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Dehydrogenative Amide Synthesis: Azide as a Nitrogen Source

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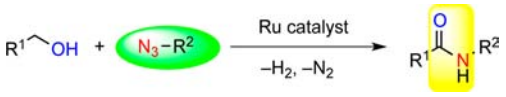
ABSTRACT



A new atom-economical strategy to amide linkage from an azide and alcohol liberating hydrogen and nitrogen was developed with an in situ generated ruthenium catalytic system. The reaction has broad substrate generality including diols for the synthesis of cyclic imides.

Atom-economical amide synthesis is one of the top challenges in synthetic organic chemistry.[1] The amide bond is the key backbone of all natural peptides in biological systems and is also a favorable functional group in all branches of organic chemistry.[2] Traditionally, amides have been synthesized by reactions of carboxylic acids and their derivatives with amines,[3] which suffers from harsh conditions and a large amount of byproduct. Over the past few years, chemists have extensively addressed new methodologies to amide linkage, aiming at a more efficient and environmentally benign pathway. Interesting approaches include native chemical ligation;[4] oxidative amidation of alcohols,[5,9] aldehydes,[6] or alkynes;[7] and oxidative coupling of an α-bromonitroalkane[8] (Scheme 1). All these systems utilize amine, mostly primary amine, as an "N" atom source of amide.

During our studies on the atom-economical and environmentally benign amidation from an alcohol with an amine prompted by a ruthenium catalytic system,[9] we envisioned that amidation of alcohols could be achieved with azides in place of amines. Herein, we report an in situ generated catalyst based on $RuH_2(PPh_3)_4$ for the direct amide synthesis from azide and alcohol. To the best of our knowledge, this is the first example of a transition-metal-based catalytic system that transforms an azide and alcohol directly into an amide in a single step.

The reaction of 2-phenylethanol (**1a**) and benzyl azide (**2a**) was chosen to investigate the catalytic conditions to realize the amidation of an alcohol with an azide (Table 1).

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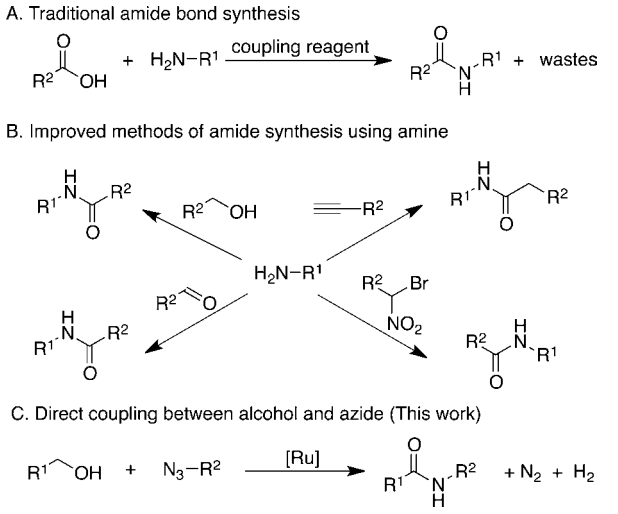
Scheme 1. Different Strategies of Amide Synthesis

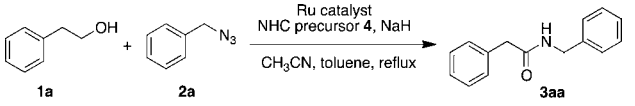


A series of ruthenium complexes with the help of the *N*-heterocyclic carbene (NHC) ligand generated from 1,3-diisopropylimidazolium bromide (**4**) and NaH, well-known catalysts for the oxidative amide synthesis from alcohols,[9] were selected as the precatalyst complexes. The role of NaH has been suggested to activate the precatalyst as well as to generate the NHC ligand from **4**.[9] The $[Ru(benzene)Cl_2]_2$-based catalyst did not exhibit any activity for the target reaction (Table 1, entry 1). A trace amount of amide was detected with catalytic systems using $[Ru(p\text{-cymene})Cl_2]_2$, $RuCl_3$, and Shvo's complex (Table 1, entries 2−4). Then we noticed that several ruthenium hydride complexes exhibited improved activities (Table 1, entries 5−7). Among them, $RuH_2(PPh_3)_4$ displayed the best activity for this transformation. The desired amide product **3aa** was obtained in 33% yield for 24 h (Table 1, entry 7). When the reaction time was prolonged to 48 h, the yield of amide **3aa** reached up to 73% (Table 1, entry 8). The reaction efficiency was sensitive to the ratio of azide and alcohol. We found that the reaction with a slightly higher amount of alcohol **1a** than that of **2a** (**2a:1a** = 1:1.2) provided the amide product **3aa** in quantitative GC yield and 92% isolated yield (Table 1, entry 12).

With the optimized conditions in hand, we examined the generality of this protocol. First, the feasibility of this method was evaluated by the reaction of benzyl azide with a range of alcohols (Table 2). Benzyl alcohol generated the corresponding amide with an excellent yield of 94%, and aliphatic alcohols also showed excellent activity (entries 1−3). Sterically hindered alcohols led to formation of the corresponding amides with lowered yields (entries 4 and 5). 2-Furanmethanol (**1f**) also provided the amide **3fa** in 80% yield (entry 6). When using 5-hexen-1-ol as a starting material, the reduction of the unsaturated double bond in the alcohol occurred with the formation of the corresponding amide in 73% yield (entry 7).

One of the most significant uses of azide is in the [3 + 2] cycloaddition reaction with alkyne.[10] To investigate the

Table 1. Catalyst Screening[a]



entry	**2a/1a**	[Ru]	time (h)	yield (%)[b]
1	1.1	$[Ru(benzene)Cl_2]_2$	24	0
2	1.1	$[Ru(p\text{-cymene})Cl_2]_2$	24	<5
3	1.1	$RuCl_3$	24	<5
4	1.1	Shvo's complex[c]	24	<5
5	1.1	$RuH_2(CO)(PPh_3)_3$	24	23
6	1.1	$RuHCl(CO)(PPh_3)_3$	24	29
7	1.1	$RuH_2(PPh_3)_4$	24	33
8	1.1	$RuH_2(PPh_3)_4$	48	73
9	1.5	$RuH_2(PPh_3)_4$	48	78
10	2.0	$RuH_2(PPh_3)_4$	48	84
11	1:1.1	$RuH_2(PPh_3)_4$	48	76
12	1:1.2	$RuH_2(PPh_3)_4$	48	100

[a] Reaction conditions: **2a** (0.5 mmol scale), **1a**, Ru complex (5 mol %), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. [b] Yields were determined by GC using dodecane as an internal standard. [c] Shvo's complex = (1-hydroxytetraphenyl cyclopentadienyl-(tetraphenyl-2,4-cyclopentadien-1-one)-μ-hydrotetracarbonyldiruthenium(II)

chemoselectivity of our catalytic system, we chose the reaction with an alcohol possessing an alkyne functional group. When 5-hexyn-1-ol and benzyl azide were employed, the corresponding amide **3ca** was obtained in 27% yield along with 1,4-disubstituted 1,2,3-triazole compound **3ha** (entry 8).[11]

Next, another noticeable result was obtained, based on our recent work including efficient synthesis of cyclic imides from amines and diols under the same catalytic system.[12] Various cyclic imides were synthesized from benzyl azide and diols in 40% to 75% yields (entries 9−12). Syntheses of five-membered succinimides (entries 9 and 11), a six-membered glutarimide (entry 10), and a phthalimide derivative (entry 12) were demonstrated.

The scope of azide components was expanded using 2-phenylethanol (Table 3). Both electron-donating and -withdrawing substituents on the aromatic ring furnished the corresponding amides with good to excellent yields (entries 2−4). The electron-withdrawing fluoro group led to a reduced yield of **3ad** (entry 4). Sterically hindered azides also generated the corresponding amides in moderate yields (entries 7 and 8). Aromatic azides such as phenyl azide gave the amide in a significantly low yield of 22% (entry 9). Sensitivity to sterics and *N*-nucleophilicity have

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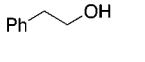
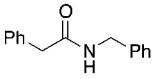
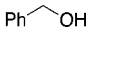
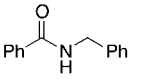
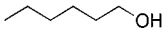
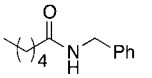
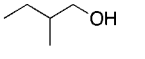
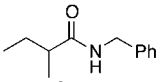
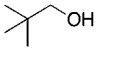
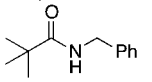
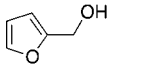
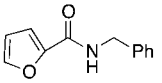
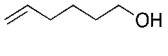
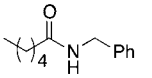
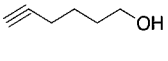
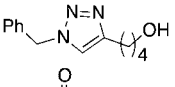
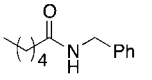
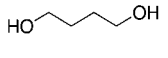
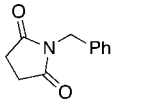
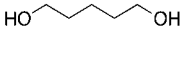
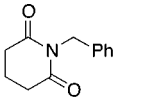
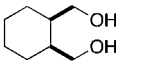
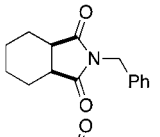
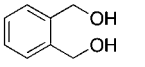
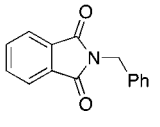
Table 2. Synthesis of Amide and Imides from Benzyl Azide **2a** and Alcohols[a]

entry	alcohol		product[b]		yield (%)[b]
1		**1a**		**3aa**	92
2		**1b**		**3ba**	94
3		**1c**		**3ca**	90
4		**1d**		**3da**	76
5		**1e**		**3ea**	49[c]
6		**1f**		**3fa**	80
7		**1g**		**3ca**	73
8		**1h**		**3ha**	35
				**3ca**	27
9		**1i**		**3ia**	75
10		**1j**		**3ja**	40
11		**1k**		**3ka**	67[d]
12		**1l**		**3la**	52[d]

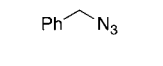
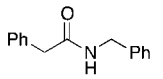
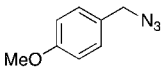
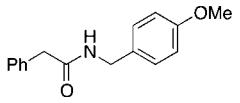
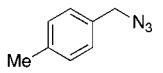
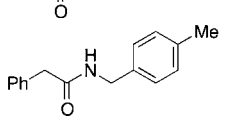
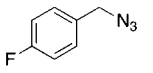
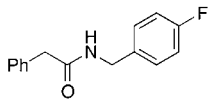
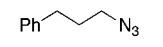
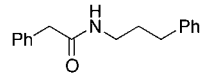
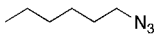
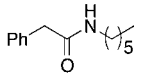
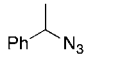
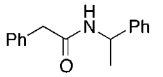
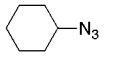
[a] Reaction conditions: **2a** (0.5 mmol, 1.0 equiv), alcohol (1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. [b] Yields are of the isolated product and represent the average of at least two runs. [c] NaH (40 mol %), toluene (0.3 mL). [d] Toluene (0.3 mL).

been also well reported in the direct amidation from alcohols and amines.[5,9]

Considering the importance of isotope labeled peptides and proteins in medical and biological studies,[13] we explored the utility of the reaction by performing an ^{15}N-isotope labeling experiment. The reaction of 2-phenylethanol and ^{15}N-labeled 3-phenylpropylazide under the optimized conditions gave the desired amide **3aj** in 73% yield. ^{15}N-labeled cyclohexylazide also gave the corresponding amide **3ak** in 46% yield (Scheme 2). As easily manageable ^{15}N-labeled azides are readily accessible in one step from alkyl halides and commercially available ^{15}N-labeled NaN_3, facile access to ^{15}N-labeled amides bearing various functional groups could be realized with this methodology.

Next, we investigated the mechanism of this direct amidation from an azide and alcohol. Initially, we suspected the involvement of an aza-ylide for the transformation. It has been well reported that an organoazide ligates carboxylic acid or an ester to give an amide in the presence of triphenylphosphine.[14] Therefore, we applied the same reaction conditions to (benzylimino)triphenylphosphorane **4a**, which is independently prepared by the Staudinger reaction of benzyl azide and triphenylphosphine, with 2-phenylethanol. However, no reaction occurred. This result excluded the possibility of aza-ylide involvement in the reaction.

Table 3. Synthesis of Amide from 2-Phenylethanol **1a**[a]

entry	azide		product		yield (%)[b]
1		**2a**		**3aa**	92
2		**2b**		**3ab**	94
3		**2c**		**3ac**	90
4		**2d**		**3ad**	77
5		**2e**		**3ae**	90
6		**2f**		**3af**	92
7		**2g**		**3ag**	54[c]
8		**2h**		**3ah**	61
9		**2i**		**3ai**	22[d]

[a] Reaction conditions: Azide (0.5 mmol, 1.0 equiv), **1a** (1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.6 mL), reflux, 48 h. [b] Yields are of the isolated product and represent the average of at least two runs. [c] NaH (40 mol %), toluene (0.3 mL). [d] Mesitylene (0.6 mL) at reflux.

(13) (a) Baillie, T. A. *Pharmacol. Rev.* **1981**, *33*, 81. (b) Baillie, T. A.; Rettenmeier, A. W. *J. Clin. Pharmacol.* **1986**, *26*, 481. (c) Mutlib, A. E. *Chem. Res. Toxicol.* **2008**, *21*, 1672. (d) Pregosin, P. S.; Randall, E. W.; White, A. I. *J. Chem. Soc., Perkin Trans. 2* **1972**, 513. (e) Ruck, R. T.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5375. (f) Kelly, N. M.; Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **1997**, *14*, 205. (g) Lankiewicz, L.; Grehn, L.; Ragnarsson, U. *J. Label. Compd. Radiopharm.* **1993**, *33*, 551.

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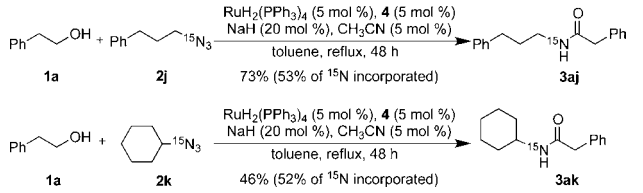
Scheme 2. Isotope Labeling Study



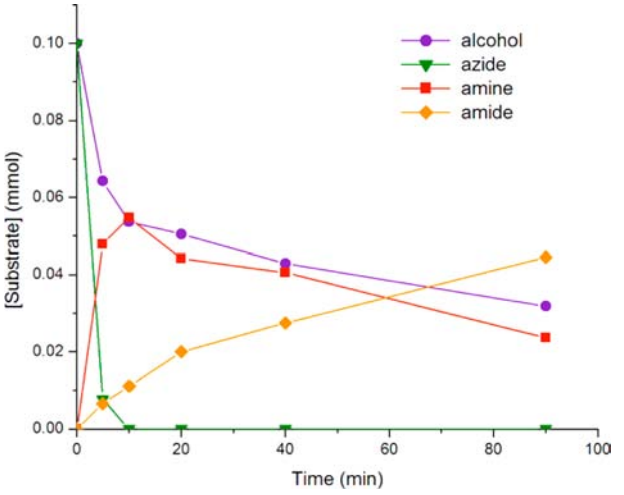
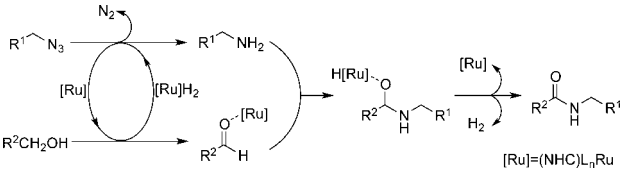


Figure 1. Reaction profiles showing the changes in amount of substrate and product. Azide (**2b**, 0.10 mmol, 1.0 equiv), alcohol (**1a**, 1.2 equiv), $RuH_2(PPh_3)_4$ (5 mol %), **4** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), toluene (0.12 mL), reflux. Average of three runs. The reaction progress was monitored by GC.

Kinetic studies, performed by monitoring the reaction progress between 2-phenylethanol (**1a**) and *p*-methoxybenzyl azide (**2b**), gave a conclusive idea regarding the mechanism (Figure 1). At the very initial stage of the reaction, *p*-methoxybenzyl amine (**5b**) was detected along with the rapid consumption of **2b**. The concentration of **5b** was slowly decreased while that of amide **3ab** increased. These results strongly led us to conclude the reaction mechanism shown in Scheme 3. First, an azide was mainly reduced to an amine by hydrogen transferred from alcohol dehydrogenation. The reason why the reaction proceeded better with a slightly higher amount of alcohols could be related to the increased transfer hydrogenation efficiency by providing an increased amount of hydrogen. The next steps followed the same reaction mechanism suggested in the oxidative amide synthesis from an alcohol and amine.[5,9] The generated aldehyde intermediate was subsequently attacked by the amine to form the hemiaminal intermediate. Finally, further dehydrogenation of the hemiaminal gave the amide product.

Scheme 3. Proposed Mechanism of Amide Synthesis Directly from Azide and Alcohol



In conclusion, we have demonstrated for the first time that direct amide synthesis from an azide and alcohol is possible. This fundamental but important transformation allows atom economical and direct synthesis of amide bond producing hydrogen and nitrogen gas as the sole byproducts. The reaction has broad substrate generality including diols for the synthesis of cyclic imides. In addition, ^{15}N-labeled amides could be prepared in one step using readily available ^{15}N-labeled azides and alcohols. This expansion of the N-source for the atom-economical amide syntheses will be a step forward toward achieving environmentally benign amide synthesis.

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Supporting Information Available. Details of experimental procedure and characterization data. This material is free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.