One-pot sequential alcohol oxidation and asymmetric α-oxyamination in aqueous media using recyclable resin-supported peptide catalyst†

Kengo Akagawa, Takuma Fujiwara, Seiji Sakamoto and Kazuaki Kudo*

Received 1st July 2010, Accepted 7th September 2010
DOI: 10.1039/c0cc02301a

An efficient tandem reaction system was developed, in which primary alcohols were used for the oxidation to the corresponding aldehydes followed by an asymmetric α-oxyamination with a resin-supported peptide catalyst.

Recent remarkable advancements in organocatalytic reactions have led to the development of various synthetic methods.[1] One of the features of organocatalysis is its applicability to sequential reactions. In addition to a number of domino reactions performed by a single organocatalyst, tandem reactions utilizing multiple catalysts have been receiving increasing attention.[2] Although the compatibility of each catalyst in one flask should be considered in tandem reactions, they have great potential for efficient synthesis of target compounds without isolating/purifying intermediates. So far, tandem reactions employing two kinds of organocatalysts[3] and those combining a metal catalyst and an organocatalyst[2a,3d,4] have been reported.

On the other hand, many organocatalytic reactions, especially amine-catalyzed ones, use aldehydes as substrates. Some aldehydes are chemically unstable and aldehydes are often commercially less available than the corresponding primary alcohols. Therefore, tandem catalytic reactions starting from the oxidation of a primary alcohol to an aldehyde are synthetically important. In spite of their expected usefulness, there has been no report on such tandem reactions. For tandem reactions that include enantioselective transformation of an aldehyde, mild reaction conditions for the first oxidation step are required. Oxidation using a catalytic amount of TEMPO and a copper salt under O_2 is a good candidate from amongst the other oxidizing methods.[5] However, to achieve an enantioselective tandem reaction catalyzed by the TEMPO/Cu system and a chiral amine, there are some obstacles: (1) the oxidation of an alcohol by TEMPO and a copper salt is commonly performed at or above room temperature, whereas many chiral-amine-catalyzed reactions need a lowered temperature for good enantioselectivity; (2) in the presence of an amine catalyst, TEMPO becomes reactive toward an aldehyde (*vide infra*); and (3) the over-oxidation of an aldehyde to a carboxylic acid causes a decrease in yield, therefore the rate of an amine-catalyzed reaction should be high.

Recently, Sibi *et al.* developed asymmetric α-oxyamination of aldehydes with TEMPO catalyzed by a chiral imidazolidinone in an organic solvent at low temperature.[6,7] The enantioselectivity becomes somewhat lower when the reaction is performed at room temperature. In this regard, we have found that the stereoselectivity of this reaction could be improved by using a peptide catalyst.[8] Resin-supported peptide **1** (Fig. 1)[9] promoted the reaction specifically in aqueous media, and worked as a highly enantioselective catalyst at room temperature. We envisaged that this reaction could be extended to the one-pot sequential reaction starting from primary alcohols in which a copper salt works both for oxidation of alcohols and for α-oxyamination of aldehydes. Furthermore, it was also expected that the use of a copper salt for α-oxyamination could provide less detrimental conditions for the catalyst because of the lower redox potential of Cu^{2+}/Cu^{+} compared with Fe^{3+}/Fe^{2+}.[10]

Initially, the asymmetric α-oxyamination of aldehyde **2** with TEMPO was tested using copper(I) chloride under an oxygen atmosphere (Scheme 1). We employed peptide **1** as a catalyst because it showed good enantioselectivity in the asymmetric α-oxyamination of aldehydes with iron(II) chloride under aerobic conditions.[8] The reaction proceeded smoothly in THF–H_2O (1 : 2) to give the oxyaminated product with good enantioselectivity (47% yield, 94% ee). When the reaction was performed in THF, the yield and selectivity were lowered (12% yield, 73% ee), indicating that the aqueous solvent system is essential for an efficient and enantioselective reaction.

Next, the conversion of alcohol **4** to aldehyde **2** was examined (Table 1). When the same conditions as those in the above asymmetric α-oxyamination were employed, the oxidation of the alcohol did not proceed at all in THF–H_2O (1 : 2) (entry 1). With the addition of 2,2′-bipyridine, which is a known additive for the Cu/TEMPO-catalyzed oxidation of alcohols under aqueous conditions,[11] the generation of the aldehyde could be observed with a moderate reaction rate (entry 2). In contrast, the oxidation of alcohol **4** occurred

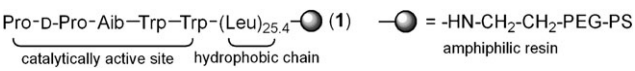
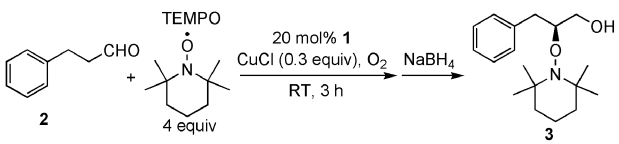


Fig. 1 Resin-supported peptide catalyst.



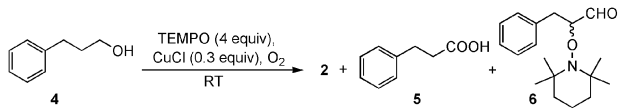
Solvent	Yield (%)	ee (%)
THF/H_2O = 1/2	47	94
THF	12	73

Scheme 1 α-Oxyamination using peptide catalyst.

Institute of Industrial Science, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo, 153-8505, Japan. E-mail: kkudo@iis.u-tokyo.ac.jp; Fax: +81-3-5452-6359; Tel: +81-3-5452-6357

† Electronic supplementary information (ESI) available: NMR, HPLC, MS data and additional experimental results. See DOI: 10.1039/c0cc02301a

Table 1 Oxidation of alcohol in the presence of TEMPO and Cu(I)



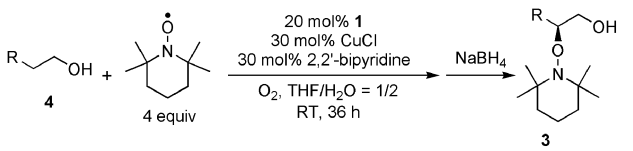
Entry	Solvent	Additive	Time/h	**4**:**2**:**5**:**6**
1	THF–H_2O = 1/2	None	2	100:0:0:0
2	THF–H_2O = 1/2	2,2′-Bipyridine (0.3 equiv)	6	57:23:20:0
3	DMF	None	2	43:43:0:14
4	DMF	2,2′-Bipyridine (0.3 equiv)	2	1:8:83:8
5	DMF–H_2O = 1/2	2,2′-Bipyridine (0.3 equiv)	6	39:22:39:0

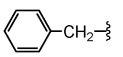
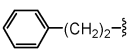
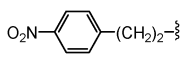
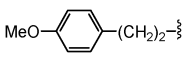
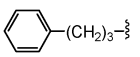
smoothly without/with 2,2′-bipyridine in DMF (entries 3 and 4), a common solvent for oxidation by the Cu/TEMPO system. In these cases, however, the formation of α-oxyaminated aldehyde **6** was observed. Such addition of TEMPO at the α-position of the resulting aldehydes was reported when an excess amount of TEMPO was used for the oxidation of primary alcohols in organic solvent.[12] This uncatalyzed addition of TEMPO is undesirable, because it decreases enantioselectivity in the chiral-amine-catalyzed oxyamination. The suppression of the background oxyamination in aqueous solvent (entries 2 and 5) implies the importance of conducting the sequential reaction under aqueous conditions. A large amount of carboxylic acid **5** was also generated in the presence of 2,2′-bipyridine. Because the degree of formation of **5** was somewhat lowered in THF–H_2O (1:2), we decided to use this solvent system for the sequential reaction.[13]

The one-pot tandem oxidation of alcohols to the chiral oxyaminated products was performed in THF–H_2O (1:2) using TEMPO, the copper salt, and peptide catalyst **1** (Table 2).‡ The two-step oxidation of alcohol **4a** without isolating the aldehyde proceeded successfully in a good enantioselective manner (entry 1). With an imidazolidinone catalyst, this one-pot reaction could not be performed efficiently under the present reaction conditions.[14] The sequential reaction system could be applied to other aromatic alcohols (entries 9 to 12) and an aliphatic alcohol (entry 13), affording the products in good yield and enantioselectivity. When 2-phenylethanol was used as a substrate, the oxyaminated product was obtained in good yield, but was nearly racemic (entry 14). This might be because the highly enolizable character of the reaction intermediate phenylacetaldehyde caused the uncatalyzed rapid addition of TEMPO. In general, heterogeneous catalysts are advantageous from the viewpoint of reusability.[15] Peptide catalyst **1** was recovered after the reaction by filtration, and was subjected to repeated use. Even after being reused seven times, the sequentially oxidized product was obtained without substantial loss in both yield and enantioselectivity (entries 2 to 8).[16] Such high tolerance for the recycling use of the peptide catalyst could be attained presumably because of the mild reaction conditions using the copper salt as a reagent.[17,18]

In conclusion, the one-pot sequential oxidation of alcohols to α-oxyaminated aldehydes was realized using the resin-supported peptide catalyst **1**. In particular, the aqueous media was important for high enantioinduction by inhibiting the uncatalyzed addition of TEMPO to an aldehyde. This study

Table 2 One-pot tandem reaction including oxidation of primary alcohols and asymmetric α-oxyamination



Entry		R	Yield (%)	ee (%)[a]
1	**a**		66	93
2		(1st reuse of peptide)	60	92
3		(2nd reuse of peptide)	70	91
4		(3rd reuse of peptide)	75	92
5		(4th reuse of peptide)	73	92
6		(5th reuse of peptide)	73	91
7		(6th reuse of peptide)	71	92
8		(7th reuse of peptide)	71	91
9	**b**		76	90
10	**c**		70	87
11	**d**		85	91[b]
12	**e**		76	86
13	**f**		74	92[b]
14	**g**		85	4[c]

[a] Determined by chiral HPLC analysis using Chiralcel OD-H, unless otherwise noted. [b] Determined by chiral HPLC analysis using Chiralpak IA. [c] Determined by chiral HPLC analysis using Chiralcel OJ.

demonstrates that the combination of peptide catalysis under aqueous conditions with another catalytic system has potential for developing new reactions. Currently, other one-pot sequential reactions starting from primary alcohols are under investigation in our laboratory.

Notes and references

‡ Typical procedure (Table 2): To a mixture of alcohol **4** (0.1 mmol), TEMPO (0.4 mmol), 2,2′-bipyridine (0.03 mmol), and peptide catalyst **1** [9c] (150 mg, 0.02 mmol of the terminal prolyl group) in 0.33 mL of THF and 0.67 mL of distilled water, copper(I) chloride (0.03 mmol)

was added. The mixture was stirred under oxygen atmosphere at room temperature for 36 h, then the catalyst was filtered off and washed with chloroform. To the filtrate solution, 10% citric acid aqueous solution was added, and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and excess TEMPO was removed by sublimation using a vacuum pump. The residue was dissolved in 1 mL of THF, and sodium borohydride (0.5 mmol) was added. The mixture was stirred for 1 h, then saturated ammonium chloride aqueous solution was added. The resulting solution was extracted with chloroform, and the organic layer was dried over anhydrous magnesium sulfate. After the removal of the solvent under reduced pressure, the crude product was purified using preparative TLC (hexane–ethyl acetate = 2 : 1) to afford oxyaminated product **3**. The absolute configurations of the major products were determined according to the literature.[6] In the examination of recycling peptide catalyst **1**, the collected catalyst by filtration after the reaction was washed with DMF and dichloromethane, and dried *in vacuo* before the next use. Copper(I) chloride and 2,2′-bipyridine were added in each cycle.

1 For reviews, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (*b*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*d*) H. Pellissier, *Tetrahedron*, 2007, **63**, 9267; (*e*) A. Erkkil, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416; (*f*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*g*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*h*) P. Melchiorre, M. Marigo, A. Carlone and G, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*i*) R. M. de Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 2575.

2 For reviews, see: (*a*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745; (*b*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*c*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (*d*) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1; (*e*) G. Guillena, D. J. Ramón and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693.

3 For examples, see: (*a*) S. T. Scroggins, Y. Chi and J. M. J. Frechét, *Angew. Chem., Int. Ed.*, 2010, **49**, 2393; (*b*) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2009, **48**, 9834; (*c*) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6844; (*d*) B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 4349; (*e*) T. Akiyama, T. Katoh and K. Mori, *Angew. Chem., Int. Ed.*, 2009, **48**, 4226; (*f*) S. P. Lathrop and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 13628; (*g*) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming and W.-J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 6946; (*h*) Y. Chi, S. T. Scroggins and J. M. J. Frechét, *J. Am. Chem. Soc.*, 2008, **130**, 6322; (*i*) G.-L. Zhao and A. Córdova, *Tetrahedron Lett.*, 2007, **48**, 5976; (*j*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051.

4 For recent examples, see: (*a*) G.-L. Zhao, F. Ullah, L. Deiana, S. Lin, Q. Zhang, J. Sun, I. Ibrahem, P. Dziedzic and A. Córdova, *Chem.–Eur. J.*, 2010, **16**, 1585; (*b*) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 7428; (*c*) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796; (*d*) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182; (*e*) M. Terada and Y. Toda, *J. Am. Chem. Soc.*, 2009, **131**, 6354; (*f*) K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2008, **130**, 14452; (*g*) W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782; (*h*) T. Yang, A. Ferrali, L. Campbell and D. J. Dixon, *Chem. Commun.*, 2008, 2923; (*i*) M. Rueping, A. P. Antonchick and C. Brinkmann, *Angew. Chem., Int. Ed.*, 2007, **46**, 6903; (*j*) S. Mukherjee and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 11336; (*k*) Q. Ding and J. Wu, *Org. Lett.*, 2007, **9**, 4959; (*l*) S. Chercheja, T. Rothenbücher and P. Eilbracht, *Adv. Synth. Catal.*, 2009, **351**, 339; (*m*) S. Chercheja and P. Eilbracht, *Adv. Synth. Catal.*, 2007, **349**, 1897; (*n*) I. Ibrahem and A. Córdova, *Angew. Chem., Int. Ed.*, 2006, **45**, 1952; (*o*) I. Ibrahem, J. S. M. Samec, J. E. Bäckvall and A. Córdova, *Tetrahedron Lett.*, 2005, **46**, 3965.

5 For reviews, see: (*a*) R. A. Sheldon and I. W. C. E. Arends, *Adv. Synth. Catal.*, 2004, **346**, 1051; (*b*) A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1996, 1153.

6 M. P. Sibi and M. Hasegawa, *J. Am. Chem. Soc.*, 2007, **129**, 4124.

7 Originally, the catalytic process was considered to include the oxidation of the enamine intermediate by a metal reagent. Recently, MacMillan *et al.* published the paper posing a question for the mechanism proposed by Sibi; J. F. V. Humbeck, S. P. Simonovich, R. R. Knowles and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 10012.

8 K. Akagawa, T. Fujiwara, S. Sakamoto and K. Kudo, *Org. Lett.*, 2010, **12**, 1804.

9 (*a*) K. Akagawa, T. Yamashita, S. Sakamoto and K. Kudo, *Tetrahedron Lett.*, 2009, **50**, 5602; (*b*) K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Tetrahedron: Asymmetry*, 2009, **20**, 461; (*c*) K. Akagawa, H. Akabane, S. Sakamoto and K. Kudo, *Org. Lett.*, 2008, **10**, 2035.

10 A. J. Bard, R. Parsons and J. Jorda, *Standard Potentials in Aqueous Solution*, Marcel Dekker, New York, 1985.

11 (*a*) P. Gamez, I. W. C. E. Arends, R. A. Sheldon and J. Reedijk, *Adv. Synth. Catal.*, 2004, **346**, 805; (*b*) P. Gamez, I. W. C. E. Arends, J. Reedijk and R. A. Sheldon, *Chem. Commun.*, 2003, 2414.

12 T. Inokuchi, K. Nakagawa and S. Torii, *Tetrahedron Lett.*, 1995, **36**, 3223.

13 The amounts of carboxylic acid **5** generated in the α-oxyamination of an aldehyde and the tandem reaction of an alcohol under different reaction conditions are described in the supplementary information.

14 When (5*R*)-(+)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone monohydrochloride (Aldrich 663069) was used instead of peptide catalyst **1**, **3a** was obtained in 28% yield and 66% ee.

15 For a review, see M. Gruttadauria, F. Giacalone and R. Noto, *Chem. Soc. Rev.*, 2008, **37**, 1666.

16 The resin catalyst was filtered off and washed after each cycle of the reuse. Gravimetric analysis of the dried resin indicated that 0 to 80% of copper–bipyridine complex remained inside the resin. The fairly broad range in the amount of the residual copper complex might be due to the difference in washing conditions. In the reuse of the peptide catalyst, the copper salt and bipyridine were added in order to ensure the reproducibility regardless of the way of washing.

17 For example, when cerium(IV) ammonium nitrate, a much stronger oxidizing agent than a copper salt, was employed for the asymmetric α-oxyamination of an aldehyde, recycling peptide catalyst **1** drastically decreased yield and enantioselectivity. In case of **2a**, the reaction gave the product with 71% yield and 89% ee in the first reuse of **1**, but with 14% yield and 58% ee in the second reuse.

18 During the revision of this manuscript, Maruoka *et al.* reported the elegant asymmetric α-oxyamination using TEMPO and benzoyl peroxide: T. Kano, H. Mii and K. Maruoka, *Angew. Chem., Int. Ed.*, 2010, **49**, 6638, DOI: 10.1002/anie.201002965. This paper also includes the one-pot reaction from an alcohol. However, it is not a tandem-type method, but an orthogonal one in which reagents are added sequentially.

