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Organocatalytic Oxidation of Secondary Alcohols Using 1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA)

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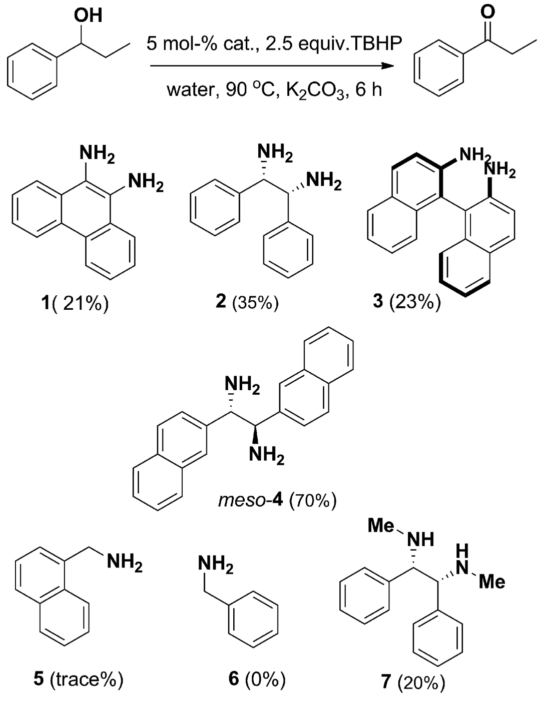
Diamine, 1,2-di(1-naphthyl)-1,2-ethanediamine (NEDA), efficiently catalyzes the oxidation of alcohols by using TBHP as an oxidant. Notably, secondary benzyl alcohols are oxidized in almost quantitative yields, and the catalyst also displays high activity towards even hindered cycloaliphatic secondary alcohols. With enantiopure (*R*,*R*)-NEDA, oxidative kinetic resolution can be realized and depending on the alcohol *ee* up to 99 % are achieved.

Oxidation is of great importance in organic synthesis.[1] In particular, green, efficient and selective alcohol oxidation methods are highly sought after in the chemical industry,[2] and in the synthesis of fine chemicals.[3] To date, many excellent metal based catalytic methods have been developed for this transformation.[4] However, organocatalytic oxidation methods are less common.[5] Among those developed, the nitroxyl radical based methods have attracted particular attention; TEMPO is often used as a catalyst with bleach (sodium hydrochlorite) or a hypervalent iodine(III) species as terminal oxidant.[6] When the removal of residual metals from the reaction product is essential e.g. in the production of pharmaceutical intermediates, metal-free catalyzed systems are considered particularly beneficial.

We recently reported the activation of molecular oxygen by 9,10-diaminophenanthrene (DAPHEN).[7] Whereas this reaction leads to catalytic oxidation of benzylic alcohols with moderate activity, a peroxy intermediate in an imine resonance isomer was detected by nuclear magnetic resonance (NMR) spectroscopy. This observation prompted us to investigate other diamines for catalytic alcohol oxidation.

To find an appropriate diamine based catalyst we first examined the chemical behaviour of DAPHEN (**1**) (Scheme 1) as a prototypical example of such catalysts. In our model reaction, oxidation of propylphen-1-ol, low conversion was detected (Scheme 1, **1**, 21 %). Next we investigated structurally related primary diamines and from those **2** and **3** were found to be reactive. Surpisingly, *meso*-1,2-di(1-naphthyl)-1,2-ethanediamine (**4**), resulted in a marked improvement of conversion (70 %). Catalytic competence of the corresponding ethylenediamine fragment with binaphthyl substituents was further evaluated; only trace amount of propiophenone was detected from benzylamine (**5**) and naphthylmethylamine (**6**). Notably, the synthesized aliphatic secondary amine **7** derived from catalyst **2** shows lower reactivity (20 %). Primary diamine centers together with ethanenaphthyl moiety of naphthylethanediamine are crucial structural moieties of the efficient oxidation catalyst.



Scheme 1. Various amines studied as an organocatalyst in oxidation of propylphen-1-ol into propiophenone.

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Different oxidants were assessed for NEDA-catalyzed 1-phenyl-1-propanol oxidation. With H_2O_2 and TBHP (1.5 equiv.) 40 % and 70 % conversion, respectively, were obtained in 8 h (Table 1, entries 1 and 2). It is noteworthy that the catalyst also works using oxygen as oxidant under the same conditions but with reduced (9 %) conversion (Table 1, entry 3). Further experiments were performed with TBHP to illustrate the catalytic ability of NEDA and to improve the conversion. Adding 2.5 equiv. of the TBHP increases the conversion to 94 % and propiophenone was obtained with 91 % isolated yield (Table 1, entry 4).[8] A control experiment with TBHP alone gave 10 % conversion (Table 1, entry 5).

Table 1. Influence of oxidant and other variables in NEDA-catalyzed oxidation of 1-phenyl-1-propanol.[a]

Entry	Additive	T [h]	Oxidant	Temp. [°C]	Conversion [%]
1	K_2CO_3	6	H_2O_2[b]	70	40
2	K_2CO_3	6	TBHP	95	70
3	K_2CO_3	6	O_2	95	9
4	K_2CO_3	9	TBHP	95	94[c]
5	K_2CO_3	16	TBHP	95	10[d]

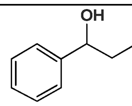
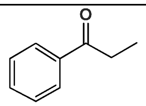
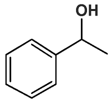
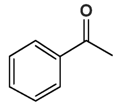
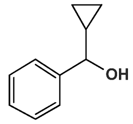
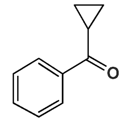
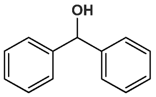
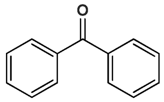
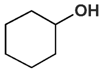
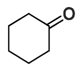
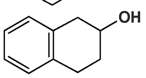
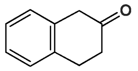
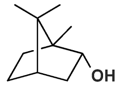
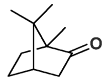
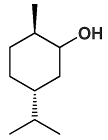
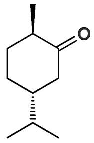
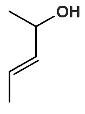
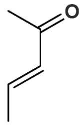
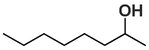
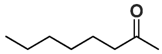
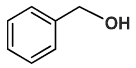
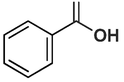
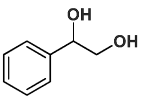
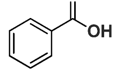
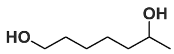
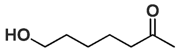
[a] Substrate (2.0 mmol), NEDA (0.046 mmol, 2.2 mol-%), TBHP (2.5 equiv., 6.2 mmol 70 % solution in water), 2 mL of solvent. The results were collected via GC–MS. [b] MeCN as solvent. [c] Isolated yield 91 %. [d] No catalyst.

The scope of this oxidation method was studied under the optimized reaction conditions (Table 2). All reactions were carried out under reflux in presence of 2.2 mol-% catalyst and 2.5 equiv. of TBHP in alkaline water. Various benzylic, aliphatic cyclic primary and secondary alcohols were converted into the corresponding ketones in good yields.

The secondary benzyl alcohols with different steric and electronic environment were converted in almost quantitative yields (Table 2, entries 1–4) demonstrating the generality of the approach used. Interestingly, also cyclohexanol (entry 5) and even tetranol, isoborneol and menthol (entries 6–8) were viable substrates. However, aliphatic and allylic secondary alcohols such as 2-buten-1-ol and octan-2-ol displayed lower reactivity, with 25 % and 49 % yields respectively (Table 2, entries 9 and 10)[9].

Similar reaction conditions can also be employed to the oxidation of primary alcohols. For example, benzyl alcohol was oxidized to benzoic acid with 61 % conversion after 23 h (entry 11). Finally, the catalyst displays interesting regioselectivity for a vicinal diol such as 1,5-hexandiol; the secondary hydroxy group is oxidized leaving the primary alcohol function intact (Table 1, entry 13). Only a handful of methods are known for selective oxidation of secondary alcohols in the presence of primary alcohols.[10]

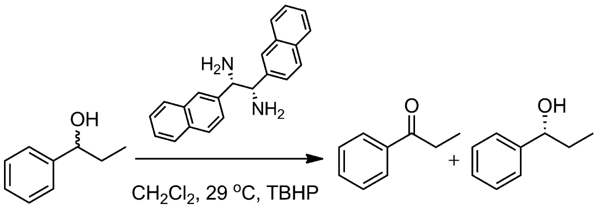
Table 2. Oxidation of various secondary alcohols to yield ketones.[a]

Entry	Substrate	Product	Time [h]	Yield
1			9	97[c]
2			9	94
3			16	72
4			7	98
5			10	87
6			10	91
7[b]			16	60
8			16	45
9			16	21
10[b]			16	49
11[d]			23	71
12[c]			16	74
13[c]			12	65

[a] Reaction conditions: substrate (2.0 mmol), racemic NEDA (2.2 mol-%), TBHP (80 % solution in water, 6.2 mmol), alkaline water (pH = 9–10) as solvent (2 mL), at 95 °C, yields refer to GC/MS using decane as internal standard, and ^1H NMR spectra (average of three experiments). [b] MeCN as solvent. [c] Isolated yield. [d] Side product 20 % of aldehyde.

Encouraged by the efficient organocatalyzed oxidations, we explored the possibility to use enantiopure (R,R)-NEDA in kinetic resolution of racemic secondary alcohols (OKR) (Scheme 2). Enantioenriched alcohols are ubiquitous in the structures and syntheses of natural products and pharmaceuticals. Generally, they have been prepared by many methods, among the known processes, the oxidative kinetic resolution of racemic alcohols to obtain enantioenriched alcohols is an attractive and efficient method to these molecules.[10,11]

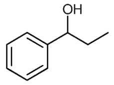
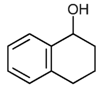
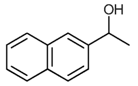
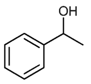
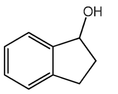
When CH_2Cl_2 solution of racemic 1-phenylpropanol and chiral NEDA was treated with TBHP at 29 °C for 5 h, (R)-1-phenylpropanol was recovered with moderate enantio-



Scheme 2. Kinetic resolution of 1-phenylethanol using (*R*,*R*)-NEDA catalyst.

selectivity 51% *ee* (Scheme 2 and Table 3, entry 1). The use of same reaction but with higher dilution as well prolonged time significantly improved the *ee* value of the (*R*)-1-phenylpropanol to 98% with yield of 52%. Under the optimized conditions, the *R* enantiomers were obtained with 83–88% *ee* and 39–52% yields from the reaction of 1-phenyl-1-ethanol and 1-(2-naphthyl) ethanol(Table 3, entry 4 and 5). Cyclic carbinols were also oxidized, and good enantiomeric selectivity was obtained from 1-tetranol and 1-indanol at similar reaction conditions (Table 3, entry 3 and 6). Although we applied this system for few substrates, this clearly exemplifies potential of diamine based organocatalysts (NEDA) in oxidative kinetic resolution. Moreover, this research provided useful insights for development of catalytic systems applicable to a wider range of substrates.

Table 3. Oxidative kinetic resolution of racemic secondary alcohols using NEDA as a catalyst in the presence of TBHP.[a]

Entry	Substrate	*t* [h]	% Conversion[e]	% *ee*[f,g]
1[b]		5	40	52 (*R*)
2[c]		20	52	98 (*R*)
3[d]		22	53	82 (*R*)
4[d]		22	52	88 (*R*)
5		20	39	83 (*R*)
6[d]		20	55	67 (*R*)

[a] Reaction conditions: substrate (0.5 mmol), NEDA (0.025 mmol, 5 mol-%), TBHP (70% solution in water, 1.6 mmol), K_2CO_3 (0.020 mmol) and CH_2Cl_2 as solvent, room temp. [b] Same reaction was carried out using H_2O and MeCN both showed poor *ee*%. [c] Same reaction with prolonged time and higher dilution (0.1 M substrate). [d] Same reaction with high dilution and room temperature. [e] Product conversion was determined by GC–MS or ^1H NMR methods. [f] The *ee* were determined by GC or HPLC analysis using chiral column. [g] Determined by comparison of the optical rotation with literature value.

We carried out a detailed kinetic study of the oxidation of 1-phenylethanol and determined dependencies on TBHP and NEDA concentrations. Starting with TBHP effect via different TBHP amounts we noticed a clear increase of the reaction rate in a second order plot,[8] the logarithmic graph of slopes (rate constant, *k*) against TBHP concentrations, revealing an approximately first order (1.07) correlation with the reaction rate. Similarly NEDA concentration correlated with the reaction rate in approximately first order (0.95), which indicates the involvement of a single catalyst molecule in the turnover-limiting step of the catalytic cycle. Furthermore, ESI-MS experiments, a hydroperoxy-NEDA (*tert*-butylOO-NEDA) species was observed.[8] The observations lead us to postulate that the mechanism proceeds via single electron transfer, however further mechanistic studies are ongoing.

In conclusion, we successfully developed an efficient organocatalytic oxidation for secondary alcohols using NEDA as a catalyst and *t*BuOOH as a terminal oxidant. Under mild reaction conditions a wide range of secondary alcohols converted into corresponding ketones in high yields. The chiral NEDA also shows promising enantioselectivity in oxidative kinetic resolution of racemic secondary alcohols with *ee* values up to 98%. High enantioselectivity and mechanistic observations propose involvement of one single catalytic centre carrying a peroxy moiety in the diamine skeleton.

The results reported here highlight the substantial scope for the nonmetal catalytic oxidation of alcohols with preferential oxidation of secondary alcohols by diamines. Thus, the simplicity, high chemoselectivity and the mildness of the reaction associated with this organocatalyic system, suggests its potential for the use in synthetic chemistry. Efforts to further expand the scope of diamine catalysed oxidations; oxidative kinetic resolution studies and the catalytic mechanism are currently in progress.

Experimental Section

General Procedure for Metal-Free Catalytic Alcohol Oxidation: NEDA (16.8 mg, 2.2 mol-%), 1-phenyl-1-propanol (250 mg, 2.0 mmol) and 4 mol-% K_2CO_3 were added into 2 mL water and stirred at 95 °C for 9 h. The 6.2 mmol(2.2 equiv.)TBHP (80% TBHP solution in water, 668 µL) was added slowly in 1h with rate 12 µL/min rate using a pump system (syringe pump equipped with a glass syringe and PFTE 1:16 in. tubing into the reaction). Decane was added as internal standard and the reaction was quenched by using $NaHSO_3$ (100 mg) in 1.5 mL ethyl acetate. The solids were filtered off and the organic layer was collected and dried using Na_2SO_4, concentrated and its composition was analyzed via GC–MS and/or NMR spectroscopy. The product was isolated by flash chromatography (n-pentane/Et_2O eluent, 8:2) to afford the product propiophenone (244 mg, 91 % yield). Every catalytic reaction under the same reaction conditions was repeated at least 3 times, and the average values are reported.

Supporting Information (see footnote on the first page of this article): Materials and methods, general reaction procedures, spectral data, general oxidative kinetic resolution conditions, high resolution ESI-MS measurement, optimization studies, full spectra of the NEDA catalyst reaction, NMR spectra, references.

Acknowledgments

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