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Metallopeptoids as efficient biomimetic catalysts†

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Metallopeptoid catalysts incorporating phenanthroline–copper and TEMPO, and at least one non-catalytic group perform in the oxidation of various benzylic, allylic and aliphatic primary alcohols with a TON of up to 16 times higher than a mixture of the two catalytic groups or the peptoid dimer that is lacking the non-catalytic group.

Enzymatic catalysis is largely based on cooperativity between a metal center and functional organic molecules located at its surrounding folds. This concept has inspired the design of cooperative catalytic systems,[1] particularly the combination of a transition metal catalyst and an organocatalyst.[2,3] In synthetic systems, however, such a combination has been achieved mainly when the two catalysts were used as a mixture in solution. Such systems typically require high catalyst loadings, which significantly reduce their turnover number (TON) and limit their efficiency. One approach for increasing catalytic efficiencies is to design intramolecular catalytic systems, in which both the transition metal catalyst and the organocatalyst are tethered in close proximity to each other. This configuration creates a confined catalytic pocket similar to enzymatic catalytic sites. A few intramolecular catalytic systems were previously reported,[4,5] but high catalyst loading, long reaction times and occasional high temperatures were still required for conversion. Therefore, there is a need for new biomimetic catalysts in which the distance, orientation and interactions between the two active groups can be tuned in a precise manner towards optimized efficiency and significant decrease in catalyst loading.

One possibility for generating efficient intramolecular catalysts is the use of easily constructed backbones with high sequence specificity, similar to peptide scaffolds.[6] However, despite decades of research in the field of peptidomimetics,[7] there are currently only a few examples of such molecules that function as catalysts.[8] A major focus of research in our group is the design of peptidomimetics, known as peptoids, which are *N*-substituted glycine oligomers that can bind metal ions.[9] Peptoids can be efficiently generated by a solid-phase method that employs primary amines,[10] thus enabling high-sequence diversity. In addition, peptoid oligomers possessing chiral and bulky side chains can adopt secondary structures in a solution even at oligomer lengths as short as five residues, forming polyproline-type helices with a pitch of roughly three residues per turn.[11] Based on these features, in addition to previous work with catalytic peptoids incorporating (2,2,6,6,-tetramethyl-1-piperidinyl)oxydanyl (TEMPO),[8e] we decided to use the peptoid backbone as a tool for studying the cooperativity between two catalytic groups placed on one scaffold. Herein, we describe metallopeptoids incorporating TEMPO and demonstrate their high performance as intramolecular cooperative catalysts in the aerobic oxidation of various benzylic, allylic and aliphatic primary alcohols with low catalyst loading and high TON.

Current protocols for catalytic aerobic alcohol oxidation involve either noble metal (*e.g.* Pd[12] and Ru[13])-based catalysts, or first-row transition metals,[14] including Cu-[15] and Cu-TEMPO[16]-based catalysts. Among those, there is only one example in which the Cu catalyst and TEMPO are tethered together. This catalyst shows high activity in the oxidation of primary aliphatic alcohols but requires high catalyst loading (10 mol%) in addition to high temperatures.[5] Recently, Stahl *et al.*[17] reported a useful procedure for the selective oxidation of various primary alcohols, which combines Cu(I)-bipyridine(bipy) and TEMPO as catalysts in a single solution mixture.

This system employs 5 mol% catalysts; therefore, the highest TON possible, at the maximum of 100% conversion is 20. Although this system is highly practical, the low TON is a significant drawback. Therefore, as a proof of concept, we choose to investigate the catalytic aerobic oxidation of primary alcohols using a modified system, which utilizes Cu(I)-phenanthroline and TEMPO as the oxidation catalysts. Our biomimetic approach advocates that if the two catalysts will be placed on one backbone rather than being used as a mixture in solution, the efficiency of the overall catalytic system will increase (Scheme 1). In order to evaluate our hypothesis, we sought to generate peptoids for the incorporation of

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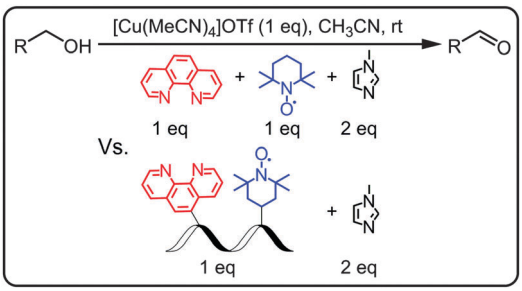

Scheme 1 Alcohol oxidation by a combination of distinct reactive catalysts *vs.* an intramolecular catalytic system.

both 1,10-phenanthroline (Phen), which can be successfully placed only at the N-terminus of peptoids,[18] and TEMPO. The first set of peptoid catalysts was designed to evaluate the optimal method for the creation of a catalytic site by placing the two catalytic groups next to each other in space or next to each other in the sequence. Toward this goal, we prepared peptoids **Helix i+3**, in which Phen and TEMPO are in the respective positions *i* and *i* + 3 of a helical oligomer facing the same side of the helix, and **Helix i+1**, in which Phen and TEMPO are in the respective positions *i* and *i* + 1 of the same oligomer (Fig. 1). The unstructured peptoid **Nonhelix i+3** and a mixture of **Phen + TEMPO** were used as the control catalysts. The peptoids were synthesized using a solid-phase method, cleaved from the solid support and purified by HPLC (>95% purity). The molecular weight measured by electrospray mass spectrometry was consistent with the mass expected for their sequences (ESI†). The four catalytic systems were tested in the oxidation of benzyl alcohol, as a test substrate, according to the protocol described by Stahl *et al.* but using only 0.5 mol% of the catalyst(s). The results are summarized in Table 1.

Our first observation was that the insertion of the two catalysts on one backbone indeed improves the efficiency of the reaction to be four to six times higher than that of the control catalytic system. To probe whether the presence of the amine group on Phen in the peptoid sequences has an effect on the higher reactivity of the peptoids, a control catalytic system that includes 5-amino-Phen and TEMPO was used, showing a TON of 18, which is similar to the simplest control system **Phen + TEMPO** (Table 1, entries 4–5). Our second observation was that the location of the two catalytic groups is important for their activities; in this experiment, the highest TON was achieved with **Helix i+1** (TON = 194).

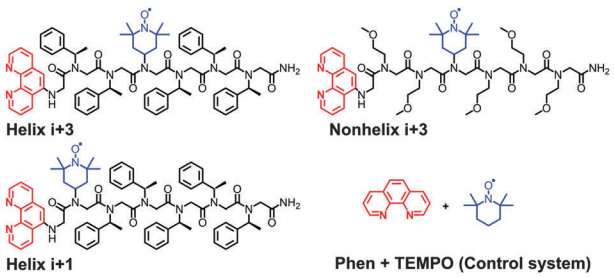

Fig. 1 The first set of peptoids incorporating Phen and TEMPO, and the control system, which were used to evaluate intramolecular cooperative catalysis in benzyl alcohol oxidation.

Table 1 Benzyl alcohol oxidation catalyzed by the first set of peptoids

Entry	Catalyst	Conversion[a]	TON
1	**Helix i+3**	85	170
2	**Helix i+1**	97	194
3	**Nonhelix i+3**	65	130
4	**Phen + TEMPO**	16	32
5	**5-amino-Phen + TEMPO**	18	36

Reactions were performed in dry acetonitrile (0.1 mL) at rt for 3 h with 330 μmol benzyl alcohol, 0.5 mol% catalyst(s), 0.5 mol% $[Cu(MeCN)_4]$-OTf and 1 mol% *N*-methyl imidazole (NMI). [a] As determined by gas chromatography.

Notably, the pre-organization of the two catalytic groups in **Helix i+3** did show higher reactivity compared with the unstructured peptoid catalyst **Nonhelix i+3** (TON = 170 and 130, respectively).

These results suggest that higher activity is achieved when the two catalytic groups are next to each other in the sequence rather than in space. We then sought to design a second set of peptoid catalysts, which includes shorter oligomers containing the two catalytic groups next to each other in the sequence: a peptoid dimer incorporating only Phen and TEMPO (**DI**), a trimer having an additional non-catalytic aliphatic monomer (**MT**, incorporating a methoxyethyl group at the C-terminus), and two trimers having an additional non-catalytic aromatic monomer (**BT** and **RBT**, bearing a benzyl group at the C-terminus and between Phen and TEMPO, respectively), as shown in Fig. 2. These trimers were designed to evaluate whether an additional monomer as well as its type and location in the sequence can influence the overall catalytic activity.

These new peptoids were synthesized, purified (>95% purity), characterized by ESI-MS and by ^{1}H NMR (see ESI†), and used for the oxidation of benzyl alcohol in the same conditions as the first set (Table 2, entries 1–6). The most striking observation from these experiments was that **DI**, which catalyses this reaction to provide >99% conversion when used in 5 mol%, is almost unreactive when used in 0.5 mol%; only 10% conversion was obtained in 3 h with a total TON of 20, similar to the control system. Surprisingly, the addition of one monomer has an enormous effect on peptoid reactivity. In this experiment, the highest conversion and TON were achieved with **BT** (TON = 198), when the additional monomer is a benzyl group located at the C-terminus. No product was detected in the absence of NMI, and lower conversions and TON were obtained with **MT** and **RBT** (TON = 170). Moreover, reducing **BT** loading from 0.5 mol% to 0.1 mol% resulted in a TON as high as 490 in 12 h, about 16 times higher than the mixture of **Phen + TEMPO**.

In addition, the results with **RBT** are consistent with those obtained from the first set of peptoids regarding the requirement for Phen and TEMPO to be next to each other in the sequence.

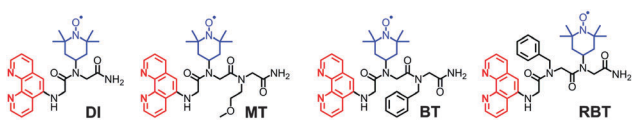

Fig. 2 The second set of peptoids used to evaluate intramolecular cooperative catalysis in benzyl alcohol oxidation.

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Table 2 Benzyl alcohol oxidation catalyzed by the second and third sets of peptoids

Entry	Catalyst	% Conversion[a]	TON
1[b]	**DI**	>99	198
2	**DI**	10	20
2	**BT**	>99	198
3[c]	**BT**	No reaction	—
4	**MT**	85	170
5	**RBT**	85	170
6[d]	**BT**	**49**	**490**
7[d]	**Phen + TEMPO**	3	30
8	**NT**	98	196
9	**TT**	97	32
10	**PT**	85	170

Reactions were performed in dry acetonitrile (0.1 mL) at rt for 3 h with 330 μmol benzyl alcohol, 0.5 mol% catalyst(s), 0.5 mol% $[Cu(MeCN)_4]OTf$ and 1 mol% NMI. [a] As determined by gas chromatography. [b] 5 mol% catalyst. [c] Without NMI. [d] 0.1 mol% catalyst, 12 h.

Overall, the observations from this set of experiments imply that an efficient intramolecular peptoid catalyst must contain at least one non-catalytic group and that the two catalytic groups Phen and TEMPO should be placed next to the other on the peptoid scaffold.

In our catalytic systems, both the Phen-Cu and TEMPO are anchored on one backbone and located in close proximity to the other, aiming to enhance reactivity by an intramolecular mode of action. Our results suggest, however, that an efficient catalytic pocket is being created only when there is at least one monomer near the catalytic groups. We therefore propose that the amide bond between Phen and TEMPO in **DI** allows for the free rotation of these two groups such that in the most stable conformation they are located at a great distance from each other in an orientation that prevents the formation of a catalytic pocket (Fig. 3, left). In contrast, the presence of an additional non-catalytic group should induce steric hindrance that decreases the free rotation, thus constricting the distance and orientation between the two catalytic groups and enabling the generation of a catalytic pocket (Fig. 3, right).

The mechanism of this oxidation was described in detail by Stahl *et al.* and was supported by their experimental results.[19] We assumed that our catalytic system performs through a similar mechanism because the catalytic centers in our peptoids are almost identical to the ones published by Stahl *et al.* To provide some evidence for our assumption, we followed the catalytic reaction, both with **DI** and **BT**, by ESI-MS and could identify most of the reactive intermediates that are present in the published mechanism (Fig. S32, ESI†). However, the great difference between the activity of **DI** and **BT**, and conversely, the similarity in activity between **DI** and the control system (**Phen + TEMPO**), suggest that **DI** might perform as an intermolecular cooperative catalyst, whereas **BT** performs as an intramolecular cooperative catalyst. To test this hypothesis, we performed benzyl alcohol oxidation using 5 mol% catalyst(s) and then systematically lowered the catalyst loading to 0.05 mol% (Fig. S33, ESI†). Both catalytic systems, **DI** and **Phen + TEMPO**, show almost identical catalytic behaviour, reflected by a strong dependence of the conversion on the concentration with a constant conversion decrease as the catalyst concentration is reduced. In contrast, **BT** performance does not change from 5 mol% to 0.5 mol% and only at a catalyst loading of 0.2 mol%, the activity starts to decrease with a decrease in concentration. These results provide strong evidence for **DI** reactivity as an intermolecular cooperative catalyst (just as the control system) and to the performance of **BT** as an intramolecular cooperative catalyst.

We then sought to investigate the influence of the bulkiness of the non-catalytic group on catalyst reactivity. Therefore, we decided to test a third set of peptoid trimers in which Phen and TEMPO are next to each other in the sequence and the non-catalytic monomer at the C-terminus is either the bulky aromatic group naphthyl (peptoid **NT**), the bulky alkyl group *t*-butyl (peptoid **TT**) or the non-bulky alkyl group 1-pentyl (peptoid **PT**), as shown in Fig. S34 (ESI†). These new peptoids were synthesized, purified (>98% purity), characterized in the same way as the second set of peptoids, and used for the oxidation of benzyl alcohol in the same conditions as before; the results are summarized in Table 2 (entries 8–10). Both **NT** and **TT**, bearing bulky non-catalytic groups, show similar conversions and TON to that of **BT**, in addition to catalyst loading as low as 0.1 mol% (Table S2, ESI†). Similarly, **PT**,

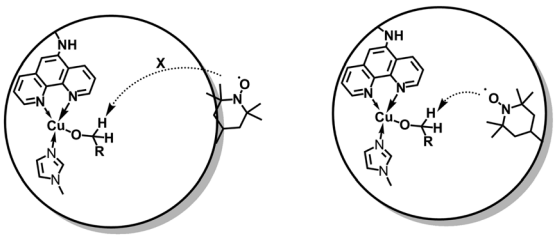
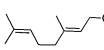


Fig. 3 Representation of **DI** (left) and **BT** (right), demonstrating that the cooperativity is only possible when a nearby bulky group enables the two catalytic groups to be close enough to the other in space.

Table 3 Oxidation of various benzylic, allylic and aliphatic primary alcohols catalysed by **BT**, **DI** and the control system **Phen + TEMPO**[a]

Substrate	**BT**	**DI**	**Phen + TEMPO**
	>99 (198), 49 (490)[b]	10 (20), 6 (30)[c]	16 (32), 7 (35)[c]
	>99 (198), 45 (450)[b]	16 (32)	18 (36)
	>99 (198), 42 (420)[b]	18 (36)	17 (34)
	>99 (198), 79 (395)[c]	17 (34)	20 (40)
	94 (188), 37 (370)[b]	19 (38)	16 (32)
	95 (190)[d], 68 (340)[c]	20 (40)	22 (44)
	>99 (198)[d]	20 (40)	18 (36)
	97 (194)[d], 36 (360)[b,d]	20 (40)	18 (36)

Reactions were performed in dry acetonitrile (0.1 mL) at rt for 3 h with 330 μmol benzyl alcohol, 0.5 mol% catalyst(s), 0.5 mol% $[Cu(MeCN)_4]$-OTf and 1 mol% NMI. [a] As determined by gas chromatography. [b] 0.1 mol% catalyst, 12 h (unless in combination with (d), the reaction time was 24 h). [c] 0.2 mol% catalyst, 12 h (unless in combination with (d), the reaction time was 24 h). [d] Air balloon, 24 h.

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possessing an alkyl non-catalytic group, shows the same conversion and TON as that of **MT**. We therefore concluded that a bulkier non-catalytic monomer relates to the higher catalytic activity.

To evaluate the potential scope of **BT**, we tested its activity in the oxidation of various primary aromatic and aliphatic alcohols and compared its activity with the activities of **DI** and **Phen + TEMPO** (Table 3). The results demonstrate that **BT** is a superior catalyst for a wide range of alcohols in this catalytic system compared with **DI** and **Phen + TEMPO**. Moreover, by using **BT** as a catalyst, we could obtain almost full conversions with less reactive alcohols such as 2-thiophene methanol, furfuryl alcohol[17] and 2-methyl butanol.

In summary, we have shown that the use of a peptoid backbone for tethering together two catalysts is a unique opportunity for biomimetic intramolecular catalysis. The ease of peptoid synthesis permits the rapid screening of catalytic activity by simply tuning the distance, ordination and interactions between the two catalytic groups on the peptoid scaffold. These features allowed the development of a very active Cu-TEPMO-based catalyst for the aerobic oxidation of primary alcohols, operating in a loading of 0.1 mol% with a high TON. Based on their inherent modularity, peptoids hold great potential as intramolecular cooperative catalysts for highly efficient chemical reactions, including asymmetric transformations, by simply incorporating various catalytic and non-catalytic groups (*e.g.* chiral) in their sequences.

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