0)	$AgSbF_6$/KOAc[b]	–
8	$RuCl_3(H_2O)_n$ (5.0)	$AgSbF_6$	2
9	$[Ru(O_2CMes)_2(p\text{-cymene})]$ (5.0)	$AgSbF_6$	3
10	$[RuBr_2(p\text{-cymene})]_2$ (5.0)	$AgSbF_6$	74
11	$[RuCl_2(p\text{-cymene})]_2$ (2.5)	$AgSbF_6$	62
12	**$[RuCl_2(p\text{-cymene})]_2$ (5.0)**	**$AgSbF_6$**	**82**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (20 mol %), THF (2.0 mL). [b] KOAc (0.5 equiv).

Scheme 1. Scope of Ruthenium-Catalyzed C−H Amidation with Pyrazoles **1**



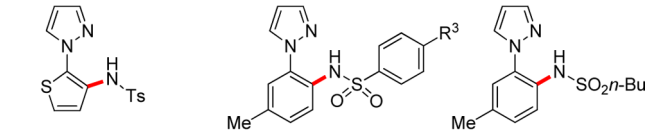
1 **2** **3**



R^2 = H (**3a**): 82%
R^2 = Me (**3b**): 42%

R^1 = H (**3c**): 42%
R^1 = OMe (**3d**): 57%

3e: 70%



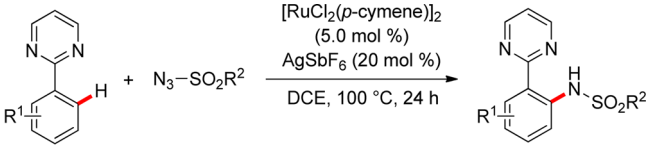
3f: 43%

R^3 = H (**3g**): 65%
R^3 = OMe (**3h**): 59%
R^3 = CF_3 (**3i**): 62%
R^3 = F (**3j**): 82%
R^3 = Cl (**3k**): 59%
R^3 = Br (**3l**): 52%
R^3 = NO_2 (**3m**): 50%

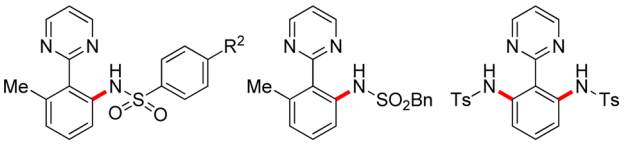
3n: 57%

In consideration of the broad synthetic utility of substituted pyrazoles,[8] we initially explored reaction conditions for the direct amidation of substrate **1a** utilizing complex $[RuCl_2(p\text{-cymene})]_2$ as the catalyst (Table 1). The desired transformation was not accomplished in the absence of additives or the ruthenium complex (entries 1 and 2). While the use of a carboxylate or KPF_6 as cocatalytic additives only gave unsatisfactory results (entries 3 and 4), silver salts of weakly coordinating anions proved to be more promising (entries 5−12). Among a set of representative silver(I) additives, $AgSbF_6$ was identified as being most effective, while $[RuCl_2(p\text{-cymene})]_2$ was the optimal ruthenium precursor (entries 8−12). Interestingly, the presence of

Scheme 2. Ruthenium-catalyzed C−H Amidation with Substituted Pyrimidines **4**



4 **2** **5**

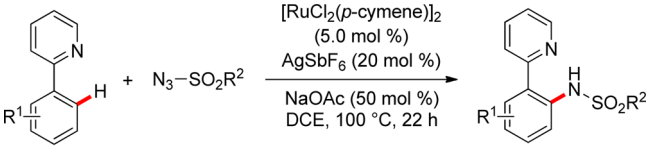


R^2 = H (**5a**): 62%
R^2 = OMe (**5b**): 70%
R^2 = Me (**5c**): 95%
R^2 = NO_2 (**5d**): 50%

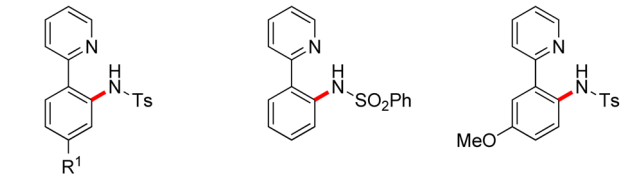
5e: 51%

5f: 64%

Scheme 3. Acetate-assisted Ruthenium-catalyzed C−H Amidation with Pyridines **6**



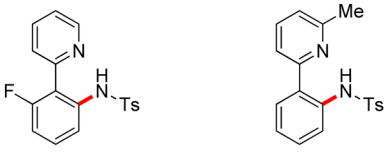
6 **2** **7**



R^1 = H (**7a**): 70%
R^1 = Me (**7b**): 76%

7c: 84%

7d: 67%



7e: 69%

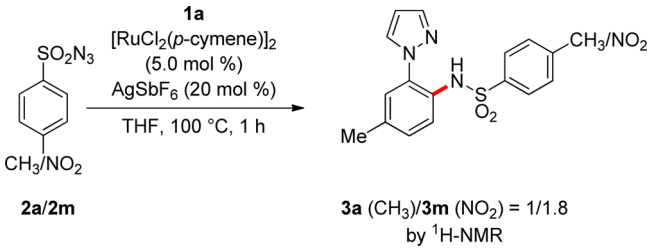
7f: 63%

KOAc completely inhibited the C−H bond amidation of substrate **1a** (entry 7), a striking difference to the recently reported procedure.[7] As to the reactions site-selectivity, the sterically less congested C−H bond was exclusively functionalized, providing anilide **3a** in all reactions as the sole product.

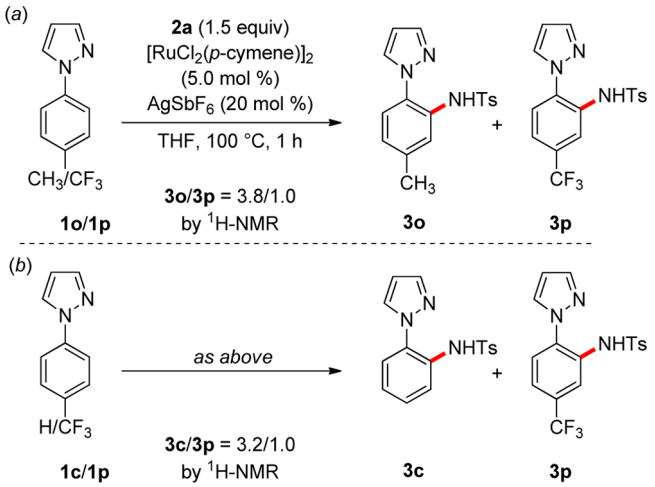
With an optimized catalytic system in hand, we tested its scope and limitations in the direct nitrogenation of differently substituted *N*-arylpyrazoles **1** (Scheme 1). A substituent in proximity to the coordinating nitrogen in substrate **1b** significantly reduced the yield of the desired product **3b**. Substituents in *meta*-, *para*- or even *ortho*-position on the arenes **1** were well tolerated by the catalytic system, as was heteroaromatic substrate **1f**. Differently decorated sulfonyl azides **2** with aromatic or aliphatic substituents could be successfully employed. The cationic ruthenium(II) catalyst displayed a remarkable chemo-selectivity in that valuable functional groups were well tolerated, most notably chloro, bromo or nitro substituents.

The optimized catalytic system was not limited to arenes bearing electron-rich pyrazoles. Indeed, starting materials with electron-deficient pyrimidine moieties were found to be viable substrates for the chelation-assisted C−H bond amidation as well (Scheme 2).

Scheme 4. Competition Experiments with Azides **2**



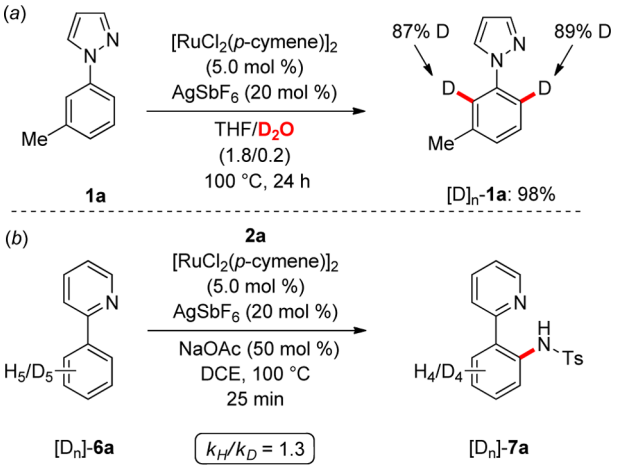
Scheme 5. Intermolecular Competition Experiments with Arenes **1**



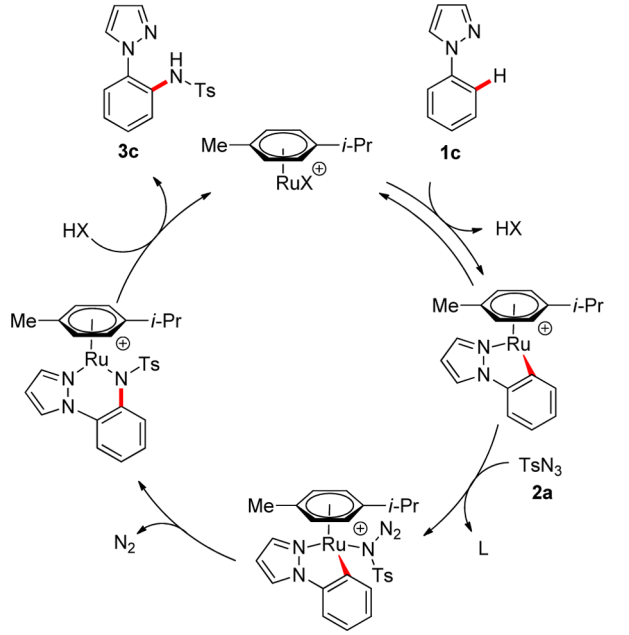
Likewise, pyridyl-substituted arenes were found to be suitable substrates, provided that NaOAc was present as an additive (Scheme 3). The carboxylate-assisted[9] ruthenium-catalyzed direct amidation thereby allowed for the conversion of numerous substituted sulfonyl azides **2** as well as *para*-, *meta*- or *ortho*-substituted arenes **6**. Notably, the electron-deficient substrate **6e** furnished efficiently desired product, as did the more hindered starting material **6f**.

As to the catalysts working mode, we conducted a series of competition experiments with substituted azides **2** highlighting a slight preference for the less electron-rich derivative **2m** (Scheme 4).

Scheme 6. Mechanistic Studies with Isotopically Labeled Compounds



Scheme 7. Proposed Mechanism



Intermolecular competition experiments between pyrazolyl-substituted substrates **1** revealed electron-rich arenes to be converted preferentially (Scheme 5), which is suggestive of an electrophilic-type ruthenation manifold.

Finally, we utilized D_2O as a cosolvent, which indicated a significant H/D scrambling exclusively in the *ortho*-position of arene **1a** (Scheme 6a). Moreover, an intermolecular competition experiment with isotopically labeled [D_5]-**6a** was indicative of a reversible ruthenation event with a kinetic isotope effect (KIE) of $k_H/k_D \approx 1.3$ (Scheme 6b).

On the basis of these mechanistic studies, we propose the C−H bond activation to occur by a reversible electrophilic-type metalation, as illustrated for pyrazole **1c** in Scheme 7. This proposed working mode in turn rationalizes the high catalytic activity of cationic ruthenium complexes.

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In summary, we have reported on ruthenium(II)-catalyzed direct amidations of arenes displaying heteroaromatic groups. The chelation-assisted C−H bond functionalization proceeded most efficiently with cationic complexes using various alkyl and aryl sulfonyl azides, which enabled C−N bond formations on pyrazolyl-, pyrimidyl- or pyridyl-substituted arenes and heteroarenes. The catalysts displayed an excellent site- and chemo-selectivity as well as a remarkably broad substrate scope.

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Supporting Information Available. 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.

The authors declare no competing financial interest.