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Ruthenium(II) Porphyrin-Catalyzed Amidation of Aromatic Heterocycles

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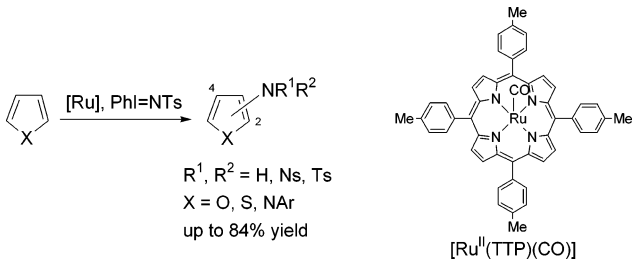
ABSTRACT



Ruthenium(II) porphyrin-catalyzed amidation of aromatic heterocycles with iminoiodanes under mild conditions (CH_2Cl_2, 4 Å molecular sieves, ultrasound, 40 °C) was achieved in moderate to good yields (up to 84%) and conversions (up to 99%). Only the *N*,*N*-ditosylamidated product was obtained for reactions involving heteroarenes, where X = O, S, or NTs. *N*-Alkyl- and *N*-aryl-substituted pyrroles, on the other hand, were shown to give the 3,4-diaminated adduct.

Transition metal-catalyzed nitrene insertion into C−H bonds is increasingly attractive as a C−N bond formation strategy.[1−6] Innovative works by Breslow,[2] Müller,[3] and Du Bois[4] showed that dirhodium(II,II) complexes with bridging carboxylate ligands and derivatives are effective catalysts for amidation of saturated C(sp^3)-H bonds using *N*-(*p*-toluenesulfonyl)-imino-phenyliodinane (PhI═NTs) or "PhI($OAc)_2$ + NH_2-SO_2R" (usually R = Ar) as a nitrogen source. Studies in our laboratory demonstrated that highly enantioselective amidation of saturated C−H bonds can be accomplished using chiral ruthenium porphyrin catalysts.[5] Despite these advances, examples of amidation of aromatic C(sp^2)-H bonds are sparse in the literature. A recent notable achievement is that of Pérez and co-workers showing that copper(I)−homoscorpionate complexes can effect benzene amidation by PhI═NTs in moderate yields.[6] In the present work, we describe amidation of C(sp^2)-H bonds of heteroarenes such as furan, pyrrole and thiophene using ruthenium(II) porphyrin as a catalyst and PhI═NTs as a nitrogen source. Although reactions of these heterocycles with metallocarbenoids to give cyclopropanes are known,[7] examples of protocols for catalytic amidation of heteroarenes have limited precedent in the literature. It is well-known that amino-functionalized het-

(1) (a) Müller, P. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, p 113. (b) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, p 607. (c) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905 and references therein.

(2) (a) Breslow, R.; Gellman, S. H. *Chem. Commun.* **1982**, 1400. (b) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728. (c) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531.

(3) Nageli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087.

(4) (a) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (b) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

(5) (a) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (b) Zhou, X.-G.; Yu, X.-Q.; Huang, J.-S.; Che, C.-M. *Chem. Commun.* **1999**, 2377. (c) Liang, J.-L.; Yu, X.-Q.; Che, C.-M. *Chem. Commun.* **2002**, 124. (d) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465.

(6) Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078.

(7) Selected examples: (a) Doyle, M. P.; Chapman, B. J.; Hu, W.; Peterson, C. S.; McKervey, M. A.; Garcia, C. F. *Org. Lett.* **1999**, *1*, 1327 and references therein. (b) Hughes, C. C.; Kennedy-Smith, J. J.; Trauner, D. *Org. Lett.* **2003**, *5*, 4113.

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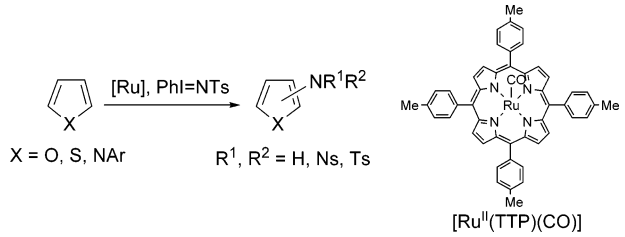
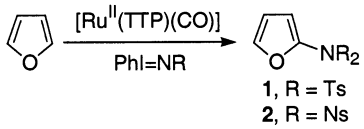
erocycles are prevalent in many natural and therapeutic products of biological significance.[8]

Scheme 1



At the outset of this study, we found that ultrasound treatment of furan (1 equiv) with 10 mol % [Ru^{II}(TTP)(CO)] [H_2(TTP) = *meso*-tetrakis(tolyl)porphyrin] and PhI=NTs (1.5 equiv) in CH_2Cl_2 containing 4 Å molecular sieves[9] at 40 °C gave *N*,*N*-ditosylamido-2-furan (**1**) in 73% isolated yield (Table 1, entry 1).[10] The molecular structure of **1** has been established by X-ray crystal analysis (Figure 1).[11] Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy and mass spectrometry revealed that **1** was the sole product. Under our experimental conditions, formation of the monotosylated amide (i.e., *N*-furan-2-yl-tolylsulfonamide) was not detected.

Table 1. Optimization of Reaction Conditions[a]



entry	temp (^{o}C)	catalyst loading (mol %)	product	% yield[b]
1[c]	40	10	**1**	73
2	40	10	**1**	41
3[c,d]	40	10	**1**	10
4[c]	40	2	**1**	40
5	40	2	**1**	43
6	65	2	**1**	45
7[e]	40	10	**2**	63

[a] All reactions were performed in CH_2Cl_2 for 2 h with a catalyst:heteroarene:PhI=NTs ratio of 1:1:5 in the absence of ultrasound. [b] Isolated yield based on the amount of heteroarene consumed. [c] Reaction conducted with ultrasound treatment. [d] Reaction conducted with 5 equiv of PhI=NTs. [e] Reaction conducted with PhI=NNs.

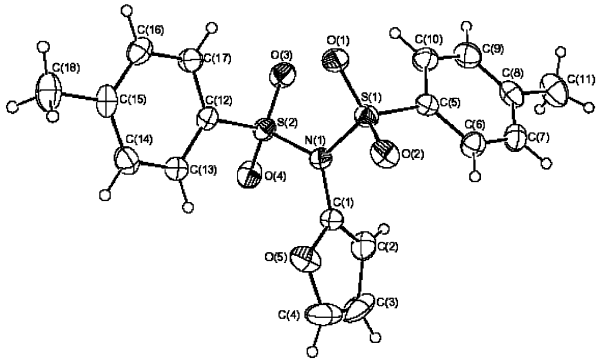


Figure 1. Perspective view of **1**. Selected bond lengths (Å) and angles (deg): O(5)−C(1) 1.347(3), N(1)−C(1) 1.404(3), S(1)−N(1) 1.689(2), C(1)−C(2) 1.334(4), C(2)−C(3) 1.447(5), S(1)−N(1)−S(2) 122.7(1), C(2)−C(1)−N(1) 128.9(3), C(1)−C(2)−C(3) 103.1(3).[11]

The reason for formation of the *N*,*N*-ditosylamidated product remains ill understood. However, attempts to obtain the putative monotosylated compound were futile. For example, conducting the above catalytic reaction in the presence of a proton source such as TsOH (1.5 equiv) led to compound **1** in a trace amount (<5%), and no *N*-furan-2-yl-tolylsulfonamide was found.

It is noteworthy that employment of both the ultrasound and Ru catalyst for the amidation reaction was essential. As shown in Table 1, conducting the reactions without ultrasound treatment afforded **1** in lower yields of 41 and 43% (entries 2 and 5). *No conversion of furan was observed in the absence of ruthenium(II) porphyrin catalyst even though ultrasound treatment was employed.* A lower product yield (36%) was obtained on changing the [Ru^{II}(TTP)(CO)] catalyst to [Ru^{II}(F_{20}-TPP)(CO)] [H_2(F_{20}-TPP) = *meso*-tetrakis(pentafluorophenyl)porphyrin] at a lower catalyst loading of 5 mol %. In addition, reaction with excess PhI=NTs (5 equiv) was found to be detrimental to product yield, with **1** being obtained in only 10% yield (entry 3). Furan amidation with *N*-(*p*-nitrophenylsulfonyl)imino-phenyliodinane (PhI=NNs) as a nitrene source and [Ru^{II}(TTP)(CO)] as a catalyst (10 mol %) can also be accomplished, furnishing sulfonamide **2** in 63% yield (entry 7). The analogous ultrasound-assisted reaction of furan with PhI=NTs and [$Rh_2(CH_3CO_2)_4$] as a catalyst gave **1** in only 21% yield in our hands. Trace quantities of **1** were obtained when the [$Rh_2(CH_3CO_2)_4$]-catalyzed reaction was performed without ultrasound.

In this work, catalytic amidation reactions of some substituted aromatic heterocycles have also been examined. The results are summarized in Table 2.

Subjecting methyl 2-furoate and benzofuran to the protocol "ultrasound + [Ru^{II}(TTP)(CO)] (10 mol %) + 1.2 equiv of PhI=NTs" in CH_2Cl_2 at 40 °C gave the corresponding *N*,*N*-ditosylamides **3** and **4** in low yields (<20%). However,

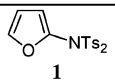
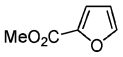
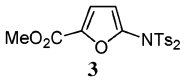
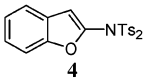
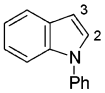
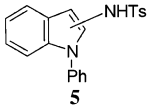
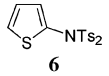
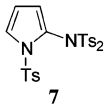
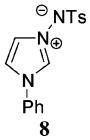
(8) Selected examples: (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Reymond, J. L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128. (c) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *J. Org. Chem.* **1996**, *61*, 2202. (d) Marcotte, F.-A.; Rombouts, F. J. R.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 6984.

(9) Amount of 4 Å molecular sieves employed is equivalent to the amount (by mass) of PhI=NTs used.

(10) See Supporting Information for full experimental details.

(11) See Supporting Information. Also, CCDC 219719−219720 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 2. [Ru^{II}(TTP)(CO)]-Catalyzed Amidation of Aromatic Heterocycles with PhI=NTs[a]

entry	substrate	product	% yield[b]/ (conversion)[c]
1[d]		 **1**	73 (99)
2		 **3**	34 (50)
3[e]			40 (65)
4		 **4**	58 (50)
5[d]		 **5**	64 (99)[f]
6		 **6**	33 (56)
7		 **7**	80 (22)
8[g]		 **8**	91 (99)

[a] Reactions were performed in CH_2Cl_2 under ultrasound with 4 Å molecular sieves at 40 °C for 2 h with a [Ru^{II}(TTP)(CO)]:heteroarene:PhI=NTs ratio of 1:10:50. [b] Isolated yield based on the amount of heteroarene consumed. [c] Values in parentheses denote substrate conversion determined by GC analysis. [d] Reaction conducted with 1.2 equiv of PhI=NTs. [e] Reaction conducted with [Ru^{II}(F_{20}-TTP)(CO)] (5 mol %) as a catalyst. [f] Obtained along with 1-phenylisatin in 9% yield. [g] Reaction conducted with 1.5 equiv of PhI=NTs.

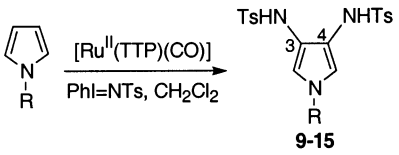
increasing the amount of PhI=NTs to 5 equiv was found to afford **3** and **4** in moderate to good substrate yields (up to 58%) and substrate conversions (entries 2 and 4). For amidation of methyl 2-furoate, when [Ru^{II}(F_{20}-TPP)(CO)] (5 mol %) was employed as a catalyst, **3** was obtained in 40% yield with 65% substrate conversion (entry 3). In comparison, amidation of methyl 2-furoate with [$Rh_2(CH_3CO_2)_4$] as a catalyst gave **3** in trace quantities, and the analogous reaction of benzofuran afforded **4** in 14% yield and 61% substrate conversion.

With *N*-phenylindole as a substrate, the Ru-catalyzed amidation with 1.5 equiv of PhI=NTs afforded *N*-monotosylamide **5** as a 1: 1 mixture of 2- and 3-regioisomers in 64% yield (entry 5 of Table 2). The same reaction treated with 5 equiv of PhI=NTs, however, preferentially gave 1-phenylisatin in 77% yield. Reaction of thiophene under these conditions, on the other hand, furnished *N*,*N*-ditosylamide **6** in 33% yield with 56% substrate conversion (entry 6). Similarly, reaction of *N*-tosylpyrrole was found to give the *N*,*N*-ditosylamide **7** in 80% yield but with a lower substrate conversion of 22% (entry 7). Analogous to the findings described in earlier sections, [$Rh_2(CH_3CO_2)_4$] was found to be less effective for amidation of *N*-phenylindole, furnishing **5** in 57% yield based on 56% substrate conversion, and **6** in trace amounts for the analogous reaction with thiophene.

Treatment of *N*-phenylimidazole under the conditions "ultrasound + [Ru^{II}(TTP)(CO)] (10 mol %) + 1.5 equiv of PhI=NTs" in CH_2Cl_2 at 40 °C, gave rise to a ylide product **8** in 91% yield (entry 8 of Table 2); no amidation product was observed by ^{1}H NMR analysis of the crude reaction mixture. Structural determination of **8** was made on the basis of ^{1}H and ^{13}C NMR spectroscopy and X-ray crystal analysis (see Supporting Information).[11]

Under the conditions [Ru^{II}(TTP)(CO)] (10 mol %), PhI=NTs (5 equiv), CH_2Cl_2, 40 °C and ultrasound, catalytic amidation of *N*-alkyl- and *N*-aryl-substituted pyrroles was achieved and 3,4-diaminated pyrroles **9**−**15** were obtained in good to excellent yields (up to 87%) and conversions (Table 3, entries 1−7). In a few cases, reactions conducted

Table 3. [Ru^{II}(TTP)(CO)]-Catalyzed Amidation of N-Substituted Pyrroles with PhI=NTs[a]



9-15

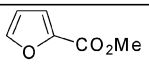
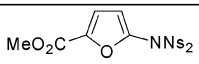
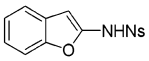
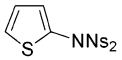
entry	R	product	% yield[b]	% conversion[c]
1	Me	**9**	68	99
2	C_6H_5	**10**	82	99
3	(*o*-Me)C_6H_4	**11**	60	99
4	(*p*-Me)C_6H_4	**12**	84	99
5	(*p*-OMe)C_6H_4	**13**	81	99
6	(*p*-F)C_6H_4	**14**	50	99
7	(*p*-NO_2)C_6H_4	**15**	87	60

[a] Reactions were performed in CH_2Cl_2 under ultrasound with 4 Å molecular sieves at 40 °C for 2 h with a [Ru^{II}(TTP)(CO)]:pyrrole:PhI=NTs ratio of 1:10:50. [b] Isolated yield based on the amount of heteroarene consumed. [c] Substrate conversion determined by GC analysis.

with no Ru catalyst showed that diaminopyrroles **9**−**11** and **14** could also be obtained, albeit in lower yields of 18−54%. In this work, amidation of *N*-methyl- and *N*-*p*-fluorophenylpyrrole with [$Rh_2(CH_3CO_2)_4$] as a catalyst afforded **9** and **14** in 64 and 30% yields, respectively. Under our experimental conditions, formation of either the 3-monoamidated or *N*,*N*-tosylamidated products were not detected by ^{1}H and ^{13}C NMR analysis. Moreover, amidation of *N*-phenylpyrrole with an equimolar amount of PhI=NTs was found to give **10** exclusively in 21% yield based on 40% substrate conversion.

In this work, we have also examined the "NH_2Ts + $PhI(OAc)_2$" protocol for catalytic amidation of heteroarenes. Treatment of methyl 2-furoate with [Ru^{II}(TTP)(CO)] (1.5 mol %), NH_2Ts (1 equiv), and $PhI(OAc)_2$ (1 equiv) in 1,2-dichloroethane at 65 °C *without ultrasound* was found to give ditosylamide **3** as the sole product in 60% yield with 15% substrate conversion. With NH_2Ns as a nitrogen source,

Table 4. [Ru^{II}(TTP)(CO)]-Catalyzed Amidation of Heteroarenes with NH_2Ns and $PhI(OAc)_2$[a]

entry	substrate	product	% yield[b]/ (conversion)[c]
1[d]		 **16**	76 (60)
2[e]		 **17**	50 (80)
3[f]		 **18**	60 (70)

[a] All reactions were carried out in 1,2-dichloroethane with 4 Å molecular sieves at 65 °C. [b] Isolated yield based on the amount of heteroarene consumed. [c] Values in parentheses denote substrate conversion determined by GC analysis. [d] [Ru^{II}(TTP)(CO)]:heteroarene:NH_2Ns:$PhI(OAc)_2$ = 1.5:100:100:100, 12 h. [e] As described in footnote d but with 250 equiv of NH_2Ns and $PhI(OAc)_2$. [f] [Ru^{II}(TTP)(CO)]:heteroarene:NH_2Ns:$PhI(OAc)_2$ = 1:50:100:100, 2 h.

up to 76% yield and 60% substrate conversion was achieved for amidation of methyl 2-furoate (Table 4, entry 1). Likewise, benzofuran was converted to its *N*-nosylamide **17** in 50% yield (80% substrate conversion) under similar reaction conditions (entry 2), and thiophene was converted to *N*,*N*-dinosylsulfonamide **18** in 60% yield (entry 3). Under similar conditions, the analogous reactions of methyl 2-furoate, benzofuran and thiophene conducted at a higher catalyst loading of 10 mol % were found to give comparable product yields and substrate conversions.

To probe the mechanism of the catalytic reactions, we examined the stoichiometric amidation of furan and *N*-phenylpyrrole with [Ru^{VI}(TMP)($NTs)_2$] (H_2(TMP) = *meso*-tetrakis(2,4,6-trimethylphenyl)porphyrin). While reduction of Ru(VI) to Ru(IV) could be observed by UV/vis spectrophotometry under a variety of conditions, no amidation product was detected by ^{1}H NMR and TLC analyses of the crude mixtures.[12] On the basis of this finding, we surmise that the involvement of a bis(imido)ruthenium(VI) species as a reactive intermediate in the catalytic reactions is insufficient to instigate insertion of "NTs" or "NNs" into the aromatic C−H bond and that amidation could have occurred via an in situ substrate activation step. In addition, the near quantitative recovery of **17** (97%) from its reaction with "NH_2Ns + $PhI(OAc)_2$" in the presence of [Ru^{II}(TTP)(CO)] suggests that formation of the *N*,*N*-ditosylamidated product is unlikely to come from consecutive tosylation of a monosulfonamide species.

In summary, we describe the first metalloporphyrin-catalyzed amidation of aromatic heterocycles under mild conditions. Efforts are currently underway to examine the scope of the present amidation protocol with respect to other heteroarene substrates and the possible reaction mechanism.

Acknowledgment. We thank Dr. Nian-Yong Zhu for assistance in solving the crystal structures reported in this paper. This work is supported by the Area of Excellence Scheme (AoE/P-10-01) established under the University Grants Committee (HKSAR), the Hong Kong Research Grants Council (No. 7099/00P), and the University Development Fund of The University of Hong Kong.

Supporting Information Available: Detailed experimental procedures and characterization data, including X-ray crystallographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Reactions conducted in the presence of $PhI(OAc)_2$ or benyzl peroxide as an additive were found to give similar outcomes (i.e., reduction of Ru(VI) to Ru(IV) with no amidation product detected). Also, see Supporting Information for experimental details.