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SHORT COMMUNICATION

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Organocatalytic α-Addition of Isocyanides to Aldehydes

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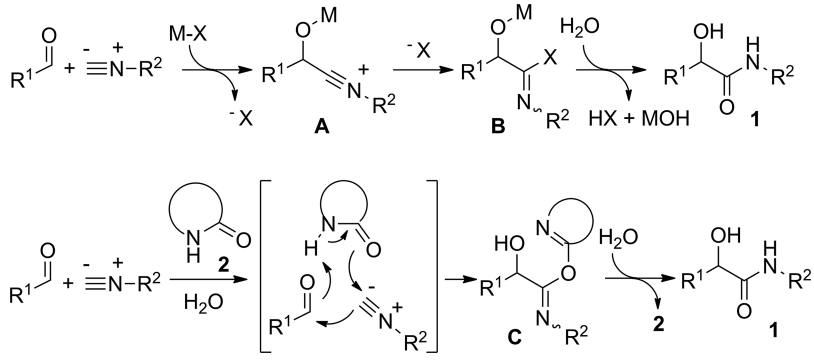
α-Hydroxyamide is an important chemical component widely observed in biologically active natural products. One of the most direct methods to access a α-hydroxyamide is the Passerini-type reaction. However, this catalytic process was limited. Herein, we report the first examples of 3,5,6-trifluoro-2-pyridone-catalyzed α-addition of isocyanides to aldehydes, in the presence of water in benzene, to provide α-hydroxyamides. Various aldehydes and isocyanides performed well in this reaction to provide the α-hydroxyamides. Even highly constrained substrates were well tolerated. The reaction is not restricted by requirements of either inconvenient temperature control, inert atmosphere or dry solvent. The new catalytic reaction may open the way to development of asymmetric organocatalytic α-addition of isocyanides.

Introduction

The α-hydroxyamide moiety is commonly found in biologically active natural products,[1] especially depsipeptide compounds.[2] The significance of the α-hydroxyamide moiety is increasingly being recognized in medicinal chemistry.[3] Therefore, the convenient formation of α-hydroxyamide has attracted much attention. The most common approach toward α-hydroxyamide is condensation of lactic acid with an amine. This requires preparation of lactic acid followed by protection of the hydroxy group before the condensation with the amine. Yet perhaps the most direct method to access a α-hydroxyamide is the Passerini-type reaction.[4–6] Although this approach has been well studied, the catalytic process remains restricted.[4,5] Denmark and co-workers reported the catalytic enantioselective α-addition of isocyanides to aldehydes by using a stoichiometric amount of silicon tetrachloride and chiral bisphosphoramide, as a method of catalytic synthesis of α-hydroxyamides with high enantioselectivity.[4] However, the highly acidic silicon tetrachloride restricts the application of acid-sensitive substrates. Another catalytic approach, with the achiral diphenylborinic acid and phenylphosphinic acid, was explored by the groups of Soeta and Alcaide, respectively.[5] These reaction conditions are very mild and a broad range of substrates can be used to provide the α-hydroxyamides in good yields. However, borinic acid and phosphinic acid are sensitive to oxygen or basic conditions, so extension of this reaction to asymmetric versions is probably difficult. Therefore, we envisioned the development of a novel organocatalytic Passerini-type reaction to provide α-hydroxyamides. Herein, we report the first example of 3,5,6-trifluoro-2-pyridone-catalyzed α-addition of isocyanides to aldehydes to provide the α-hydroxyamides.



Scheme 1. Designed catalytic cycle.

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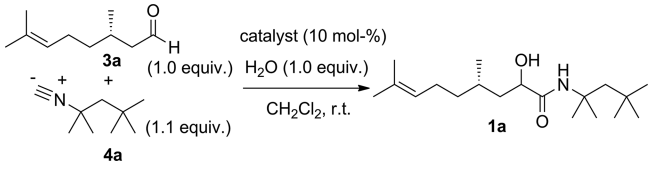
Passerini-type reactions proceed in the following sequence, 1) activation of an aldehyde by Lewis or Brønsted acid, 2) nucleophilic addition of isocyanide to the aldehyde, 3) trapping of the generated nitrilium cation **A** by a nucleophilic species, such as water or the counteranion of the corresponding acid, 4) hydrolysis of imidate or imidic acid **B** by quenching to provide the α-hydroxyamide **1** (Scheme 1). Therefore, we considered amide molecules might be potential catalysts for this reaction, because their weak acidity can activate the aldehyde and the lactim tautomer can trap the nitrilium cation **A**. Furthermore, a cyclic (*E*)-amide **2** can result in a concerted process. The generated imidate **C** would be hydrolyzed by existing H_2O in situ to provide the desired α-hydroxyamide **1**, with recycling of the amide **2**.

Results and Discussion

Catalyst screening began with the following conditions: treatment of (*S*)-citronellal (**3a**; 0.1 mmol) with *tert*-octyl isocyanide (**4a**; 1.1 equiv.) in the presence of a catalyst (10 mol-%) and water (1.0 equiv.) in dichloromethane at room temperature (Table 1).[5a] 2-Pyrrolidone, containing a cyclic (*E*)-amide, gave the desired product **1a** as a 1:1 mixture of diastereomers in poor yield, 2% (Table 1, Entry 1). Cyclic carbamate and cyclic urea were also inefficient for this reaction (Table 1, Entries 2 and 3). 2-Pyridone, containing a conjugated cyclic (*E*)-amide was also an inefficient catalyst, but generated better yield without any side products (Table 1, Entry 4). Considering the convenience to control electronic properties by introducing different substituents, we next tested various 2-pyridone analogues. According to our designed catalytic cycle, introducing an electron-withdrawing group at the C5-position should provide higher reactivity, due to the increased acidity of the NH group. As we expected, the use of 5-nitro-2-pyridone (**2a**) as a catalyst provided the α-hydroxyamide **1a** in 19% yield (Table 1, Entry 5). This was the first example of 2-pyridone-catalyzed α-addition of isocyanide to an aldehyde. We next studied the influence of the C4 substituent. Based on our assumed catalytic cycle, increasing the nucleophilicity of the amide carbonyl might enhance the reactivity. However, 4-hydroxy-2-pyridone provided only a trace amount of α-hydroxyamide **1a** (Table 1, Entry 6). Introducing the hydroxy group would be expected to decrease the acidity of the amide group, which is necessary to activate the aldehyde. We eventually found that the highly electron-deficient 3,5,6-trifluoro-2-pyridone (**2b**), which is commercially available, is the best catalyst, providing α-hydroxyamide **1a** in 55% yield (Table 1, Entry 7). This reaction did not proceed without a catalyst (Table 1, Entry 8). The amide-catalyzed reaction as described proceeded slowly, providing the corresponding α-hydroxyamide **1a** as the sole product without diastereoselectivity in all conditions. The starting aldehyde was not consumed, even after 85 h.

With 3,5,6-trifluoro-2-pyridone (**2b**) as the catalyst, various solvents were examined for this reaction (Table 2). Tetrahydrofuran and other polar solvents, such as AcOEt, MeCN, EtOH, DMF, and DMSO, gave α-hydroxyamide **1a** in low to moderate yield (Table 2, Entries, 1–6). Interestingly, reactions in water or without solvent effectively provided the product **1a** in good yield (Table 2, Entries 7 and 8). These reactions proceeded faster than with other solvents and the starting aldehyde **3b** was completely consumed after 85 h. However, the use of this solvent system provided some undesired side products. Finally, we found that the aromatic solvent, benzene, provided α-hydroxyamides in good yield, 75% (Table 2, Entry 9). Although the starting aldehyde **3b** was not consumed, even running experiments for 85 h, the reactions were very clean. Therefore, we selected benzene as the optimal solvent for further optimizations. Higher reaction temperature (40 °C), did not improve the yield (Table 2, Entry 10). Further increasing the

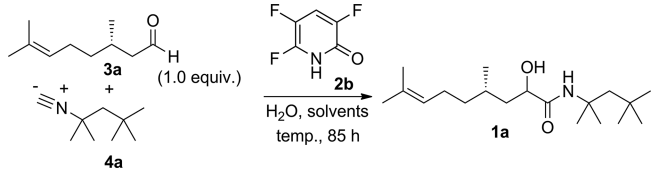
Table 1. Catalyst screening.



Entry	Catalyst	Time [h]	Yield [%][a][b][c]
1	2-pyrrolidone	46	2
2	oxazolidinone	66	No reaction
3	2-imidazolidinone	45	2
4	2-pyridone	55	5
5	5-nitro-2-pyridone (**2a**)	85	19
6	4-hydroxy-2-pyridone	85	Trace
7	3,5,6-trifluoro-2-pyridone (**2b**)	85	55
8	none	85	No reaction

[a] Yields were calculated based on ^{1}H NMR spectra. [b] *dr* = 1.0:1.0. [c] Starting aldehyde was not consumed.

Table 2. Optimization of the reaction conditions.



Entry	**4a** [equiv.]	H_2O [equiv.]	**2b** [mol-%]	Solvent	Temp.	Yield [%][a][b][c]
1	1.1	1.0	10	THF	r.t.	40
2	1.1	1.0	10	AcOEt	r.t.	54
3	1.1	1.0	10	MeCN	r.t.	24
4	1.1	1.0	10	EtOH	r.t.	14
5	1.1	1.0	10	DMF	r.t.	25
6	1.1	1.0	10	DMSO	r.t.	28
7	1.1	1.0	10	H_2O	r.t.	73[d]
8	1.1	1.0	10	none	r.t.	71[d]
9	1.1	1.0	10	Benzene	r.t.	75
10	1.1	1.0	10	Benzene	40 °C	72
11	2.0	1.0	10	Benzene	r.t.	89
12	1.1	1.0	20	Benzene	r.t.	86
13	1.1	2.0	10	Benzene	r.t.	83

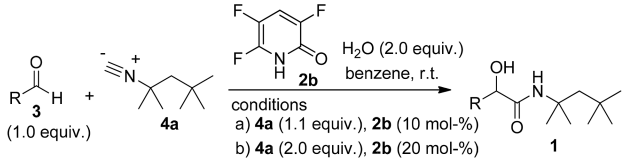
[a] Yields were calculated based on their ^{1}H NMR spectra. [b] *dr* = 1.0:1.0. [c] Starting aldehyde was not consumed. [d] Starting aldehyde was consumed.

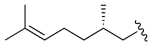
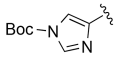
temperature decreased the yield due to the decomposition of the catalyst. Increasing the proportion of isocyanide, catalyst or water improved the yield (Table 2, Entries 11–13). Consequently, the reaction condition described in entry 13 was set as a standard condition.

With the optimized reaction conditions in hand, we next examined the application of various aldehydes to produce the corresponding α-hydroxyamide **1** (Table 3). A wide range of aliphatic aldehydes were treated with *tert*-octyl isocyanide (**4a**) in the presence of a catalytic amount of 3,5,6-trifluoro-2-pyridone (**2b**) and water in benzene. Unbranched aliphatic aldehydes were well tolerated, to provide the corresponding α-hydroxyamide **1b** in 83% yield with a small amount of starting aldehyde **3b** (Table 3, Entry 1). β-Branched aldehyde **3a** was also well tolerated (Table 3, Entry 2). The (*S*)-citronellal (**3a**) derived α-hydroxyamide **1a** was isolated in 83% yield, which was identical with the calculated yield based on the ^{1}H NMR spectra (Table 2). α-Branched aldehyde **3c** was converted into the corresponding α-hydroxyamide **1c** in good yield (Table 3, Entry 3). Although the reaction with highly constrained pivalaldehyde **3d** gave the corresponding α-hydroxyamide **1d** in moderate yield, increasing the amount of catalyst **2b** and isocyanide **4a** improved the yield to 77% (Table 3, Entries 4 and 5). On the other hand, aromatic aldehydes are poor substrates, even electron-deficient 4-chlorobenzaldehyde (**3e**) and *N*-Boc imidazolyl aldehyde **3f** provided the corresponding α-hydroxyamide **1** in low yields of 19 and 20%, respectively (Table 3, Entries 6 and 7). Glyceraldehyde (**3g**), containing an acetonide, was successfully converted into the corresponding α-hydroxyamide **1g** in good yield (*dr* = 3.0:1.0; Table 3, Entry 8). Aqueous aldehydes, such as formaldehyde (**3h**) were also good substrates for this reaction, producing the corresponding unsubstituted α-hydroxyamide **1h** in 77% yield (Table 3, Entry 9). Relatively acid-sensitive Boc and acetonide groups survived under these reaction conditions.

We next examined the application of various isocyanides to this reaction (Table 4). Benzyl isocyanide (**4b**) was treated with 3-phenylpropanal (**3b**) to produce the α-hydroxyamide **1i** in 49% yield (Table 4, Entry 1). α-Branched cyclohexyl isocyanide (**4c**) was converted into the corresponding α-hydroxyamide **1j** in very good yield (88%; Table 4, Entry 2). Amino acid derived isocyanides were also good substrates for this reaction. Reaction with ethyl isocyanoacetate (**4d**) gave the α-hydroxyamide **1k** in 43% yield, which is a potential building block for depsipeptide synthesis (Table 4, Entry 3). Interestingly, *tert*-leucine-derived, highly sterically bulky isocyanide **4e**[7] efficiently provided the corresponding product **1l** in excellent yield without diastereoselectivity (Table 4, Entry 4). The isocyanide **4e** reacted very well, even

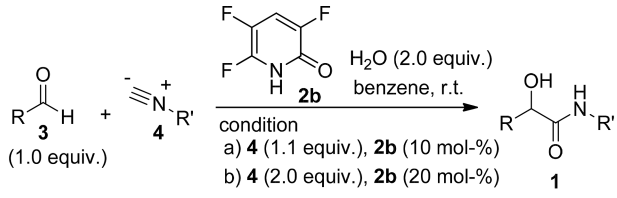
Table 3. Scope of the aldehyde component.

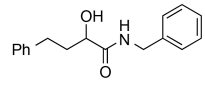
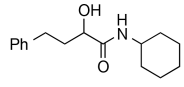
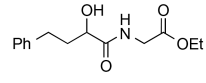
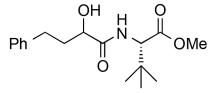
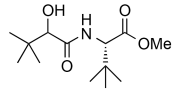
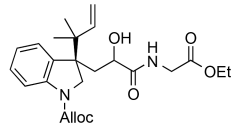


Entry	3	R	Conditions	Time [h]	1	Yield [%][a,d]
1	**b**	$PhCH_2CH_2$-	a	48	**1b**	83
2	**a**		a	96	**1a**	83[b]
3	**c**	Cyclohexyl-	a	48	**1c**	82
4	**d**	*t*Bu-	a	120	**1d**	60
5	**d**		b	96	**1d**	77
6	**e**	4-Cl-C_6H_4-	b	120	**1e**	19
7	**f**		b	120	**1f**	20
8	**g**		a	120	**1g**	85[c]
9	**h**	H-	a	120	**1h**	77

[a] Isolated yields. [b] *dr* = 1.0:1.0. [c] *dr* = 3.0:1.0. [d] Starting aldehyde was not consumed.

Table 4. Scope of the isocyanide component.



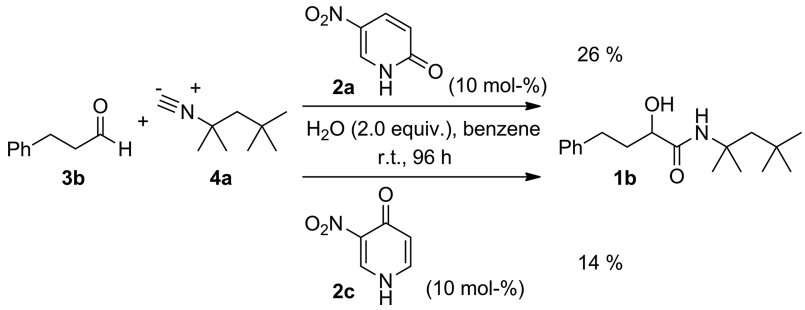
Entry	Conditions	Time [h]	Product	1	Yield [%][a]
1	a	120		**1i**	49[b]
2	a	96		**1j**	88[b]
3	a	96		**1k**	43
4	a	96		**1l**	97[c]
5	a	96		**1m**	96[c]
6	b	120		**1n**	74[b,d]

[a] Isolated yields. [b] Starting aldehyde was not consumed. [c] *dr* = 1.0:1.0. [d] *dr* = 2.5:1.0.

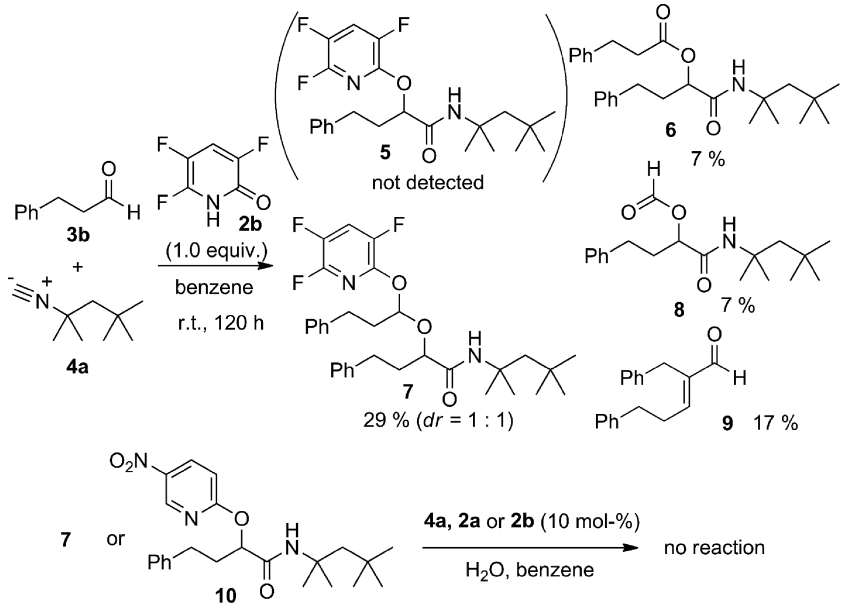
with the highly hindered pivalaldehyde **3d**, with a 96% yield and 1.0:1.0 *dr* (Table 4, Entry 5). Highly constrained aldehyde **3i**, which was an intermediate for our neoxaline synthesis,[8] was well tolerated to produce the corresponding α-hydroxyamide **1n** in 74% yield and 2.5:1.0 *dr* (Table 4, Entry 6). As described above, our reaction conditions were suited to sterically hindered aldehydes and isocyanides to produce the α-hydroxyamide. 2-Pyridone might assist the enolization of the carbonyl group and provoke undesired reactions, such as an aldol reaction.[9] Indeed, the aldol condensation product was detected in some reactions (Scheme 3). Sterically constrained substrates might prevent such undesired side reactions.

To elucidate the reaction mechanism, 5-nitro-2-pyridone (**2a**) and 3-nitro-4-pyridone (**2c**) were used as the catalyst (Scheme 2). Both promoted the reaction to provide α-hydroxyamide **1b** in 26 and 14% yield, respectively. This result suggested that the first addition step, to provide imidate **C**, would be a stepwise process (Scheme 1). However, considering the use of 2-pyridone showed a better yield than 4-pyridone, a concerted process should not be ruled out for the 2-pyridone-catalyzed reaction.

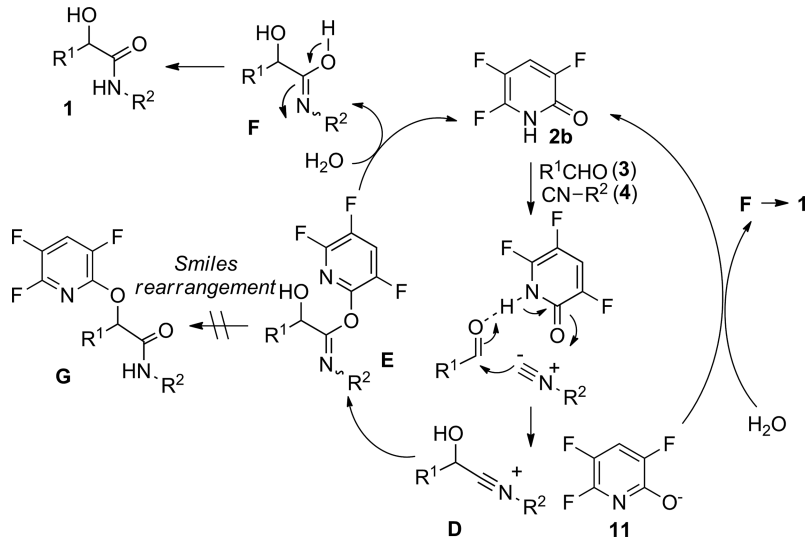
We next envisioned detection of the reaction intermediates, such as an imidate **E** or an α-aryloxyamide **G**, which is obtained by Smiles rearrangement.[10] A stoichiometric amount of 3,5,6-trifluoro-2-pyridone (**2b**) was treated with 3-phenylpropanal (**3b**) and *tert*-octyl isocyanide (**4a**) in benzene, in the absence of water (Scheme 3). Unexpectedly, Passerini reaction product **6**,[11] trifluoropyridineacetal product **7**,[12] formylated product **8**, and aldol condensation product **9** were obtained instead of the desired imidate and α-aryloxyamide **5**. α-Hydroxyamide **1b** was not obtained under these reaction conditions. This result indicates that water is necessary to produce the α-hydroxyamide **1b**. Our standard conditions have the potential to produce the same side products **6**–**9**. However, the addition of isocyanide **4a** to aldehyde **3b** occurs before the undesired oxidation of aldehyde **3b** and aldol condensation to produce **6** and **9** in the presence of water. These results suggested that the water appeared to play two important roles in our reaction conditions: 1) accelerating the addition of isocyanide **4** to the aldehyde **3** and 2) preventing undesired acetalization. Acetal product **7** was considered as a possible intermediate for the pyridone-catalyzed reaction and so the isolated acetal **7** was



Scheme 2. Attempt to elucidate the reaction mechanism: 4-pyridone-catalyzed reaction.



Scheme 3. Attempt to detect the reaction intermediate.



Scheme 4. Possible reaction mechanism.

resubmitted to standard conditions. However, compound **7** was not hydrolyzed at all to give the α-hydroxyamide **1b**.

El Kaïm and co-workers described an *O*-arylative Passerini reaction with 5-nitro-2-pyridone (**2a**), as an acid component.[10] Accordingly, we prepared the α-aryloxyamide **10**,[7] a possible intermediate for our pyridone-catalyzed reaction. Although the α-aryloxyamide **10** was treated under our standard conditions, hydrolysis of **10** did not occur. This result indicates the Smiles rearrangement is not involved in our catalytic cycle.

The possible reaction mechanism is described in Scheme 4. 3,5,6-Trifluoro-2-pyridone (**2b**) acts as a Brønsted acid to provide the nitrilium cation intermediate **D**. The nitrilium cation intermediate **D** is trapped by the generated pyridinylalkoxide **11** to give an imidate **E** that is hydrolyzed in situ to provide the imidic acid **F**, along with recycling of the catalyst **2b**. The imidic acid **F** is isomerized to α-hydroxyamide **1**. Trapping of the nitrilium intermediate **D** by water is also possible to provide α-hydroxyamide **1** directly, together with recycling of the catalyst **2b**.

Conclusions

In this report, we demonstrated the organocatalytic multicomponent reaction of aldehydes, isocyanides, and water to provide α-hydroxyamides **1**. The 3,5,6-trifluoro-2-pyridone (**2b**) was an effective catalyst for this reaction. The reaction did not require any special conditions, such as temperature control, inert atmosphere, or dry solvent. Various aldehydes and isocyanides performed well in this reaction to provide the α-hydroxyamides. Notably, even very sterically hindered aliphatic aldehydes reacted very well with isocyanides, providing the corresponding α-hydroxyamides in excellent yield. Considering the ease with which catalyst analogues can be prepared,[13] this will enable the development of a new asymmetric organocatalytic reaction system. Development of the organocatalytic asymmetric α-addition of isocyanide is in progress.

Experimental Section

General Procedure: Isocyanide (0.11 mmol) was added to a solution of aldehyde (0.1 mmol, 1.0 equiv.), 3,5,6-trifluoro-2-pyridone (1.6 mg, 10 mol-%), and H_2O (3.6 μL, 0.2 mmol) in benzene (0.1 mL) at room temperature. The reaction mixture was stirred at room temperature for 40–120 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the α-hydroxyamide.

Acknowledgments

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[1] a) Y. Konda, M. Onda, A. Hirano, S. Ōmura, *Chem. Pharm. Bull.* **1980**, *28*, 2987–2993; b) H. Suda, T. Takita, T. Aoyagi, H. Umezawa, *J. Antibiot.* **1976**, *29*, 100–101; c) K. Yokoi, K. Nagaoka, T. Nakashima, *Chem. Pharm. Bull.* **1986**, *34*, 4554–4561; d) N. B. Perry, J. W. Blunt, M. H. G. Munro, *J. Am. Chem. Soc.* **1988**, *110*, 4850–4851.

[2] a) R. Süssmuth, J. Müller, H. von Döhren, I. Molnár, *Nat. Prod. Rep.* **2011**, *28*, 99–124; b) M. P.-Gimeno, J. T.-Puche, F. Albericio, *Mar. Drugs* **2013**, *11*, 1693–1717; c) T. Fukuda, M. Arai, H. Tomoda, S. Ōmura, *J. Antibiot.* **2004**, *57*, 117–124; d) H. Tomoda, H. Nishida, X.-H. Huang, R. Masuma, Y. K. Kim, S. Ōmura, *J. Antibiot.* **1992**, *45*, 1207–1215; e) K. Shiomi, R. Matsui, A. Kakei, Y. Yamaguchi, R. Masuma, H. Hatano, N. Arai, M. Isozaki, H. Tanaka, S. Kobayashi, A. Turberg, S. Ōmura, *J. Antibiot.* **2010**, *63*, 77–82.

[3] a) S. Ahmad, A. Ashfaq, M. Alam, G. S. Bisacchi, P. Chen, P. T. W. Cheng, J. A. Greytok, M. A. Hermsmeier, P.-F. Lin, K. A. Lis, Z. Merchant, T. Mitt, M. Skoog, S. H. Spergel, J. A. Tino, G. D. Vite, R. J. Colonno, R. Zahler, J. C. Barrish, *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1729–1734; b) G. S. Sheppard, J. Wang, M. Kawai, N. Y. BaMaung, R. A. Craig, S. A. Erick-

son, L. Lynch, J. Patel, F. Yang, X. B. Searle, P. Lou, C. Park, K. H. Kim, J. Henkin, R. Lesniewski, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 865–868; c) H. A. Schenck, P. W. Lenkowski, I. C. Mukherjee, S. H. Kob, J. P. Stables, M. K. Patel, M. L. Brown, *Bioorg. Med. Chem.* **2004**, *12*, 979–993; d) S. D. Kuduk, R. K. Chang, R. M. DiPardo, C. N. Di Marco, K. L. Murphy, R. W. Ransom, D. R. Reiss, C. Tang, T. Prueksaritanont, D. J. Pettibone, M. G. Bock, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5107–5110.

[4] Catalytic asymmetric reaction: a) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, *125*, 7825–7827; b) S. E. Denmark, Y. Fan, *J. Org. Chem.* **2005**, *70*, 9667–9676.

[5] Catalytic reactions: a) T. Soeta, Y. Kojima, Y. Ukaji, K. Inomata, *Tetrahedron Lett.* **2011**, *52*, 2557–2559; b) B. Alcaide, P. Almendros, C. Aragoncillo, R. Callejo, M. P. Ruiz, *J. Org. Chem.* **2013**, *78*, 10154–10165.

[6] a) W. C. Lumma, *J. Org. Chem.* **1981**, *46*, 3668–3671; b) L. B. Mullen, J. D. Sutherland, *Angew. Chem. Int. Ed.* **2007**, *46*, 8063–8066; *Angew. Chem.* **2007**, *119*, 8209; c) P. He, J. Wu, Y.-B. Nie, M.-W. Ding, *Tetrahedron* **2009**, *65*, 8563–8570; d) J. S. Kumar, S. C. Jonnalagadda, V. R. Mereddy, *Tetrahedron Lett.* **2010**, *51*, 779–782; e) A. Ramazani, A. Mahyari, H. Lashgari, K. Śleopokura, T. Lis, *Helv. Chim. Acta* **2011**, *94*, 611–614; f) T. Sela, A. Vigalok, *Adv. Synth. Catal.* **2012**, *354*, 2407–2411; g) M. Bayat, S. Nasri, H. Hosseini, F. Hassanzadeh, *Monatsh. Chem.* **2012**, *143*, 801–804.

[7] See the Supporting Information.

[8] T. Ideguchi, T. Yamada, T. Shirahata, T. Hirose, A. Sugawara, Y. Kobayashi, S. Ōmura, T. Sunazuka, *J. Am. Chem. Soc.* **2013**, *135*, 12568–12571.

[9] a) A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru, V. G. Nenajdenko, *Chem. Rev.* **2010**, *110*, 5235–5331; b) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.

[10] a) L. E. Kaim, M. Gizolme, L. Grimaud, *Org. Lett.* **2006**, *8*, 5021–5023; b) L. E. Kaïm, M. Gizolme, L. Grimaud, J. Oble, *J. Org. Chem.* **2007**, *72*, 4169–4180.

[11] N. Shapiro, A. Vigalok, *Angew. Chem. Int. Ed.* **2008**, *47*, 2849–2852; *Angew. Chem.* **2008**, *120*, 2891.

[12] Acetal **7** was considered to be generated from α-hydroxyamide **1b** with another equivalent of aldehyde see ref. 10. However, the acetal **7** was not produced by exposing α-hydroxyamide **1b** to our reaction conditions.

[13] a) G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, A. Vomg, *J. Org. Chem.* **2005**, *70*, 7208–7216; b) A. Baron, G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, A. Vong, *J. Org. Chem.* **2005**, *70*, 9377–9381.

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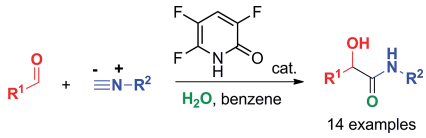
Organocatalysis

3,5,6-Trifluoro-2-pyridone is an efficient catalyst for the α-addition of isocyanides to aldehydes in the presence of water in benzene. Various aldehydes and isocyanides performed well in this reaction to provide the α-hydroxyamides. Even highly constrained substrates were well tolerated. This is the first example of pyridone-catalyzed α-addition of isocyanides.



Keywords: Organocatalysis / Multicomponent reactions / Amides / Pyridone / Isocyanide

