



A metallopeptoid as an efficient bioinspired cooperative catalyst for the aerobic oxidative synthesis of imines



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ABSTRACT

Enzymatic catalysis is largely based on intramolecular cooperativity between a metal center and functional organic molecules located on one scaffold. Inspired by this concept we have designed the metallopeptoid trimer **BT**, which is a unique intramolecular cooperative oxidation catalyst incorporating two catalytic centers, phenanthroline-copper and TEMPO, as well as one non-catalytic benzyl group. Herein we explore the capability of **BT** to act as an efficient catalyst for the oxidative synthesis of imines, which are versatile intermediates in the fine chemicals and pharmaceutical industries. We demonstrate that **BT**, combined with CuI, can catalyze the production of benzyl, aryl, heteroaryl, allylic and aliphatic imines from various alcohols and amines with a turn-over-number up to 45 times higher than this achieved when phenanthroline, copper and TEMPO are mixed in solution. Moreover, in low catalyst(s) loading, **BT** enables transformations that are not possible when a mixture of the individual catalysts is employed.

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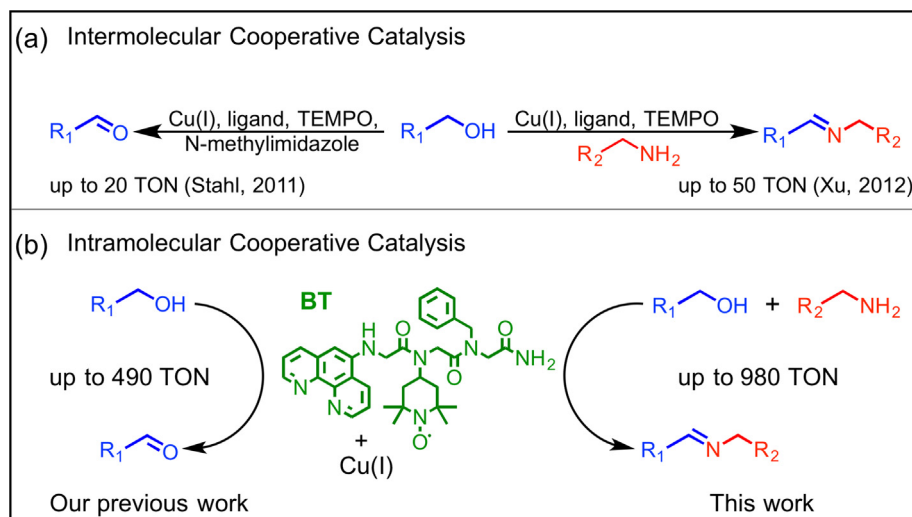
1. Introduction

The search for new catalysts is one of the highest priorities for chemists, both in academia and industry, seeking to run processes at ambient temperatures and pressures, with reasonable reaction rates and a high turnover numbers, and with high selectivity. The gains from improving catalysts are enormous both financially and environmentally, leading to increased reaction efficiency, selectivity and products availability, as well as to the reduction of harmful waste. In nature, enzymes promote chemical and biological reactions with exquisite efficiency and selectivity under very mild conditions. Enzymatic catalysis is largely based on the cooperativity between a metal center and functional organic molecules located at the surrounding folds of the protein (intramolecular cooperative catalysis). This cooperativity leads to the creation of catalytic pockets, which enable enzymes' high specificity and efficiency [1]. The concept of cooperativity has inspired the design of cooperative catalytic systems [2], specifically the combination between a transition metal catalyst and an organocatalyst, which are used as a mixture in solution (intermolecular cooperative catalysis) [3,4]. One example is the combination between Cu(I) complexes and nitroxyl catalysts, which has led to the development of various homogeneous catalytic systems for the aerobic oxidation of alcohols to aldehydes and ketones (Scheme 1a, left) [5–8],

lactonization of diols [9] and oxidative coupling of alcohols and amines to imines [10] or to nitriles and amides [11,12]. Among these transformations, the production of imines is especially important because the highly reactive C=N bond can undergo a variety of subsequent organic reactions such as reduction, addition, cyclization, and aziridination [13], enabling the synthesis of fine chemicals as well as of pharmaceutically and biologically active compounds [14]. Several protocols for the synthesis of imines have been developed [15], with the most attractive one being the oxidative cross-coupling of alcohols with amines (Scheme 1a, right) [16], which has a potential to utilize widely available and inexpensive starting substrates, while producing only hydrogen and water as byproducts [17]. Various homogeneous catalytic systems have been reported for this reaction sequence, some exploit earth abundant metal ions such as Cu [10,18] and Fe [19], mild conditions and air or molecular oxygen as the oxidant. These systems, however, employ 2–5 mol% catalysts, therefore the highest turn-over-number (TON) possible, at the maximum of 100% conversion is 50. Although these systems are practical and applies to a large scope of substrates, the low TON is a significant drawback. Moreover, such systems often require addition of base, ligands, and the use of excess alcohols or amines, which can lead to separation problems. Consequently, recyclable heterogeneous catalytic systems were also developed, and high TON could be achieved after multiple recoveries of the catalyst [20]. But these systems also have some drawbacks including requirements for high reaction temperatures, stoichiometric oxidants and less available noble

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Scheme 1. Intermolecular (a) vs. intramolecular (b) catalytic system utilized for the oxidation of primary alcohols and for the oxidative synthesis of imines.

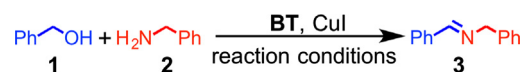
metal ions. In order to overcome the limitations of both homogeneous and heterogeneous procedures there is a need to design a catalyst that will operate in mild conditions, preferably at room temperature and under air or oxygen atmosphere, and will perform with both high conversions and high TON towards the production of imines from a broad scope of alcohol and amines.

One approach for increasing catalytic efficiencies (and selectivities) while maintaining mild reaction conditions is to design intramolecular cooperative catalytic systems in which the catalytic groups are tethered in close proximity to each other [21,22]. This configuration will create a confined catalytic pocket similar to the catalytic sites in enzymes [23]. Adopting such approach, we have recently developed a peptidomimetic catalyst, namely a metal-binding peptoid [24] trimer bearing 1,10-phenanthroline (Phen), TEMPO and a non-catalytic benzyl group (**BT**, Scheme 1b) [25]. We have discovered that the presence of at least one bulky non-catalytic group induces steric constraints on the two catalytic groups, leading to a highly active intramolecular cooperative catalyst [25]. This catalyst, in the combination with Cu(I) and N-methyl imidazole (NMI), enabled the oxidation of various benzylic, allylic and less activated aliphatic primary alcohols at room temperature with TON of up to 16 times higher than a mixture of the Phen, TEMPO, CuI and NMI (the intermolecular cooperative catalytic system, Scheme 1) [25]. Herein we were interested to exploit **BT** as an intramolecular cooperative catalyst for the oxidative synthesis of imines and investigate whether it can enable high TON in mild conditions.

2. Results and discussion

The peptoid catalyst **BT** was synthesized on solid support using the submonomer method [26], as was previously published. The peptoid was characterized by Reverse Phase High Performance Liquid Chromatography (RP-HPLC) and mass spectrometry (MS), cleaved from the resin, purified by HPLC (>99%) and lyophilized to dryness. The ability of **BT**, in combination with a Cu salt, to catalyze the oxidative coupling of alcohols and amines was initially tested using benzyl alcohol **1** and benzyl amine **2** (Table 1), which were chosen as the model substrates to perform and optimize the reaction protocol described in Scheme 1b (right). We have started our investigations by stirring these two substrates in acetonitrile for 12 hours at room temperature under air, with 1 mol% of **BT** and 1 mol% of CuI, and gradually decreased the loading of **BT** and

Table 1
Optimization studies.^a



Entry	CuI (mol%)	BT (mol%)	Time (h)	Conversion (%) ^b	TON
1	1	1	12	>99	100
2	0.5	0.5	12	>99	200
3	0.25	0.25	12	>99	400
4	0.2	0.2	12	90	450
5	0.1	0.1	12	51	510
6	0.05	0.05	24	32	640
7	0.01	0.01	24	2	–
8 ^c	0.2	0.2	12	>99	500
9 ^c	0.1	0.1	12	54	540
10 ^{c,d}	0.1	0.1	12	77	770
11 ^c	0.1	0.1	24	98	980
12	–	0.2	24	NR	–
13	0.2	–	24	Trace	–

^a Reactions were performed in acetonitrile (0.5 mL) at room temperature and under air, with 1.0 equiv. of benzyl alcohol, with 1.1 equiv. amine.

^b Conversions were determined by gas chromatography.

^c Under oxygen atmosphere.

^d 30 °C.

CuI to 0.01 mol% (Table 1, entries 1–7). In the first three reactions, >99% of (E)-N-benzylidene-1-phenylmethanamine **3** was obtained as detected by GC, thus we have succeeded to increase the overall TON of the reaction from 50, as was previously reported, to 400 by using **BT** and Cu as an intramolecular cooperative catalytic system (Table 1, entries 1–3). No other products such as benzyl aldehyde or (E)-N-benzylidene-1-phenylmethanamide were detected, thus the overall selectivity of the reaction was 100%. Further decrease in the catalyst loading to 0.2 and 0.1 mol%, resulted in a decrease in the overall conversion from about 100% to 90% or 51%, respectively and 10% or 49% of unreacted alcohol were observed by the GC in each case correspondingly (Table 1, entries 4–5). Using lower catalyst loadings required a longer reaction time and the product formation in these cases was not sufficient (Table 1, entries 6–7).

In order to maintain a low catalyst loading we decided to attach a small oxygen balloon in atmospheric pressure to the reaction vessel and conduct the reaction with 0.2 mol% of **BT** and CuI under oxygen atmosphere. In these conditions, 99% of imine was obtained, leading to an increase in the TON from 400 to about

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