

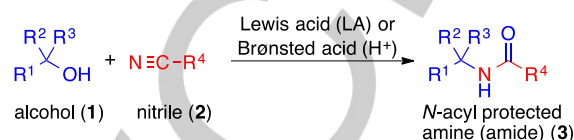
# Environmentally Benign Ritter Reaction Using Bismuth Salts as a Catalyst

Masaharu Ueno,\* Ryo Kusaka, Satoshi D. Ohmura and Norikazu Miyoshi

**Abstract:** We developed an environmentally benign Ritter reaction of alcohols with nitriles using a commercially available bismuth salt as a less harmful catalyst. The detailed reaction profiles revealed that consumption of the ether by-product as the reaction proceeded was the key for optimizing this reaction, and the yield of the target amide was improved by adding a small amount of water. This finding clearly reveals the significance of using a bismuth salt as the catalyst, as it is not deactivated in the presence of water. This catalyst system has a broad substrate scope, and even with 1 mol% of the catalyst, the reaction progresses smoothly. It is also possible to react stoichiometric amounts of nitriles and alcohols, thus reducing the amount of organic solvent required for the reaction. Furthermore, as the inexpensive bismuth catalyst can be easily removed using aqueous hydrochloric acid, a purification process that only required washing and drying without any organic solvents was successfully established.

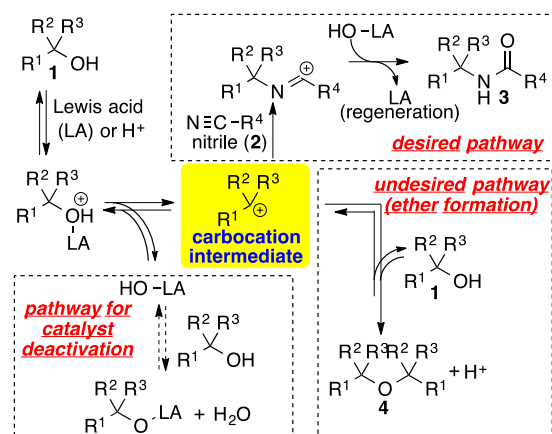
The Ritter reaction is one of the useful synthetic methods for preparing *N*-acyl-protected amines, which are ubiquitous functional groups in various natural and synthetic materials, from alcohols or alkenes and nitriles (Scheme 1).<sup>[1-3]</sup> As the reaction mechanism is proposed to involve a carbocation intermediate, this reaction is useful for synthesising bulky amines. However, a general drawback of the classical Ritter reaction is that at least stoichiometric amounts of a strong Brønsted acid (i.e. conc. H<sub>2</sub>SO<sub>4</sub>) or Lewis acid under harsh conditions are required.<sup>[4]</sup> To overcome this problem, several catalytic systems have been developed recently.<sup>[5-8]</sup> Akhlaghinia *et al.* reported an Al(HSO<sub>4</sub>)<sub>3</sub>-catalysed Ritter reaction,<sup>[6]</sup> however, this catalyst is not commercially available (it must be prepared from aluminium chloride and sulfuric acid) and the reaction generally requires 50 mol% of the catalyst. Sadeghi *et al.* reported an inexpensive and less harmful salt, KAl(SO<sub>4</sub>)<sub>2</sub>·12H<sub>2</sub>O (alum), as a catalyst.<sup>[7]</sup> Although this reaction was conducted under neat conditions without a solvent, the amount of catalyst required was still high (21 mol%). From a 'green chemistry' perspective, a more environmentally friendly and inexpensive catalyst is required for this reaction. Additionally, as the catalyst must be removed from the reaction system, it is desirable that no organic solvents are used during any operation, including the work-up and purification processes.

When using an alcohol as a starting material for the Ritter reaction, it is necessary to solve two main problems (Scheme 2).



**Scheme 1.** The Ritter reaction.

The first is the possibility of deactivating the Lewis acid via the formation of an alcoholate. At the same time, as a by-product of alcoholate formation, equimolar amounts of water are generated that can deactivate the Lewis acid by acting as a Lewis base.<sup>[9]</sup> The second is that dehydration of the substrate can proceed, especially in highly concentrated solutions, to give ethers via a self-coupling reaction. We hypothesised that these problems would be solved by using bismuth salts as environmentally benign and less harmful catalysts for the Ritter reaction, as these salts are known to behave as water-compatible Lewis acids.<sup>[10,11]</sup> Focusing on these points, our laboratory has already reported the reductive etherification of carbonyl compounds with alcohols,<sup>[12]</sup> asymmetric Strecker reactions,<sup>[13]</sup> allylation reactions,<sup>[13b]</sup> aldol reactions,<sup>[14]</sup> and Michael reactions<sup>[14]</sup> using bismuth salts as a catalyst. Barrett *et al.* screened several metal triflates for the catalytic Ritter reaction in water.<sup>[6]</sup> Although Bi(OTf)<sub>3</sub> was found to exhibit the best performance, 20 mol% of the catalyst was still required. In this paper, we report the Ritter reaction of alcohols with nitriles using bismuth salts as a catalyst. With this reaction system, we improved the catalyst turnover number to 84. Moreover, we succeeded in obtaining pure *N*-acyl-protected amines in high yields without using any organic solvents, not only in the reaction system but also during the work-up procedure.



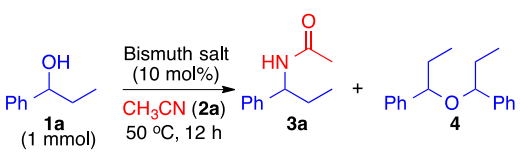
**Scheme 2.** Proposed mechanism for the Ritter reaction.

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First, we tested the Ritter reaction of 1-phenyl-1-propanol **1a** with acetonitrile as a solvent in the presence of 10 mol% bismuth salts at 50 °C (Table 1). Among the nine bismuth salts tested, we found that BiBr<sub>3</sub> exhibited catalytic activity for the model reaction, providing desired product **3a** in 21% yield (entry 8). However, as expected, dehydrated ether compound **4** was also formed (22% yield).

**Table 1.** Screening of bismuth salts as catalysts for a model Ritter reaction



Entry	Bismuth salt	Yield / % <sup>[a]</sup>	
		<b>3a</b>	<b>4</b>
1	Bi(NO <sub>3</sub> ) <sub>3</sub> ·5H <sub>2</sub> O	16	7
2	Bi <sub>2</sub> (SO <sub>3</sub> ) <sub>3</sub>	18	8
3	Bi(OH) <sub>3</sub>	NR	NR
4	Bi <sub>2</sub> O <sub>3</sub>	NR	NR
5	BiOCl	NR	NR
6	BiF <sub>3</sub>	NR	NR
7	BiCl <sub>3</sub>	19	19
8	BiBr <sub>3</sub>	21	22
9	BiI <sub>3</sub>	4	4

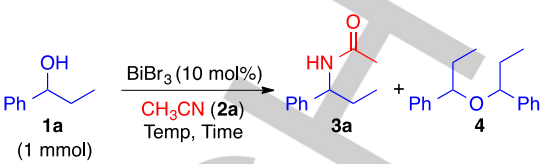
[a] Yield was determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard. NR: no reaction.

As the ether cleavage reaction might proceed under high temperature conditions in the presence of a Lewis acid, we continued to search for optimal conditions (Table 2). No improvement was achieved when the reaction time was simply prolonged (entry 2); thus, we elevated the reaction temperature. At higher temperatures, we found that not only the yield of the amide increased, but also, the yield of the ether product decreased (entries 3–5). Furthermore, we suspected that the ether compound was consumed via transformation into the amide when the reaction time was prolonged at temperatures above 90 °C (entry 5).

To clarify the temperature-dependence of the consumption of the ether and its concomitant conversion to the amide product, reaction profiles were obtained at 50 and 90 °C (Figure 1). At 50 °C, both the amide and ether were obtained as the starting material was consumed; however, after 6 h, the formation of the amide by the Ritter reaction continued to proceed gradually with almost no change in the ether compound yield. In contrast, at 90 °C, although the rate of amide formation was higher, the ether compound was preferentially afforded until 6 h. Further, the amide formation rate corresponded to the consumption rate

of the ether. In general, the ether cleavage reaction is very difficult to proceed as compared with the ether formation

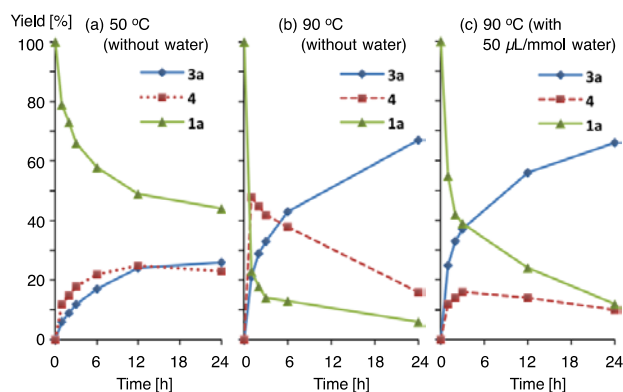
**Table 2.** Effect of temperature and reaction time on a model Ritter reaction



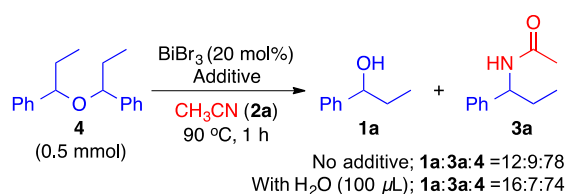
Entry	Temp./°C <sup>[a]</sup>	Time / h	Yield / % <sup>[b]</sup>	
			<b>3a</b>	<b>4</b>
1	50	12	21	22
2	50	24	26	23
3	90	24	67	16
4	120	24	72	14
5	120	48	75	11

[a] Bath temperature. [b] Yield was determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard.

reaction because the by-product of the ether formation reaction is water, which deactivates the Lewis acid. Therefore, the formation of ether causes the dead-end path of the catalyst, and the method in which ether is not produced is important for development of conventional Ritter reaction. On the other hand, bismuth salts can afford the amide product even with simultaneous ether formation. When the reaction profile was confirmed under the condition of adding 50 μL/mmol of water, there was almost no difference in the production rates of the amide product **3a**. However, it was found to be effectively suppress the formation of the ether compound in the initial stage (Figure 1c). We also performed the Ritter reaction of the ether product both with and without water at 90 °C (Scheme 3). The ether product **4** was converted to the amide product **3a** and the starting alcohol **1a** at almost the same conversion rate with and without water, respectively. However, the conversion rate of **1a** to **3a** is faster than that of **4** to **3a**. Therefore, suppression of the formation of the ether product by adding water promotes the completion of the Ritter reaction. We think that this is one of the attractive features of bismuth salts as catalysts.



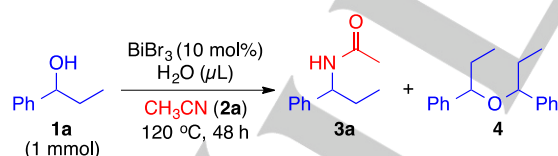
**Figure 1.** Reaction profiles at 50 and 90 °C (without or with water). The yields were determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard.



**Scheme 3.** Initial ratio of the Ritter reaction of the ether product **4** with and without water. The yields were determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard.

As bismuth salts act as a catalyst without decomposition in water, the further effect of accelerating the decomposition of the ether compound was investigated by adding water (Table 3). As expected, an improvement in the yield was observed with the addition of water (entries 1–3), but the presence of excess water tended to inhibit the reactivity (entry 4). Finally, by reducing the reaction concentration, we succeeded in obtaining the desired amide in 90% yield (entry 5).

**Table 3.** Effect of water and concentration on a model Ritter reaction

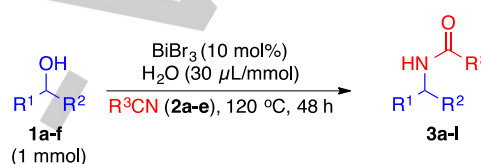


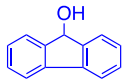
Entry	H <sub>2</sub> O / μL	Concentration / M	Yield / % <sup>[a]</sup>	
			3a	4
1	0	0.5	75	11
2	30 (16.7 eq.) <sup>[b]</sup>	0.5	88	8
3	50 (27.8 eq.) <sup>[b]</sup>	0.5	82	8
4	100 (55.6 eq.) <sup>[b]</sup>	0.5	70	11
5	30 (16.7 eq.) <sup>[b]</sup>	0.2	90	5

[a] Yield was determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard. [b] Equivalents of water relative to BiBr<sub>3</sub> in the parenthesis.

Under the optimized conditions, we screened the substrate scope of the Ritter reaction of several secondary alcohols with nitriles to prepare the corresponding *N*-acyl protected amines (Table 4). The reaction proceeded smoothly even in the presence of 10 mol% BiBr<sub>3</sub> as a catalyst. To improve the catalyst activity, we reduced the amount of the catalyst for the model reaction (entry 13, 14). Even if the catalyst amount was reduced to 1 mol%, the reaction progressed without deactivating the catalyst, and it was possible to achieve a very high catalyst turnover number as a Ritter reaction using alcohol as a starting material.<sup>15</sup>

**Table 4.** Substrate scope of the Ritter reaction under optimised conditions

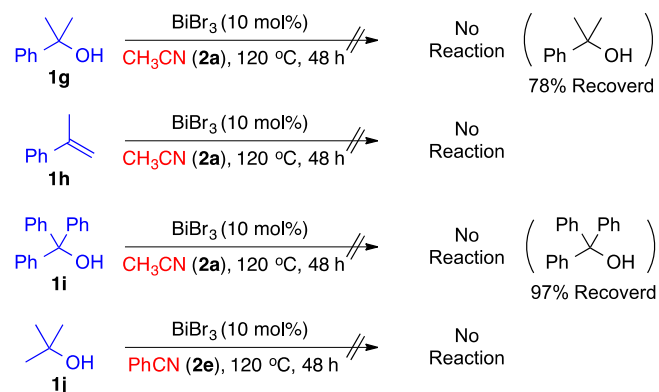


Entry	Alcohol (R <sup>1</sup> , R <sup>2</sup> )	Nitrile (R <sup>3</sup> )	Yield [%] <sup>a</sup>
1	R <sup>1</sup> = Ph, R <sup>2</sup> = Et ( <b>1a</b> )	Me ( <b>2a</b> )	90 ( <b>3a</b> )
2	<b>1a</b>	Et ( <b>2b</b> )	92 ( <b>3b</b> )
3	<b>1a</b>	Pr ( <b>2c</b> )	92 ( <b>3c</b> )
4	<b>1a</b>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub> ( <b>2d</b> )	72 ( <b>3d</b> )
5	R <sup>1</sup> = (4-Cl)-C <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = Et ( <b>1b</b> )	<b>2a</b>	82 ( <b>3e</b> )
6	R <sup>1</sup> = (4-CH <sub>3</sub> )-C <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = Et ( <b>1c</b> )	<b>2a</b>	54 ( <b>3f</b> )
7	R <sup>1</sup> = Ph, R <sup>2</sup> = Me ( <b>1d</b> )	<b>2a</b>	86 ( <b>3g</b> )
8	R <sup>1</sup> = Ph, R <sup>2</sup> = Ph ( <b>1e</b> )	<b>2a</b>	95 ( <b>3h</b> )
9	<b>1e</b>	<b>2b</b>	96 ( <b>3i</b> )
10	<b>1e</b>	Ph ( <b>2e</b> )	93 ( <b>3j</b> )
11	 ( <b>1f</b> )	<b>2a</b>	99 ( <b>3k</b> )
12	<b>1f</b>	<b>2b</b>	92 ( <b>3l</b> )
13 <sup>[b]</sup>	<b>1a</b>	<b>2a</b>	97 ( <b>3a</b> )
14 <sup>[c]</sup>	<b>1a</b>	<b>2a</b>	84 ( <b>3a</b> )

[a] Yield was determined by <sup>1</sup>H-NMR analysis using 4,4'-di-*tert*-butyl-1,1'-biphenyl as a standard. [b] 5 mol% BiBr<sub>3</sub> was used for 72 h. [c] 1 mol% BiBr<sub>3</sub> was used for 1 week.

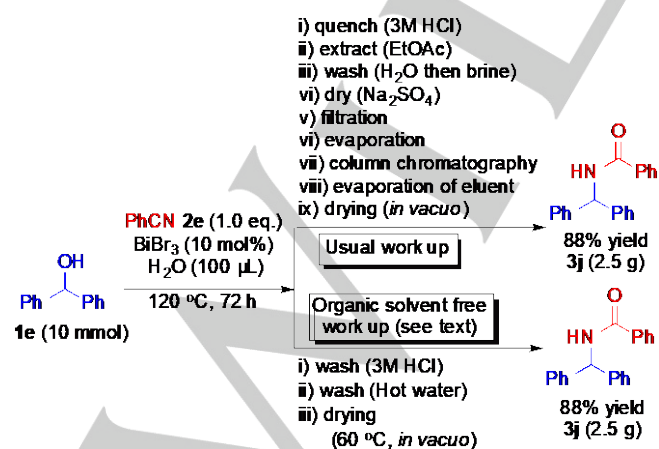
Ritter reaction with tertiary alcohols and styrene as starting materials did not proceed due to the unique features of BiBr<sub>3</sub>;

therefore, the desired amides were obtained only with secondary alcohols (Scheme 3). This is considered one of the characteristic points of  $\text{BiBr}_3$ , which has not too strong Lewis acidity and large molecular radius. Interestingly, this functional group selectivity, i.e. only the secondary alcohol undergoes the Ritter reaction, is not found when other catalysts, including  $\text{Bi}(\text{OTf})_3$ , are used.



**Scheme 4.** Attempted  $\text{BiBr}_3$ -catalysed Ritter reactions of tertiary alcohols and  $\alpha$ -methyl styrene.

Finally, as  $\text{BiBr}_3$  showed high reactivity as the catalyst, we tried reducing the nitrile used as the solvent to the stoichiometric amount (Scheme 5). From the viewpoint of mass production, it is desirable that excess amounts of a reagent are not used as a solvent. However, because the amide product can also behave as a Lewis base, it can suppress the reaction, especially at high concentration. Therefore, we conducted experiments to demonstrate the capability of the Lewis-acidic bismuth catalyst in the gram-scale synthesis of amides at high concentration. When only 1 equivalent of nitrile, without any excess as a solvent, and a small amount (10  $\mu\text{L}$ /mmol) of water were used, it was necessary to prolong the reaction time. After completion of the reaction, the usual work-up was performed, and the desired amide was successfully obtained in 88% yield.



**Scheme 5.** Gram-scale synthesis via an organic-solvent-free process

Although this procedure successfully reduced the amount of organic solvent used in the reaction stage, we obtained the desired amide in 88% yield after a conventional work-up on laboratory scale that involved many steps (namely, quenching the reaction, extraction, drying with a desiccant, removal of the desiccant by filtration, concentration, column purification, concentration of the eluent, and drying *in vacuo*) and generated large amounts of organic solvent waste (Scheme 5, upper route). As a truly effective green chemistry approach, a simple purification method that did not use organic solvents was examined. After completion of the reaction, in addition to the desired product, the reaction vessel contains a small amount of unreacted nitrile, the catalyst residue, and the ether by-product. Thus, we considered whether these materials could be removed by washing. It was found that the nitrile and bismuth salt could be removed by washing with 3 M hydrochloric acid aqueous solution, whereas the ether compound could be removed by washing with hot water (90  $^{\circ}\text{C}$ ). After washing, the residual material was dried in an oven under reduced pressure to obtain the target amide in the same yield as by purification via the conventional procedure (Scheme 5, bottom route). This procedure is important from the viewpoint of green chemistry, as it allows the product produced on gram scale to be purified in a small number of steps by simple washing and drying without organic solvents or silica gel.

## Experimental Section

### General procedure for substrate scope of the Ritter reaction (Table 4)

To the 10 mL reaction tube with stirring bar, bismuth bromide (44.9 mg, 0.1 mmol), alcohols (**1**) (1.0 mmol) in nitriles (**2**) (5.0 mL), and deionized water (30  $\mu\text{L}$ ) were added then heated at 120  $^{\circ}\text{C}$  for 48 h. The reaction mixture was quenched by 3M HCl aqueous solution (3.0 mL) after cooling, then organic materials were extracted with ethyl acetate (10 mL) three times, and the combined organic layers were washed successively with water, brine, respectively and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane / ethyl acetate then warmed methanol) to give the corresponding amide (**3**).

## Acknowledgements

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**Keywords:** Ritter reaction • Bismuth • Lewis acids • Organic solvent free process • Catalyst

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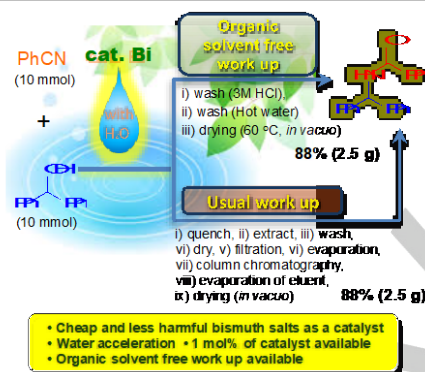
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## COMMUNICATION

We developed the environmentally benign Ritter reaction using commercially available, less harmful bismuth salt as a catalyst. The reaction proceeded smoothly even using stoichiometric amount of nitrile to alcohol without any solvents. We also succeeded in establishing a purification process without using any organic solvents.



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 Satoshi D. Ohmura and Norikazu  
 Miyoshi

Page No. – Page No.

Environmentally Benign Ritter  
 Reaction Using Bismuth Salts as a  
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Layout 2:

## COMMUNICATION

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Text for Table of Contents