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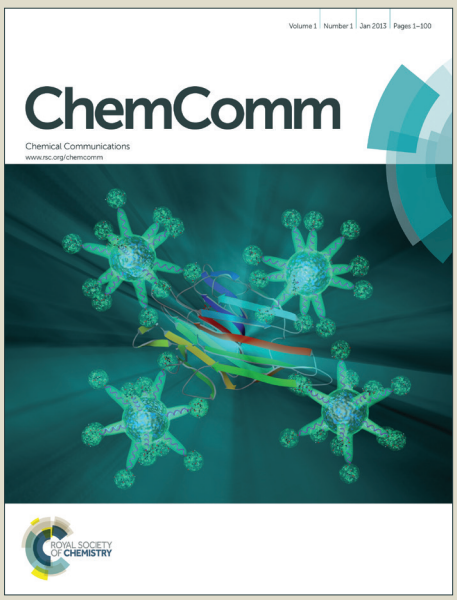

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Metallopeptoids as Efficient Biomimetic Catalysts

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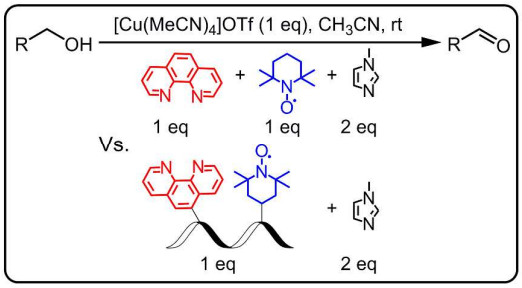
Metallopeptoid catalysts incorporating phenanthroline-copper and TEMPO, and at least one non-catalytic group perform in the oxidation of various benzylic, allylic and aliphatic primary alcohols with TON of up to 16 times higher than a mixture of the two catalytic groups or the peptoid dimer that is lacking 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] specifically the combination between a transition metal catalyst and an organocatalyst.[2,3] Cooperativity between transition metal catalysts and organocatalysts in synthetic systems, however, has been achieved mainly when the two catalysts were used as a mixture in solution. Such systems typically require high catalysts loadings, which significantly reduce their turn over 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 the catalytic sites in enzymes. A few intramolecular catalytic systems were previously reported,[4,5] but high catalyst loading, long reaction times and sometimes 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 the scaffold of peptides.[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 research interest in our group is the design of peptidomimetics called peptoids, *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 having chiral bulky side chains can adopt secondary structures in 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, and on previous work with catalytic peptoids incorporating 2,2,6,6, -tetramethyl-1-piperidinyloxy (TEMPO),[8e] we have 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 metals (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 show high activity in the oxidation of primary aliphatic alcohols but requires high catalyst loading (10 mol %) in addition to high temperature.[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 one solution mixture.

Scheme 1 Alcohol oxidation by a combination of distinct reactive



catalysts vs. an intramolecular catalytic system.

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Electronic Supplementary Information (ESI) available includes: (i) materials and methods, (ii) synthetic procedures, (iii) complementary HPLC, MS, NMR, CD and catalytic data. See DOI: 10.1039/x0xx00000x

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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 that being used as a mixture in solution, the efficiency of the overall catalytic system will increase. In order to evaluate our hypothesis, we sought to generate peptoids incorporating 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 way to create a catalytic site; by placing the two catalytic groups next to each other in space or next to each other in the sequence. To this aim we have prepared peptoids **Helix i+3**, where Phen and TEMPO are in positions i and i+3 of a helical oligomer facing the same side of the helix, and **Helix i+1**, where Phen and TEMPO are in 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 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 (see Supporting Information). The four catalytic systems were tested in the oxidation of benzyl alcohol, as a test substrate, according to the protocol described in Scheme 1 but using 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 is indeed improving the efficiency of the reaction, with of 4-6 times higher than that of the control catalytic system. In order 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 preformed, 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 activity; in this experiment, the highest TON was achieved with **Helix i+1** (TON=194).

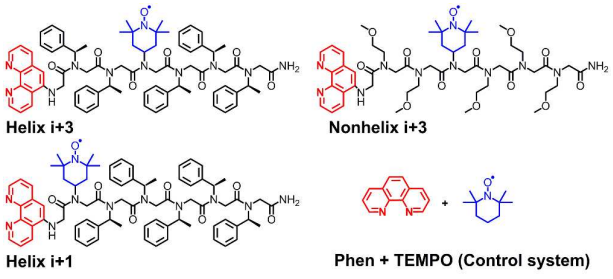

Fig. 1 The first set of peptoids incorporating Phen and TEMPO, and the control system, which were used to evaluate intramolecular cooperative catalysis in the oxidation of benzyl alcohol.

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	**Non helix 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 hrs. with 330 µmol benzylalcohol, 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, pre-organization of the two catalytic groups in **Helix i+3** did show higher reactivity compared to 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), 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 SI), 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 give >99% conversion when used in 5 mol%, is almost unreactive when used in 0.5 mol%; only 10 % conversion was obtained in 3 hours with a total TON of 20, similar to the control system. Surprisingly, addition of one monomer has an enormous effect on the 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 with **RBT** (TON=170). Moreover, reducing the loading of **BT** from 0.5 mol % to 0.1 mol % resulted in TON as high as 490 in 12 hours, about 16 times more than the mixture of **Phen + TEMPO**.

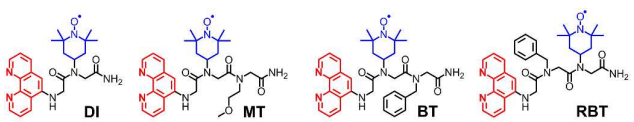

Fig. 2 The second set of peptoids used to evaluate intramolecular cooperative catalysis in the oxidation of benzyl alcohol.

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Table 2 Oxidation of benzyl alcohol 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 hrs. with 330 µmol benzylalcohol, 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 hrs.

In addition, the results with **RBT** are consistent with those obtained with the first set of peptoids regarding the requirement for Phen and TEMPO to be next to each other in the sequence. 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 each 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 each 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 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 enable the generation of a catalytic pocket (Fig 3 right).

The mechanism of this oxidation was described in details by Sthal et al. and was supported by their experimental results.[19]

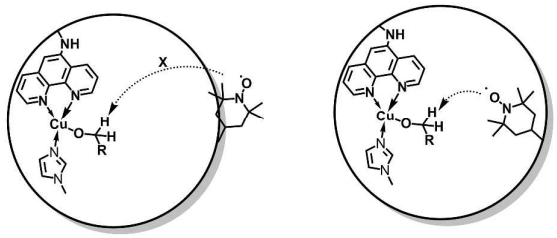

Fig. 3 Representation of **DI** (left) and **BT** (right), in which the cooperativity is only possible when a nearby bulky group enables the two catalytic groups to be close enough to each other in space.

We assumed that our catalytic system performs in a similar mechanism because the catalytic centers in our peptoids are almost identical to the ones published by Sthal et al. In order 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). However, the great difference between the activity of **DI** and **BT,** and, on the other hand, the similarity in activity between **DI** and the control system (**Phen** + **TEMPO**), suggest that **DI** might perform as an intremolecular cooperative catalyst, while **BT** performs as an intramolecular cooperative catalyst. In order to test this hypothesis we performed the oxidation of benzylalcohol using 5 mol% catalyst(s) and then lowered the catalysts loading systematically to 0.05 mol% (Fig. S33). Both catalytic systems, **DI** and **Phen + TEMPO**, show almost identical catalytic behaviour, namely strong dependence of the conversion on the concentration with constant decrease in conversion as the catalysts concentration is reduced. In contrast, the performance of **BT** does not change from 5 mol% to 0.5 mol%, and only at catalyst loading of 0.2 mol% the activity starts to decrease with the decrease in concentration. These results provide a strong evidence for the reactivity of **DI** as an intermolecular cooperative catalyst (just as the control system) and to the performance of **BT** as an intramolecular cooperative catalyst.

Next we wished to investigate the influence of the bulkiness of the non-catalytic group on the catalyst reactivity. To this aim, 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**), Fig. S34. 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 **BT**, also in catalysts loading as low as 0.1 mol % (Table S2). Likewise, **PT**, having an alkyl non-catalytic group, shows the same conversion and TON as **MT**. We therefore concluded that the bulkier is the non-catalytic monomer is, the higher is the catalytic activity.

In order to evaluate the potential scope of **BT** we tested its activity in the oxidation of various primary aromatic and aliphatic alcohols and compared to the activity 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 in comparison to **DI** and **Phen + TEMPO**. Moreover, with **BT** used 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 using the peptoid backbone for tethering together two catalysts is a unique opportunity for biomimetic intramolecular catalysis. The ease of peptoid synthesis permits rapid screening of catalytic activity by simply tuning the distance, ordination and interactions between the two catalytic

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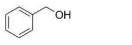
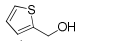
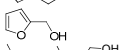
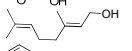
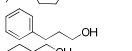
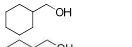
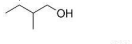
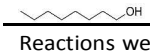
Table 3 Oxidation of various benzylic, allylic and aliphatic primary alcohols catalysed by **BT**, **DI** and the control system **Phen+TEMPO**[a]

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 hrs. 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 hrs (unless it is in combination with (d), then the reaction time was 24 hrs). [c] 0.2 mol % catalyst, 12 hrs. (unless it is in combination with (d), then the reaction time was 24 hrs). [d] Air balloon, 24 hrs.

groups on the peptoid scaffold. These features enabled to develop a very active Cu-TEPMO based catalyst for the aerobic oxidation of primary alcohols, operating in loading of 0.1 mol% with 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 sequence.

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