Amide Bond Formation

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Highly Efficient Ruthenium(II) Porphyrin Catalyzed Amidation of Aldehydes**

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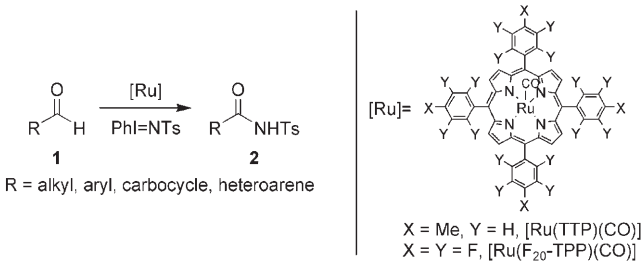
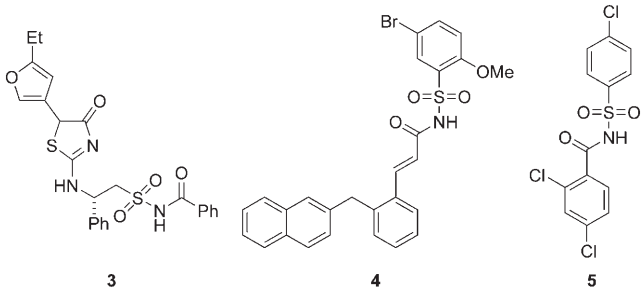
The installation of the amide bond functionality is of immense interest in organic synthesis owing to the prevalence of this structural motif in a myriad of compounds of biological, pharmaceutical, and materials interest.[1] Conventional routes to this ubiquitous class of nitrogen-containing compounds have relied heavily upon the coupling of activated carboxylic acid and amine precursors.[2] Although these methodologies have been shown to be exceptionally efficient for the synthesis of small peptides, many classes of amides, including those found in many natural products, bioconjugates, and pharmaceutical targets, along with the lability of the activated carboxylic acid derivatives, pose significant challenges. In view of these shortcomings, alternative amide bond formation strategies have been actively pursued.[3–5] One such strategy is the direct reaction of the acyl C–H bond of aldehydes with amines in the presence of a transition-metal catalyst under oxidative conditions.[5] According to the seminal reports by the groups of Li,[5a] Beller,[5b] and others,[5c,d] these catalytic systems are thought to involve the formation of a carbinolamine intermediate that undergoes metal-catalyzed oxidation to furnish the amide product. However, catalytic systems that can effect amide bond formation for a wide range of aldehydes through nitrogen atom insertion have remained sparse. In this context, and attracted by recent reports by Che and co-workers showing ruthenium(II) porphyrins to be efficient catalysts in C–H bond amidation reactions with PhI=NTs as the nitrogen source,[6,7] we envisioned that a "Ru + PhI=NTs" strategy could hold promise as the basis for a new approach to amide-bond synthesis. Herein, we report the first chemoselective ruthenium(II) porphyrin catalyzed amidation of a wide range of aldehydes with PhI=NTs as the nitrogen source; these reactions proceed with product yields up to 99% (Scheme 1). While insertions of a putative reactive metal–nitrene/imido species into C(sp^3)–H bonds of alkanes[6–8] and, more recently, C(sp^2)–H bonds of benzene[9] and heteroarenes[10] have been extensively examined, to our knowledge the analogous nitrogen-atom transfer reactions to the acyl C(sp^2)–H bond of aldehydes is not known. It also



Scheme 1. Ruthenium porphyrin catalyzed amidation of aldehydes. Ts = toluene-4-sulfonyl.

noteworthy that the acylsulfonamides obtained herein are themselves a class of biologically active compounds of current therapeutic interest.[11] Acylsulfonamides **3**–**5** (Scheme 2), for example, have been reported to exhibit potent HCV NS5B polymerase allosteric inhibitor activity,[11a] anti-inflammatory activity,[11b] and antitumor activity,[11d] respectively.



Scheme 2. Examples of bioactive compounds containing the acylsulfonamide moiety.

At the outset of this study, we focused our attention on developing a catalytic system that would effect amide bond formation regardless of the aliphatic or aromatic nature of the aldehyde starting material. With this aim in mind, we examined the amidation of isovaleraldehyde **1a** as a model substrate to establish the reaction conditions (Table 1). We found that treating one equivalent of **1a** with PhI=NTs (2 equiv) and 10 mol% [Ru(TTP)(CO)][12] as catalyst in CH_2Cl_2 at room temperature for 30 minutes gave the best result, furnishing 3-methyl-*N*-tosylbutanamide **2a** as the sole product in 94% yield (Table 1, entry 1). Under these conditions, no byproduct that could be attributed to amidation at the tertiary carbon center of **1a** was detected. As shown in entries 2–5 in Table 1, a comparable yield of 93% was obtained on increasing the amount of PhI=NTs to four equivalents, but slightly lower product yields (76–82%) were afforded on decreasing PhI=NTs to one equivalent or catalyst

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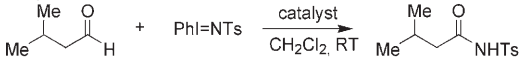
Table 1: Optimization of reaction conditions.[a]



1a **2a**

Entry	Equiv PhI=NTs	Catalyst	Yield [%][b]
1	2	[Ru(TTP)(CO)]	94
2	4	[Ru(TTP)(CO)]	93
3	1	[Ru(TTP)(CO)]	82
4[c]	4	[Ru(TTP)(CO)]	76
5[d]	4	[Ru(TTP)(CO)]	80
6	2	[$Rh_2(OAc)_4$]	31
7	2	[Ru(F_{20}-TPP)(CO)]	58
8	–[e]	[Ru(TTP)(CO)]	24

[a] Unless otherwise stated, all reactions were carried out in CH_2Cl_2 (2 mL) with molar ratio catalyst/**1a** = 1:10 at room temperature for 0.5 h. [b] Yield of isolated product. [c] Reaction conducted with 1 mol% catalyst. [d] Reaction conducted with 5 mol% catalyst. [e] Reaction conducted with $PhI(OAc)_2$ and *p*-$TsNH_2$ in place of PhI=NTs with molar ratio **1a**/$PhI(OAc)_2$/*p*-$TsNH_2$ = 1:1.25:1.5 at room temperature for 24 h.

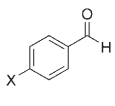
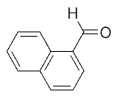
loadings to 1 or 5 mol% using four equivalents of PhI=NTs. In contrast, the analogous reactions with [Ru(F_{20}-TPP)(CO)][12] or [$Rh_2(OAc)_4$] as catalyst gave **2a** in markedly lower yields (Table 1, entries 6–7).

To define the scope of the [Ru(TTP)(CO)]-catalyzed amidation reactions, we applied this process to a series of aliphatic and aromatic aldehydes **1b–t** (entries 2–20 in Table 2). These reactions afforded the corresponding acylsulfonamides **2b–t** in good to excellent yields (60–99%). Notably, for reactions of substrates also containing a tertiary carbon center, C–N bond formation was found to occur chemoselectively at the aldehyde functional group, which is consistent with our earlier findings for the amidation of **1a** (Table 2, entries 1, 2, and 6–8). Furthermore, in instances where it was envisioned that the presence of a benzylic C–H or C=C bond or an alkyl bromide functionality would lead to competitive side reactions, the corresponding adducts were furnished as the sole products in good to excellent yields (Table 2, entries 9–14). On the other hand, steric effects of the aliphatic aldehyde could play a role, since a substrate containing the bulky *t*Bu group provided amide **2e** in moderate yield (Table 2, entry 5).

The [Ru(TTP)(CO)]-catalyzed amidation of a variety of aromatic aldehydes **1o–t** was also found to proceed well, with the corresponding aryl-substituted acylsulfonamides **2o–t** afforded in good to excellent yields (entries 15–20 in Table 2). Interestingly, aldehydes with a pendant heteroarene functionality (Table 2, entries 19–20) were also efficiently amidated, which is noteworthy as these are common structural motifs in a myriad of bioactive natural and pharmaceutical compounds.[1]

To gain insight into the possible mechanism of the present reaction, we conducted a deuterium-labeling experiment. Treating a CH_2Cl_2 solution of α-[D]-benzaldehyde with 10 mol% [Ru(TTP)(CO)] catalyst and PhI=NTs as the nitrogen source at room temperature for 1 h gave *N*,*N*-[D]-tosylbenzamide in 90% yield and with a deuterium content of 76% incorporated at the nitrogen atom, as determined by

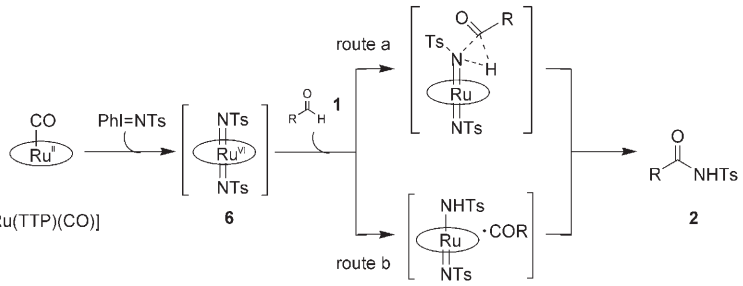
Table 2: [Ru(TTP)(CO)]-catalyzed amidation of **1a–1t**.[a]

Entry	Aldehyde		Product	Yield [%][b]
1			**2a**, R = *i*Bu	94
2		**1a–e**	**2b**, R = *i*Pr	86
3			**2c**, R = Et	97
4			**2d**, R = *n*Hex	97
5			**2e**, R = *t*Bu	60
6		**1f–h**	**2f**, *n* = 1	91
7			**2g**, *n* = 3	99
8			**2h**, *n* = 4	97
9		**1i–k**	**2i**, *n* = 1, R = Ph	86
10			**2j**, *n* = 2, R = Ph	68
11			**2k**, *n* = 4, R = Br	96
12		**1l–m**	**2l**, R^1 = *n*Pr, R^2 = H	99
13			**2m**, R^1 = R^2 = Me	91
14		**1n**	**2n**	99
15		**1o–q**	**2o**, X = H	93
16			**2p**, X = Me	92
17			**2q**, X = OMe	96
18		**1r**	**2r**	68
19		**1s,t**	**2s**, X = S	76
20			**2t**, X = O	93

[a] All reactions were carried out at room temperature for 30 min with molar ratio [Ru(TTP)(CO)]/**1**/PhI=NTs = 1:10:20. [b] Yield of isolated product.

^{1}H NMR spectroscopy and verified by mass spectrometry of the crude mixture (see the Supporting Information for details). This finding led us to speculate tentatively that the present ruthenium-catalyzed aldehyde amidation reaction proceeds by C–H bond functionalization (Scheme 3). In a manner similar to that proposed by the groups of Che, Du Bois, Sanford, and others,[13] the high-oxidation-state metal complex [Ru(TTP)$(NTs)_2$] **6** is thought to initially form from reaction of [Ru(TTP)(CO)] with PhI=NTs.[14] As shown in Scheme 3, subsequent transfer of the imido/nitrene group from this newly formed intermediate by either direct insertion or by H-atom abstraction/radical rebound (route a or b, respectively) is thought to give the amide product **2**.

In summary, we have developed a highly efficient ruthenium(II)-catalyzed strategy for the direct amidation of aldehydes using PhI=NTs as a nitrogen source. The method was shown to be applicable to a wide range of aldehydes. It is high-yielding and chemoselective, with amidation only occurring at the acyl C–H bond of the starting aldehyde. Further investigations are underway to examine the scope, mechanism, and applications of this reaction and will be reported in due course.



Scheme 3. Tentative mechanism for [Ru(TTP)(CO)]-catalyzed amidation of aldehydes with PhI=NTs.

Experimental Section

Aldehyde (0.5 mmol) was added to a suspension of [Ru(TTP)(CO)] (0.05 mmol) and PhI=NTs (1 mmol) in CH_2Cl_2 (2 mL) under a gaseous N_2 atmosphere. The reaction was stirred at room temperature for 30 min, after which the mixture was evaporated to dryness and purified by silica gel column chromatography (*n*-hexanes/EtOAc = 4:1 as eluent).

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Note: Structures **2o–q**, Table 2, corrected since publication in *Angewandte Chemie* Early View. The Editor.

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[12] a) H_2(TTP) = *meso*-tetrakis(*p*-tolyl)porphyrin; b) $H_2(F_{20}$-TPP) = *meso*-tetrakis(pentafluorophenyl)porphyrin.

[13] A similar mechanism has been proposed for the analogous metal-mediated amidations of C(sp^3)–H bonds, see references [6–8].

[14] For spectroscopic evidence for the formation of bis(imido)ruthenium(VI) complexes, see reference [7].

