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α-Amidation of Cyclic Ethers Catalyzed by Simple Copper Salt and a Mild and Efficient Preparation Method for α,ϖ-Amino Alcohols

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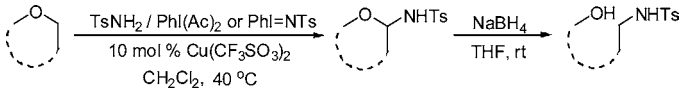
ABSTRACT



Copper(II) trifluoromethanesulfonate catalyzed the amidation of cyclic ethers with iminoiodanes under mild conditions (CH_2Cl_2, 40 °C) with good yields (up to 86% based on 97% conversion) and selectivity (only α-amino products were found). Subsequently, the tosylamidated products could undergo a reductive ring-opening reaction to give α,ϖ-amino alcohols.

Nitrene insertion into C−H bonds catalyzed by transition metal complexes is an attractive methodology for the construction of C−N bonds and many interesting organic molecules.[1−5] Such reactions could play a key role in the preparation of many natural products and pharmacologically active compounds.[6]

Although a series of studies on catalyzed inter- or intramolecular amidation reactions of saturated C−H bonds by ruthenium prophyrin have demonstrated that the method could effectively promote the formation of carbon−nitrogen bonds in alkanes and alkyl aromatics, the amidation reactions of cyclic ethers are sparse in the literature.[7] Recently, Albone and co-workers found that copper(I) chloride could activate the amidation reaction of ethers with chloramine-T as the nitrene source to give the desire product with moderate yields.[8] In this paper, we report the intermolecular amidation of saturated C−H bonds of cyclic ethers catalyzed by simple copper salts using $TsNH_2/PhI(OAc)_2$ or PhI═NTs as the

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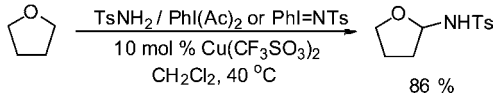
nitrene source. Moreover, the tosylamidated product could be reduced with sodium borohydride to form ω-amino alcohols, which are important compounds in organic synthesis, especially for use as potential drugs, and prepare some biologically active compounds.[9,10]

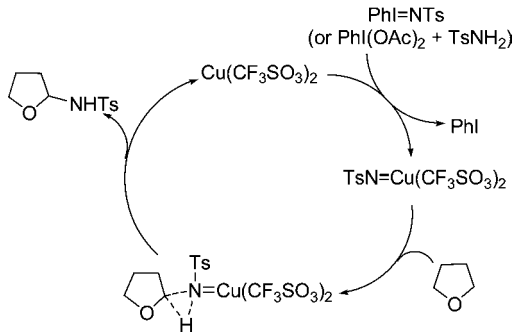
The intermolecular C−N bond formation reactions mediated by copper(II) trifluoromethanesulfonate provide a convenient access to *N*-substituted amino cyclic ethers. When using tetrahydrofuran (THF) as substrate, and with substrate: $PhI(OAc)_2$:*p*-toluenesulfonamide in the molecular ratio of 1:3:1, the product α-tosylamino tetrahydrofuran was obtained with 86% yield (Scheme 1). The reaction possibly occurred

Scheme 1



via an intermolecular nitrogen atom transfer from copper imido complexes to saturated α C−H of the cyclic ether (Scheme 2). The structure of the product was confirmed by ^{1}H NMR, ^{13}C NMR, and high-resolution MS.

Scheme 2



At the beginning of this work, in order to evaluate the catalytic efficiency of various metal complexes, the reaction of cyclic ether with $TsNH_2/PhI(OAc)_2$ or PhI═NTs was studied by using a variety of catalysts with dichloromethane as solvent. The results were shown in Table 1. It was found that only Cu(II) triflate and rhodium(II) acetate could be used as catalyst for the amidation of THF (entries 3, 7, 9, and 10).

Other metal complexes, such as CuI, Cu(II) trifluoroacetate, and several metal porphyrin complexes, displayed poor catalytic activity. As a result, we used Cu(II) triflate for the subsequent studies.

We also studied the effects of temperature, catalyst loading, and the amount of $PhI(OAc)_2$ on the intermolecular

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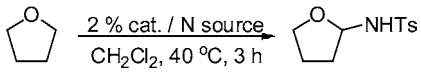
Table 1. Intermolecular Amidation Catalyzed by Various Metal Complexes

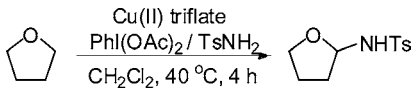


entry	nitrene Source	Catalyst	% yield[a] (conversion[b])
1	$TsNH_2/PhI(OAc)_2$	$Cu(tfac)_2$	trace (−)
2	$TsNH_2/PhI(OAc)_2$	CuI	0 (0)
3	$TsNH_2/PhI(OAc)_2$	$Cu(CF_3SO_3)_2$	21 (36)
4	$TsNH_2/PhI(OAc)_2$	Ru(TTP)(CO)	trace (−)
5	$TsNH_2/PhI(OAc)_2$	Co(TTP)(CO)	trace (−)
6	$TsNH_2/PhI(OAc)_2$	Cu(TTP)(CO)	trace (−)
7	$TsNH_2/PhI(OAc)_2$	Rh_2Ac_4	53 (57.8)
8	$TsNH_2/PhI(OAc)_2$	Mn(TTP)Cl	trace (−)
9	PhI=NTs	Rh_2Ac_4	68 (65)
10	PhI=NTs	$Cu(CF_3SO_3)_2$	33 (42)

[a] Isolated yield based on the amount of ether consumed. [b] Substrate conversion determined by GC analysis.

amidation reaction, and the results are listed in Table 2. Increasing the loading of Cu(II) triflate led to the increase of substrate conversion and product yield (entries 1−4). Excess $PhI(OAc)_2$ was found to be favorable for the product yield. When using 1.5 equiv of $PhI(OAc)_2$, the conversion was 65% (entry 4). The conversion was dramatically increased to 97% (entry 7) by adding $PhI(OAc)_2$ to 3 equiv. Temperature also affected the reaction. At lower temperature, longer reaction time was needed to achieve similar yield (entry 6). A further increase of temperature (65 °C) led to the decrease of reaction yield (entries 9 and 10). Otherwise, the bases, such as Al_2O_3, were found to be helpful for the amidation reactions.

Table 2. Optimization of Reaction Conditions[a]

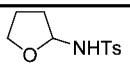
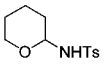
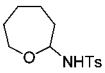
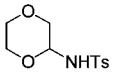
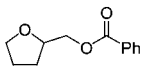
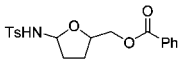
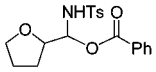
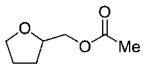
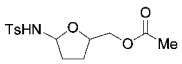
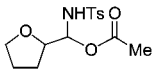
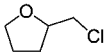
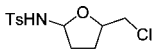
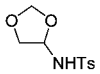
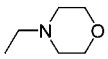
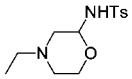
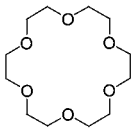
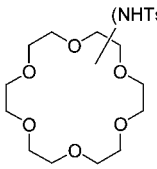
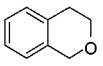
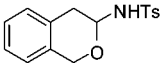


entry	temp (°C)	mol ratio of $TsNH_2/PhI(OAc)_2$	catalyst loading (mol %)	% yield[b] (conversion[c])
1	40	1:1.5	0	0
2	40	1:1.5	2	~20 (36)
3	40	1:1.5	5	70 (59)
4	40	1:1.5	10	88 (65)
5	25	1:1.5	10	85 (68)
6	25	1:3.0	10	86 (95)[d]
7	40	1:3.0	10	86 (97)
8	40	1:3.0	5	84 (57)
9[e]	65	1:1.5	10	30 (70)
10[e]	65	1:3.0	10	32

[a] Mole ratio of THF:catalyst:$TsNH_2$ was 1:0.1:1. [b] Isolated yield based on the amount of ether consumed. [c] Substrate conversion determined by GC analysis. [d] Reaction time was 10 h. [e] Reactions were performed in $ClCH_2CH_2Cl$.

To test the generality of the catalytic system, we applied several cyclic ethers to the amidation reaction. Almost all substrates could give their corresponding product with good yields, and the amino groups were always added to the α-position of the substrate (Table 3). For α-alkyl-

Table 3. Intermolecular Amidation of Saturated C−H Bonds Catalyzed by $Cu(CF_3SO_3)_2$[a]

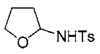
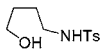
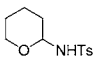
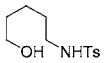
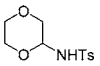
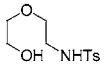
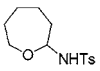
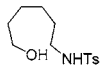
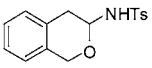
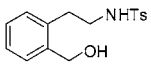
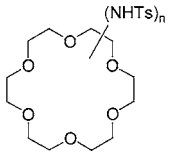
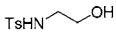
Entry	Substrate	Product	% Yield[b] (Conversion[c])
1			86 (97)
2			85 (98)
3			87 (99)
4			81 (89)
5			45 (94)
			35
6			40 (83)
			30
7			42 (85)
8			30
9			52 (64)
10			~80[d] (-)
11			70 (99)

[a] Reactions were performed in CH_2Cl_2 at 40 °C for 4 h with a catalyst/substrate/$TsNH_2$/$PhI(OAc)_2$ ratio of 0.1:1:1:3. [b] Isolated yield based on the amount of ether consumed. [c] Substrate conversion determined by GC annlysis. [d] $n = 4, 6$. Reaction was performed in CH_2Cl_2 at 40 °C for 4 h with a catalyst/substrate/$TsNH_2$/$PhI(OAc)_2$ ratio of 0.1:1:10:30.

carbonyloxymethyl THF, two amidation products were found, and the products with an amino group on the cycle were found to be the major product (entries 5and 6). For 1, 3-dioxolane and morpholine derivatives, only moderate yields were obtained (entries 8 and 9). From these results we could conclude that this method could provide a convenient and efficient method for the preparation of 2-*N*-substituented cyclic ether with commercially available reagents.

α-Amino cyclic ethers can undergo a reductive ring-opening reaction with use of sodium borohydride. The products are α,ω-amino alcohols, which can be used as intermediates in the synthesis of some biologically active compounds. Thus we used the products of the intermolecular amidation for the reductive ring-opening reactions. The results demonstrated that a series of 2-tosylamino cyclic ethers could readily be reduced to give the corresponding amino alcohol products, which were shown in Table 4. All

Table 4. Reductive Ring-Opening Reactions of 2-Tosylamino Cyclic Ethers[a]

Entry	Substrate	Product	% Yield[b]
1			94
2			92
3			84
4			93
5			90
6[c]			41

[a] Reactions were performed in THF at 25 °C for 2−4 h with $NaBH_4$ as reducing agent. [b] Isolated yields. [c] $n = 4, 6$.

ring-opening products could be obtained with excellent yields (entries 1−5) except the crown ether derivative (entry 6). The reason for the low yield of the reaction was due to tosylamino-18-crown-6 contamination of the reactant. In the amidation reaction of 18-crown-6, mono- and multi-tosyl-amino products could be formed and they were difficult to separate.

In summary, we introduced a facile and efficient preparation method of 2-tosylamino cyclic ethers and α,ϖ-amino alcohols. Copper(II) triflate could catalyze the intermolecular amidation of cyclic ethers under mild condition. The reaction proceeded in a highly selective manner, generating exclusively the α-amidation product. Subsequent reductive ring-opening reaction by $NaBH_4$ could give α,ϖ-amino alcohols, which could be important intermediates in the synthesis of some biologically active compounds.

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Supporting Information Available: Detailed experimental procedures and characterization data of central compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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