Multicomponent Reactions

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Catalytic Three-Component Ugi Reaction**

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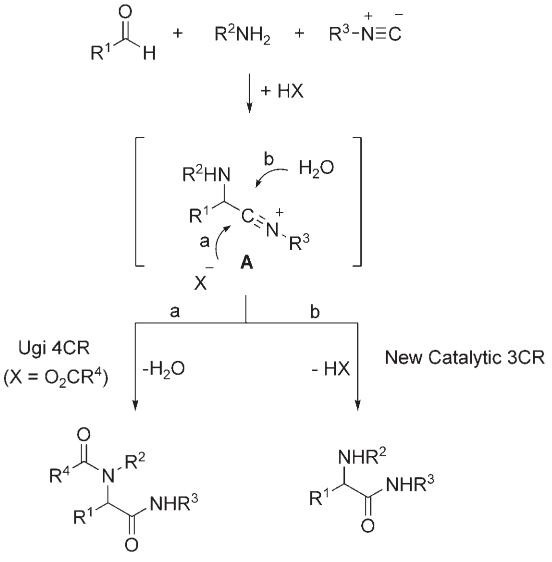
Dedicated to Professor Elias J. Corey on the occasion of his 80th birthday

Multicomponent reactions (MCRs) are one-pot processes that combine three or more substrates simultaneously.[1] Such processes are of great interest in diversity-oriented synthesis, especially to generate compound libraries for screening purposes. The Ugi four-component reaction (Ugi 4CR)[2] is one of the milestones in this field and great efforts have been devoted to the exploration of the potential of this transformation.[3] A primary amine, a carbonyl compound, a carboxylic acid, and an isocyanide react to give α-amido amides in this remarkable reaction. In recent years several modifications of the classical Ugi 4CR have been described; these include variations of one of the components or the introduction of a linkage between two of them.[4] In particular, the groups of Zhu[5] and Dömling[6] have contributed significantly to the advancement of this transformation.[7] Mechanistically, the Ugi reaction is believed to proceed via a nitrilium ion intermediate (**A**), which results from the addition of the isocyanide to an in situ generated iminium ion (Scheme 1). Nucleophilc addition of the carboxylate ion followed by Mumm rearrangement leads to the final product and water as the only by-product (Scheme 1, path a). We reasoned that it should be possible to intercept the nitrilium ion **A** not with the carboxylate ion but rather with the water molecule generated in the course of imine formation. This would require using acids (HX) other than carboxylic acids and possibly result in a catalytic cycle (Scheme 1, path b). To the best of our knowledge such a *three*-component Ugi reaction, which transforms an aldehyde, a primary amine, and an isocyanide to an α-amino amide is unknown.[8] Given the potential of these products for the synthesis of α-amino acids and their derivatives, we became interested in developing this new reaction. Here we report the first catalytic three-component Ugi reaction in which water acts as the internal nucleophile. We identified phenyl phosphinic acid (**10**) as the best catalyst for this perfectly atom-economic reaction, thus introducing a new motif for organocatalysis.



Scheme 1. Ugi 4CR and new three-component reaction.

The newly designed reaction does not proceed in the absence of catalyst. Stirring benzaldehyde (**1a**), *p*-anisidine (**2a**), and *tert*-butyl isocyanide (**3a**) at room temperature for three days in toluene resulted in no detectable quantities of the desired product (**4a**). Even heating the reaction mixture to 80 °C for 24 h did not result in the formation of product **4a**. At this point we started to investigate different Brønsted acid catalysts for this reaction (Table 1). *p*-Toluenesulfonic acid (**5**) gave no conversion to the product either at room temperature or at 80 °C (Table 1, entry 1). The desired product was obtained in poor yields when phenyl boronic acid (**6**) or diphenyl phosphate (**7**) were used as the catalysts (Table 1, entries 2 and 3). Sc(OTf)$_3$ (**8**) could also promote this reaction but with low conversion (Table 1, entry 4). Phenyl phosphonic acid (**9**) gave moderate conversion (Table 1, entry 5). Remarkably, we found phenyl phosphinic acid (**10**) to be a highly active catalyst for the reaction, giving the desired product in 95 % conversion (Table 1, entry 6),[9] whereas diphenyl phosphinic acid (**11**) and diphenyl phosphine oxide (**12**) were proved to be inactive (Table 1, entries 7 and 8). Decreasing the catalyst loading of **10** to 5 mol % resulted in considerably lower yield. Other solvents were also screened but toluene generally gave the best yields (see Supporting Information for details).

Using phenyl phosphinic acid (**10**) as the catalyst and toluene as solvent, we initiated a study to explore the scope of this new three-component reaction. First, the reaction of a variety of different aldehydes **1** with *p*-anisidine (**2a**) as the

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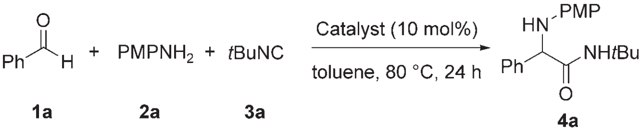
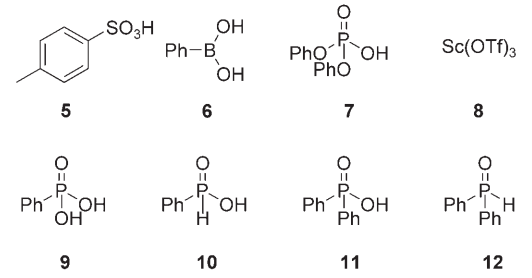
Table 1: Identification of an efficient catalyst for the three-component Ugi reaction.



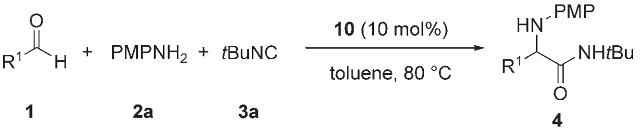


Entry	Catalyst	Conversion [%][a]
1	**5**	0
2	**6**	8
3	**7**	15
4	**8**	30
5	**9**	35
6	**10**	95
7	**11**	8
8	**12**	0

[a] Determined by gas chromatography.

amine component and *tert*-butyl isocyanide (**3a**) was examined (Table 2). The reactions took place efficiently in good yields for all the aldehydes studied. Particularly high yields were observed with aromatic aldehydes (Table 2, entries 1–5) and an α,β-unsaturated aldehyde (Table 2, entry 6). Heteroaromatic 3-pyridyl carbaldehyde can be employed in this reaction with moderate yield (Table 2, entry 7), and even aliphatic α-branched aldehydes and an α-unbranched aldehyde gave good yields (Table 2, entries 8–11).

Table 2: Catalytic three-component Ugi reaction of different aldehydes with *tert*-butyl isocyanide and *p*-anisidine.

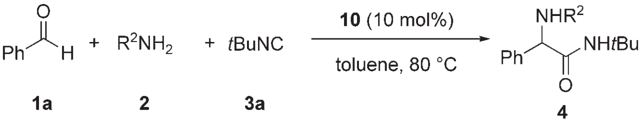


Entry[a]	R^1	Product	Time [h]	Yield [%][b]
1	Ph	**4a**	12	91
2	4-MeOC$_6$H$_4$	**4b**	12	88
3	4-ClC$_6$H$_4$	**4c**	20	78
4	2-ClC$_6$H$_4$	**4d**	20	82
5	2-naphthyl	**4e**	20	87
6[c]	(*E*)-CH=CHPh	**4f**	20	83
7	3-pyridyl	**4g**	20	51
8	*i*Pr	**4h**	20	74
9	*c*Hex	**4i**	20	81
10	*t*Bu	**4j**	20	52
11	*n*Bu	**4k**	20	61

[a] Reaction conditions: Aldehyde **1** (0.5 mmol), *p*-anisidine (**2a**, 0.5 mmol), *tert*-butyl isocyanide (**3a**, 0.5 mmol), and catalyst **10** (0.05 mmol) were stirred at 80°C in toluene (0.5 mL). [b] Yield of the product after silica gel column chromatography. [c] Using 20 mol% of catalyst **10**.

A variety of amines was investigated next using benzaldehyde (**1a**) as the aldehyde component and *tert*-butyl isocyanide (**3a**) as the other component (Table 3). It turned out that different aromatic amines can be used to give products in high yields (Table 3, entries 1–4). The electronic properties of the aromatic system of the amine component do not seem to influence the yield of the reaction. Even the heteroaromatic pyridylamine gave the desired product in good yield (Table 3, entry 5). The reaction also works with benzylamine and benzhydrylamine; however, slightly lower yields were obtained (Table 3, entries 6 and 7). Furthermore, an (allyl)amine undergoes the reaction to give the desired product in moderate yield (Table 3, entry 8). Finally a secondary amine was probed and provided product **4t** in 41% yield (Table 3, entry 9).

Table 3: Catalytic three-component Ugi reaction of benzaldehyde with different amines and *tert*-butyl isocyanide.

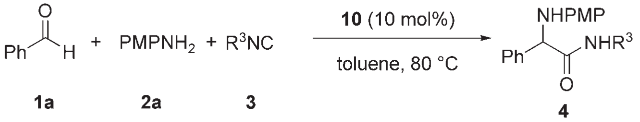


Entry[a]	R^2	Product	Time [h]	Yield [%][b]
1	2-naphthyl	**4l**	20	83
2	4-CF$_3$C$_6$H$_4$	**4m**	20	81
3	4-CO$_2$EtC$_6$H$_4$	**4n**	20	88
4	3-ClC$_6$H$_4$	**4o**	20	74
5	3-pyridyl	**4p**	20	81
6	PhCH$_2$	**4q**	20	42
7[c]	(Ph)$_2$CH	**4r**	36	36
8	Allyl	**4s**	20	40
9	R^2_2NH=(Ph)$_2$NH	**4t**	36	41

[a] Reaction conditions analogous to those described in Table 2. [b] Yield of the product after silica gel column chromatography. [c] Using 20 mol% of catalyst **10**.

The isocyanide component of our reaction can also be varied: both cyclohexyl isocyanide and benzyl isocyanide gave the corresponding products in high yields (Table 4, entries 1 and 2). Good results were also obtained with a

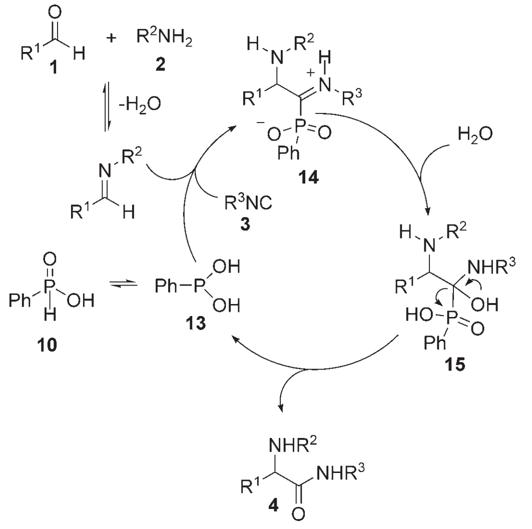
Table 4: Catalytic three-component Ugi reaction of benzaldehyde with *p*-anisidine and different isocyanides.



Entry[a]	R^3	Product	Time [h]	Yield [%][b]
1	*c*Hex	**4u**	20	78
2	Bn	**4v**	36	64
3	*t*BuCH$_2$C(Me$_2$)	**4w**	20	62
4	EtO$_2$CCH$_2$	**4x**	20	83
5	*p*TsCH$_2$	**4y**	20	68

[a] Reaction conditions analogous to those described in Table 2. [b] Yield of the product after silica gel column chromatography.

longer chain isocyanide (Table 4, entry 3) and even with functionalized isocyanides (Table 4, entries 4 and 5).



Scheme 2. Proposed mechanism for the catalytic three-component Ugi reaction.

Although no detailed mechanistic studies have been carried out at this point, a catalytic cycle leading to the α-amino amide product can be envisaged (Scheme 2). Phenyl phosphinic acid (**10**) can be considered a Brønsted acid and, in the form of its phenylphosphonous acid tautomer (**13**), a Lewis base. It is tempting to speculate that both properties may be required for effective catalysis. Thus, the catalytic cycle may be initiated by protonation of the in situ generated imine. Subsequently, the nitrilium ion that is formed after the addition of the isocyanide could be trapped by the nucleophilic phosphinate anion to give intermediate **14**. Finally, H_2O, which is released in the imine formation, reacts with intermediate **14** to generate **15**, which fragments to α-amino amide **4** and catalyst **10**. Although we have no evidence for this particular mechanism, after the submission of this manuscript Goulioukina et al.[10] reported an interesting synthetic study on α-iminophosphonates that provides some support for our mechanistic hypothesis. They observed the hydrolysis of an α-iminophosphonate to the corresponding amide as an unwanted side reaction in their studies, providing at least some support for our proposal of α-iminophosphinate **14** as an intermediate and its rapid hydrolysis to amide **4** via intermediate **15**. Nevertheless, other plausible mechanisms cannot be ruled out at this point.

In summary, we have developed an efficient and potentially useful new reaction, the phosphinic acid catalyzed three-component Ugi reaction. The desired products **4** are formed in good yields upon mixing readily available substrates with catalyst **10**. The broad scope, operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the generation of different α-amino amides. In addition to its obvious use for the synthesis of α-amino acid derivatives, our reaction may also find use in diversity-oriented synthesis[11] and for the design of pharmaceutical and agrochemical substance libraries. Further studies in our laboratory are underway to develop an asymmetric catalytic version,[12] to obtain a better understanding of the role of the phosphinic acid catalyst, and to explore other catalytic reactions with isocyanides.

Experimental Section

Aldehyde **1** (0.5 mmol), amine **2** (0.5 mmol), isocyanide **3** (0.5 mmol), and catalyst **10** (10 mol %) were placed into a dry flask and dry toluene (0.5 mL) was added. The mixture was stirred for 12–36 h at 80 °C and then directly subjected to silica gel column chromatography (ethyl acetate/hexane) to give pure product **4**.

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Keywords: α-amino amides · phosphinic acids · Ugi reactions

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[12] By using the chiral phosphoric acid catalyst 3,3′-bis [(2,4,6-tris(isopropyl)phenyl)]binaphthyl hydrogen phosphate (10 mol%), the product **4a** was obtained in 15% yield with 59:41 e.r. and by using the new chiral phosphinic acid catalyst 1,1′-binaphthyl-2,2′-diyldiphosphinic acid (10 mol%) the product **4a** was obtained in 90% yield with 52:48 e.r.