Tetrahedron Letters 52 (2011) 770–773

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Sequential oxidation/asymmetric aldol reaction of primary alcohols by resin-supported catalysts

Kengo Akagawa, Shota Takigawa, Erika Mano, Kazuaki Kudo *

Institute of Industrial Science, University of Tokyo, 4-6-1 Komaba, Meguro-ku, Tokyo 153-8505, Japan

ARTICLE INFO

Article history:
Received 8 October 2010
Revised 30 November 2010
Accepted 3 December 2010
Available online 8 December 2010

Keywords:
Sequential reaction
Asymmetric aldol reaction
Resin-supported catalyst
TEMPO oxidation
Peptide catalyst

ABSTRACT

The sequential reaction including alcohol oxidation by TEMPO/Cu system and the asymmetric aldol reaction by peptide catalysis was realized using resin-supported catalysts. The step of oxidizing primary alcohols to the corresponding aldehydes could be dramatically enhanced through the introduction of triglycyl peptide to supported TEMPO and the method of pre-adsorbing a Cu-complex into resin beads.

© 2010 Elsevier Ltd. All rights reserved.

The aldol reaction is one of the versatile C–C bond forming methods, and its asymmetric variant is of great importance for synthesizing biologically active compounds. Development of enantioselective aldol reactions is a constantly advancing field. To date, a number of methods have been established, which include those using chiral auxiliaries[1] and chiral catalysts.[2] Among them, the direct asymmetric aldol (DAA) reaction between two carbonyl compounds is synthetically advantageous, dispensing with the preparation of enolate intermediates or their equivalents.[3] Particularly, after List et al. reported a proline-catalyzed reaction,[4] organocatalytic DAA reactions have been extensively investigated because of its operational simplicity, the stability of catalysts, and ambient reaction conditions.[5]

In most organocatalytic DAA reactions, aldehydes are employed as electrophiles. Aldehydes are sometimes chemically unstable and less commercially available than primary alcohols. Therefore, if aldehydes could be prepared from the corresponding primary alcohols in situ and subsequently used as substrates for DAA reactions, it would be a practically useful methodology.[6–8]

In such a reaction system, because both the oxidation catalyst and the organocatalyst are in the same flask, an oxidizing agent that works under mild reaction conditions is required in order not to deteriorate the coexisting organocatalyst. Among various methods of oxidizing alcohols to aldehydes, the reaction catalyzed by 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and a copper complex using molecular oxygen as a terminal oxidant is noteworthy from the viewpoint of mild reaction conditions.[9] However, there is one problem that TEMPO reacts with a carbonyl compound in the presence of an organo-amine catalyst.[10] Concerning this, we previously demonstrated that otherwise incompatible acidic and basic catalysts could be used in a single flask without affecting each other through the immobilization of the two kinds of catalysts on separate resin beads.[11] It is expected that TEMPO and an amine-catalyst could also coexist by supporting them on different resins, thus the DAA reaction starting from alcohols should be realized. Here, we report the sequential oxidation/asymmetric aldol reaction of primary alcohols by resin-supported catalysts.

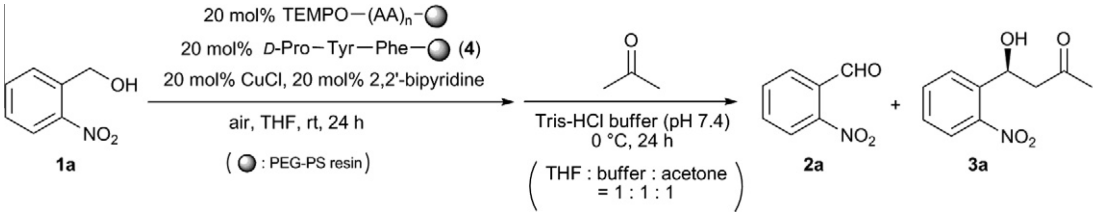
As a model reaction, we chose benzyl alcohol **1a** as a substrate for the oxidation to aldehyde **2a** by the TEMPO/Cu-system, and the subsequent DAA reaction of **2a** with acetone by organocatalysis to afford product **3a** in one pot (Table 1). As a catalyst for the DAA reaction, tripeptide D-Pro-Tyr-Phe attached on polyethyleneglycol–polystyrene (PEG–PS) resin was used according to our previous study. TEMPO having 4-carboxy group was immobilized on amino-terminated PEG–PS resin by conventional condensation. In the presence of the two kinds of supported catalysts, along with copper(I) chloride and 2,2′-bipyridine, the oxidation of **1a** to **2a** was performed under air. After 24 h, acetone and Tris–HCl buffer (pH 7.4) were added to the reaction mixture for conducting the asymmetric aldol reaction. With the simple PEG–PS-supported TEMPO catalyst, the oxidation of the alcohol was quite sluggish (entry 1). This was presumably because the copper complex, which should work cooperatively with TEMPO in the alcohol oxidation, was not present around immobilized TEMPO in the reaction mixture. There

---

* Corresponding author. Tel.: +81 3 5452 6357; fax: +81 3 5452 6359.
E-mail address: kkudo@iis.u-tokyo.ac.jp (K. Kudo).

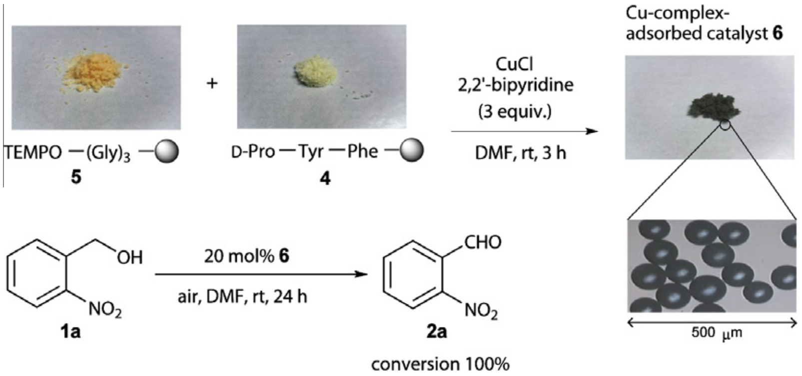
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.12.008

Table 1
Oxidation with TEMPO and copper salt followed by asymmetric aldol reaction with prolyl peptide in one-pot



Entry	(AA)$_n$	**1a**:**2a**:**3a**	ee (%) of **3a**
1	–	93:2:5	82
2	Gly	94:1:5	80
3	(Gly)$_2$	89:1:10	80
4	(Gly)$_3$ (**5**)	63:7:30	82
5[a]	(Gly)$_3$ (**5**)	78:4:18	84
6	(Gly)$_5$	95:1:4	82
7	(Leu)$_3$	89:1:10	82
8	(Phe)$_3$	80:3:17	82

[a] Oxidation reaction was performed in DMF instead of in THF.



Scheme 1. Adsorption of CuCl and 2,2′-bipyridine in resin-supported catalysts.

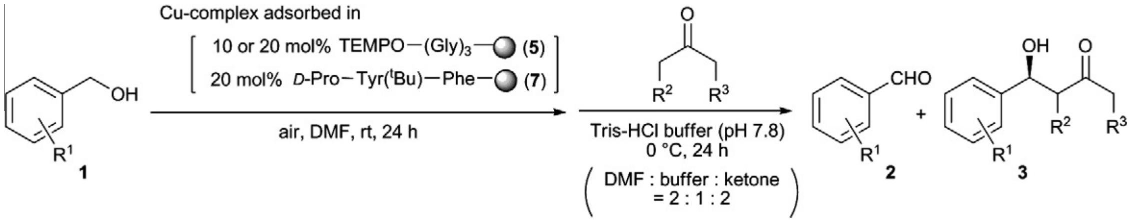
are several reports claiming that a glycine-based peptide has an ability to form a complex with a copper salt.[12] Accordingly, glycine residues were introduced between TEMPO and the PEG–PS resin to locate the copper salt close to TEMPO moiety. Although the insertion of one or two glycine(s) did not significantly improve the reactivity (entries 2 and 3), triglycine tether brought about the acceleration of the oxidation (entry 4). Introducing glycine pentamer or other amino-acid trimers were not as effective as triglycine (entries 6–8). In all cases, the formation of **3a** by the subsequent aldol reaction proceeded in an enantioselective manner, though the conversions were low. The use of the buffer was critical for suppressing the non-enantioselective background reaction caused by 2,2′-bipyridine as a base. When non-supported TEMPO was employed under the same conditions, TEMPO was quickly consumed to give the α-oxyaminated product of acetone (see Supplementary data).

Although the oxidation was enhanced by introducing the triglycyl peptide, the reaction rate was still low. One possible reason is insufficient incorporation of the copper salt to the triglycine-modified resin. Therefore, the resins were pretreated with DMF solution of an excess amount of copper(I) chloride and 2,2′-bipyridine (Scheme 1). After the resins were collected by filtration, washed, and dried, a black mixture of the beads was obtained. By employing this Cu-adsorbed catalyst, the rate of the oxidation of the alcohol was significantly enhanced. Gravimetric analysis indicated that about 1 mol equiv of the copper complex per TEMPO was adsorbed into the resin in the case of catalyst **5** having triglycyl tether, whereas only 0.3 mol equiv was entrapped in the simple TEMPO-bound PEG–PS resin. This distinct affinity of the copper complex toward the resins coincides with the different rate of the oxidation catalyzed by the two types of immobilized TEMPO (Scheme 1, entries 1 and 4).

With employing the above pre-adsorption method, the one-pot sequential reaction was performed under optimized reaction conditions (Table 2). For the asymmetric aldol reaction, catalyst **7** was employed because of the slightly better catalytic performance compared to catalyst **4**. The benzyl alcohols having 2-nitro or 2-chloro substituent were converted to aldol product **3** in good yield and enantioselectivity (entries 1 and 4). The substrates having 3-nitro or 4-nitro group also afforded the corresponding aldol products in an enantioselective manner although generated aldehyde **2** was not fully converted into aldol **3** in 24 h (entries 2 and 3). The use of cyclohexanone instead of acetone resulted in the retarded aldol reaction. Nevertheless, the reaction also proceeded enantioselectively and the isolated yield based on consumed aldehyde **2** was good (entry 5).

One of the merits of supported catalysts is their reusability with a simple operation.[13] We next attempted to reuse the catalysts. Unfortunately, in the second use of the mixed catalyst system, severe decrease in the reaction rate of the aldol reaction was observed (**1a**:**2a**:**3a** = 0:52:48, 30% isolated yield of **3a** with 84% ee). This might be because the partial deterioration of catalyst **7** was caused by the copper ion. Therefore, TEMPO catalyst **5** was removed by filtration after the alcohol oxidation, and then catalyst

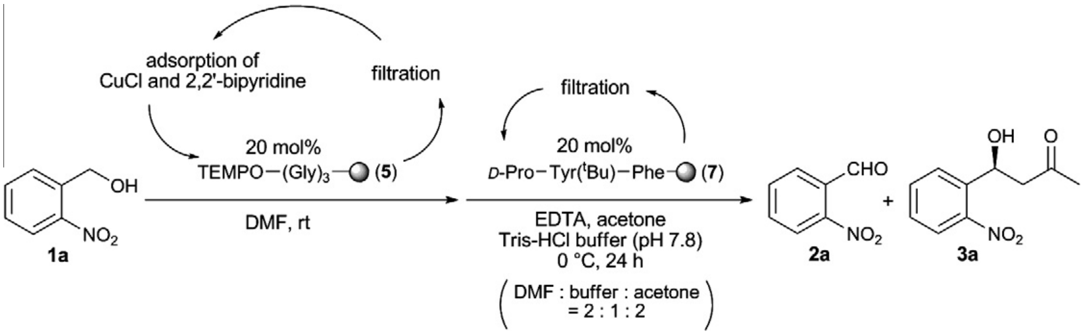
Table 2
One-pot two-step reaction using supported catalysts with pre-adsorption of Cu-complex



Entry	R^1	R^2	R^3	Amount of **5** (mol %)	**1**:**2**:**3**	Isolated yield (%) of **3**	ee (%) of **3**
1	2-NO_2	H	H	20	0:13:87	73	85
2	3-NO_2	H	H	10	0:58:42	39	73
3	4-NO_2	H	H	10	0:56:44	44	70
4	2-Cl	H	H	10	0:14:86	75	73
5	2-NO_2	–$(CH_2)_3$–		10	6:73:21[a]	18	87[b]

[a] Diastereomeric ratio was *anti*/*syn* = 92:8.
[b] Value of *anti* product.

Table 3
Reusability of supported catalysts for sequential two-step reaction



Entry	Reuse of catalysts	Conditions of oxidation	**1a**:**2a**:**3a**	Isolated yield (%) of **3a**	ee (%) of **3a**
1	1st use	Under air, 6 h	4:0:96	78	87
2	2nd use	Under air, 6 h	6:2:92	73	89
3	3rd use	Under air, 24 h	14:2:84	76	88
4	4th use	Under air, 24 h	15:1:84	71	89
5	5th use	Under O_2, 24 h	7:2:91	80	89
6	6th use	Under O_2, 24 h	3:5:92	74	88
7	7th use	Under O_2, 24 h	10:0:90	76	90
8	8th use	Under O_2, 24 h	10:0:90	75	88

7 and ethylenediaminetetraacetic acid (EDTA), a trapping agent for the leached copper ion,[14] were added to the filtrate to ensure the subsequent DAA reaction. Recovered catalysts **5** and **7** were subjected to the repeated use for the sequential reaction (Table 3). Although the reactivity of the TEMPO-supported catalyst gradually decreased, modification of the reaction conditions for the oxidation successfully realized repetitive use of the catalysts, and aldol product **3a** could be obtained without a significant loss in yield and enantioselectivity even after eight times of reuse.

In conclusion, the DAA reaction was attained utilizing primary alcohols as starting materials by combining the two catalytic systems, the TEMPO/Cu-oxidation and the prolyl-peptide-based organocatalysis. The resin-support made TEMPO and the prolyl catalyst compatible in one-pot (Tables 1 and 2), and also made the two kinds of catalysts easily separatable and reusable in the method of adding them sequentially (Table 3). The key to success of the present system was that the efficiency of the oxidation could be dramatically improved both by introducing triglycine between TEMPO and the resin and by the pre-adsorbing procedure. Further investigation on other sequential reactions involving the alcohol oxidation and organocatalytic conversion of the resulting aldehydes is now under way in our laboratory.

Supplementary data

Supplementary data (preparation of catalysts, experimental procedure, reaction between non-supported TEMPO and acetone) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.008.

References and notes

1. For selected examples, see: (a) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557; (b) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127; (c) Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812; (d) Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381; (e) Masamune, S.; Sato, T.; Kim, B.; WollMann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279; (f) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.
2. For selected examples, see: (a) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455; (b) Furuta, K.; Maruyama, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041; (c) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9366; (d) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.*

1994, *116*, 4077; (e) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837; (f) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649; (g) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814; (h) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859; (i) Denmark, S. E.; Ghosh, S. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4759.

3. For selected examples of metal catalysts, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405; (b) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871; (c) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; (d) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003; (e) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367.
4. List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
5. For selected reviews, see: (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570; (b) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem. Eur. J.* **2006**, *12*, 5383; (c) Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249; (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.
6. The aldol-type reactions starting from alcohols have been attained with metal catalysts, though the products were achiral or racemic: (a) Shimizu, K.; Sato, R.; Satsuma, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 3982; (b) Kim, S.; Bae, S. W.; Lee, J. S.; Park, J. *Tetrahedron* **2009**, *65*, 1461; (c) Denichoux, A.; Fukuyama, T.; Doi, T.; Horiguchi, J.; Ryu, I. *Org. Lett.* **2010**, *12*, 1; (d) Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896.
7. The sequential reaction including the hydroformylation of olefins by a rhodium catalyst and the subsequent proline-catalyzed aldol reaction was reported: Chercheja, S.; Eilbracht, P. *Adv. Synth. Catal.* **2007**, *349*, 1897.
8. For reviews on the electrophilic reactions using alcohols as substrates, see: (a) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851; (b) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358; For recent examples of the sequential reactions including alcohol oxidations, see: (c) Li, X.-Q.; Wang, W.-K.; Zhang, C. *Adv. Synth. Catal.* **2009**, *351*, 2342; (d) Sun, H.; Su, F.-Z.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4390; (e) Davi, M.; Lebel, H. *Org. Lett.* **2009**, *11*, 41; (f) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2039; (g) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 4375; (h) Brioche, J.; Masson, G.; Zhu, J. *Org. Lett.* **2010**, *12*, 1432; For examples of direct amide synthesis from alcohols, see: (i) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790; (j) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, 3619; (k) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672; (l) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643; (m) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559; (n) Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem. Eur. J.* **2009**, *15*, 9977; (o) Maki, B. E.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 1651; (p) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667; (q) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem. Eur. J.* **2010**, *16*, 6820; (r) Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H. *J. Org. Chem.* **2010**, *75*, 3002.
9. For reviews, see: (a) Sheldon, R. A.; Arends, I. W. C. E. *Adv. Synth. Catal.* **2004**, *346*, 1051; (b) de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153.
10. (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124; (b) Bui, N.-N.; Ho, X.-H.; Mho, S.-i.; Jang, H.-Y. *Eur. J. Org. Chem.* **2009**, 5309; (c) Akagawa, K.; Fujiwara, T.; Sakamoto, S.; Kudo, K. *Org. Lett.* **2010**, *12*, 1804.
11. Akagawa, K.; Sakamoto, S.; Kudo, K. *Tetrahedron Lett.* **2007**, *48*, 985.
12. (a) Lim, M. C.; Sinn, E.; Martin, R. B. *Inorg. Chem.* **1976**, *15*, 807; (b) Simmons, C. J.; Lundeen, M.; Seff, K. *Inorg. Chem.* **1978**, *17*, 1429; (c) Sugimori, T.; Shibakawa, K.; Masuda, H.; Odani, A.; Yamauchi, O. *Inorg. Chem.* **1993**, *32*, 4951; (d) Carcía-Raso, Á.; Fiol, J. J.; Adrover, B.; Moreno, V.; Mata, I.; Espinosa, E.; Molins, E. J. *Inorg. Biochem.* **2003**, *95*, 77.
13. For a review, see: Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 418.
14. One of the referees suggested to address the heterogeneous nature of the copper adsorbed catalyst according to the literature (Sheldon, R. A.; Wallau, M.; Arends, I. W. C. E.; Schuchardt, U. *Acc. Chem. Res.* **1998**, *31*, 485). In our system, the copper complex leaches from the resin to a substantial extent during the reaction. This is reasonable when considering the absence of specific strongly interacting functional group such as amino group or carboxylate anion in the triglycine moiety. On the other hand, according to the previous reports, the present alcohol oxidation is cooperatively catalyzed by TEMPO and copper ion. This means that the copper ion leached from the resin does not show catalytic activity, and only the copper species that are in the close proximity to the resin-immobilized TEMPO can participate in the catalytic process. This situation makes it difficult to categorize the present oxidation into either homogeneous or heterogeneous. When being focused on the copper species, because they are not rigidly bound to any part of the resin and must diffuse to TEMPO moiety to show catalytic activity, they are regarded as homogeneous. In case the main concern is the whole catalytic system including immobilized TEMPO, this should be described as heterogeneous.