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Diastereoselective and Enantiospecific Direct Reductive Amination in Water Catalyzed by Palladium Nanoparticles Stabilized by Polyethyleneimine Derivatives

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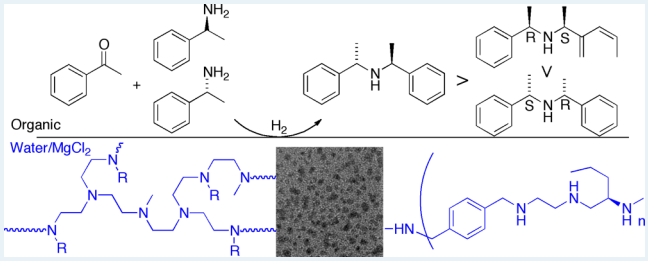
Supporting Information

ABSTRACT: Alkylated polyethylenimine or homochiral polyethylenimine derivatives, or both, were used to stabilize palladium nanoparticles dispersed in water. Such constructs have hydrophobic regions that enabled the aqueous biphasic hydrogenation of imines formed in situ by the reaction of ketones and chiral primary amines. In the presence of $MgCl_2$, good yields of the direct amination product were obtained with high diastereoselectivity. In the presence of a homochiral polyethylenimine, enantiospecific direct amination was observed via kinetic resolution, ostensibly as a result of preferred access of one enantiomer to the achiral reaction center.



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A water-soluble enzyme can be described simplistically as a homochiral polypeptide that typically folds to yield a globular structure with a relatively hydrophobic core and a more hydrophilic surface. Cross-linking via cysteine S−S bonds increases rigidity. Metalloenzymes with an achiral reaction center embedded in a hydrophobic pocket, such as cytochrome P-450 with its heme active moiety, can catalyze stereoselective reactions.[1] Importantly, enzymes can thus catalyze stereoselective transformations of hydrophobic substrates in an aqueous medium and allows reactions without organic solvents. We are intrigued by the possibility of preparing synthetic enzyme mimics that could be prepared in a bottom-up synthetic stratagem. Originally, modification of water-soluble achiral polyethylenimines with various alkyl groups led to such so-called "synzymes".[2−9] Further attachment of catalytic moieties to the polyethylenimine chain allowed the mimicking of transamination and benzoin condensation reactions through addition of pyridoxamine and thiazolium groups.[10−13]

In our group, we have shown that constructs formed by the incorporation of molecular compounds such as polyoxometalates into alkylated polyethylenimines can be used to catalyze the aqueous biphasic epoxidation and carbon−carbon bond cleavage of alkenes.[14] Further cross-linking of such constructs, analogous to cysteine-based cross-linking in proteins, led to more rigid hydrogels that catalyzed the lipophiloselective oxidation of secondary alcohols.[15] Colloidal or nanoparticles of palladium were also incorporated into alkylated polyethylenimine derivatives that then catalyzed the aqueous biphasic chemoselective hydrogenation of alkenes.[16] It should be noted that also hyperbranched polymers and dendrimers, whose synthesis is more demanding, can also incorporate catalysts into their cores, although typically, these assemblies are not water-soluble.[17−24]

The generation of homochiral synzymes represents the next level of complexity in this approach. The question that can be asked is, Can a chiral polyethylenimine globule with a hydrophobic core induce stereoselectivity to a catalytic center by relatively weak interactions based on hydrogen bonding and/or van der Waals and $\pi-\pi$ interactions? A first example was the preparation of a cross-linked chiral polyethylenimine polymer that contained a molecular manganese(III)salen epoxidation catalyst.[25] Incorporation of an achiral manganese(III)salen catalyst showed only low enantioselectivity. Interestingly, however, incorporation of chiral Jacobsen catalyst into the chiral polyethylenimine construct showed a synergetic effect where the presence of the chiral polyethylenimine "medium" significantly increased the enantioselectivity.

Reduction of imines is a fundamental synthetic transformation because of their versatility as intermediates for the preparation of amines common as pharmaceuticals and agrochemicals.[26,27] The classic, conventional reagent for this transformation is $NaBH_4$, and its derivatives, such as $NaBH_3CN$,[28] $NaBH(OAc)_3$,[29,30] and $NaBH_4-ZnCl_2$.[31,32] There are some examples using water as solvent for imine reduction, such as hydrogenation at high H_2 pressure of 35 bar and above,[33,34] with the use of aldehydes or the more reactive α-ketoacids,[35] and the use of noble metals with Al metal as a reducing agent at high temperatures, 120 °C.[36] Methods for one pot direct reductive amination (DRA) of aldehydes and

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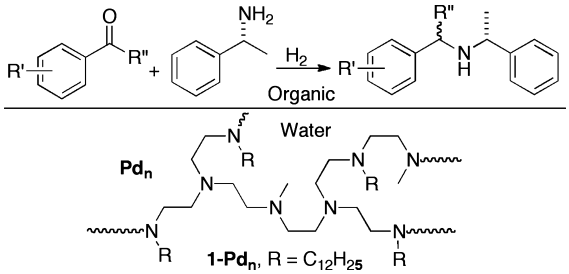
ketones,[37−39] including stereoselective DRA,[40−42] have recently been reported. Typically, organic solvents have been used for the DRA reaction, even in a biocatalytic reaction;[43] however, stabilization of the intermediate imine by an electron-withdrawing group, such as in the DRA of a α-ketoacid such as oxaloacetic acid, can facilitate a reaction in water.[44] In fact, the option of using water as a solvent for imine formation or DRA is somewhat counterintuitive, since water is usually excluded from the reaction to drive the formation of imine forward, coupled with the high reactivity of most hydride based reducing agents with water itself. Thus, hindered imine formation and DRA of ketones to secondary amines is usually achieved under strong dehydrating conditions using molecular sieves;[45,46] azeotropic removal of water;[47,48] or strong Lewis acids, such as $Ti(OiPr)_4$[38] and $TiCl_4$.[49]

Herein, we report that (1) Pd nanoparticles stabilized by alkylated polyethylenimine derivatives[16] catalyze the diastereoselective direct reductive amination of ketones by hydrogenation under mild conditions to the corresponding secondary amines at aqueous biphasic reaction conditions and (2) Pd nanoparticles similarly stabilized by homochiral polyethylenimine derivatives catalyze the mildly enantiospecific direct reductive amination of ketones with chiral secondary amines.

As previously described,[16] branched PEI (M_w = 60 000 with ~25% primary and tertiary amines and ~50% secondary amines) was alkylated with 1-iodododecane to yield alkylated polyethylenimine, **1**. After removal of HI, K_2PdCl_4 was added to an aqueous solution of **1** that was treated with $NaBH_4$, leading to a brown-black suspension of stabilized palladium nanoparticles **1-Pd$_n$**. A transmission electron micrograph of the dispersion prepared by freeze fracture of the aqueous solution confirmed the formation of palladium nanoparticles with particle sizes ranging around 2 nm (see Supporting Information Figure S1).

The aqueous biphasic direct reductive amination of acetophenone (R′ = H, R″ = Me) with (*R*)-1-phenylethanamine was used as a model reaction (Scheme 1). The results

Scheme 1. Aqueous Biphasic Direct Reductive Amination of Acetophenone Derivatives with (*R*)-1-Phenylethanamine



show that at 22−55 °C, low yields of bis(1-phenylethyl)amine were obtained, however, with high diastereomeric excesses of >90% to the chiral (*RR*) versus minor meso (*RS*) product.[50] The formation of the *RR* product is typically observed in such reactions.[51] The imine intermediate compounds were always observed in only trace amounts. Clearly, the competitive reduction of acetophenone to 1-phenylethanol was the major factor in the low yields (Table 1).

The solubilities of acetophenone and 1-phenylethanamine in water are 2.4 and 793 g/L, respectively, at pH = 7, 25 °C. Thus, it can be intuitively understood that the significantly greater solubility of acetophenone in the hydrophobic core of the

Table 1. Aqueous Biphasic Direct Reductive Amination of Acetophenone with (*R*)-1-Phenylethanamine[a]

T, °C	PhC(O)Me conv, mol %	DRA yield, mol %	de, %	alcohol yield, mol %
22	86	8	93	77
50	>99	12	91	87
100	>99	3	82	96
50[b]	>99	52	90	48

[a](*R*)-1-Phenylethanamine (0.2 mmol), acetophenone (0.2 mmol), **1-Pd$_n$** (1 mL of H_2O, 1.05 mg of **1**, 0.87 mg of Pd$_n$), 3 bar H_2, 21 h. The conversion was determined by GC−FID, and the % de, by GC−MSD. The imine was observed in trace amounts. The results are an average of three experiments. [b]With 300 mg of $MgCl_2$.

alkylated polyethylenimine leads to its competitive hydrogenation. Therefore, it was surmised that addition of a salt to the aqueous solution would increase the yield of the direct amination reaction through reduction of the solubility of (*R*)-1-phenylethanamine in the water phase. Among the salts tested, the apparent order of efficiency in raising the yield without loss of diastereoselectivity was $MgCl_2$ ~ $CaCl_2$ ~ LiCl > NaCl > KCl > Na_2SO_4. The addition of 300 mg of $MgCl_2$ to the reaction led to a 52% yield (90% de; *R*,*R*) of the amine product. Under these somewhat optimized conditions, a series of acetophenone derivatives were reacted with (*R*)-1-aminoethylbenzene (Table 2).

Table 2. Aqueous Biphasic Direct Reductive Amination of Various Ketones with (*R*)-1-Phenylethanamine[a]

ketone	conversion, mol %[b]	DRA yield, mol %	% de	TON[c]
R′ = H, R″ = Me	99	52	90	1052
R′ = 4-Me, R″ = Me	61	54	91	1136
R′ = 4-Et, R″=Me	48	39	92	821
R′ = H, R″ = Et	18	12	90	252
R′ = 3-OH, R″ = Me	70	58	94	1221
R′ = 4-Br, R″ = Me	>99[d]	15[d]	95	315
R′ = 4-Cl, R″ = Me	>99[d]	22[d]	95	463
R′ = 4-F, R″ = Me	35	30	95	631
$PhCH_2COCH_3$	62	49	84	1031

[a](*R*)-1-Phenylethanamine (0.2 mmol), ketone (0.2 mmol), **1-Pd$_n$** (1 mL of H_2O, 2.82 mg of **1**, 0.92 mg of Pd$_n$), 300 mg of $MgCl_2$, 3 bar H_2, 21 h. The conversion was determined by GC−FID, and the % de, by GC−MSD. The imines were observed in only trace amounts. The results are an average of three experiments. [b]Conversion of ketone. [c]Calculated for the amount of DRA product per Pd atoms on the surface of a sphere 2.5 nm in diameter. [d]All the ketone underwent dehydrohalogenation to yield the coupled product, acetophenone and 1-phenylethanol.

The results show that the reaction was effective for a range of substrates. Interestingly, in the direct reductive amination of acetophenone derivatives (R″ = H), the non-ring-substituted compound (R′ = H) gave the highest total conversion of the ketone. For R′ = 3-OH > 4-Me > 4-Et > 4-F, the conversions were significantly reduced, but perhaps more importantly, the selectivity toward the direct amination product was significantly increased, that is, less ketone was reduced to the 1-phenylethanol derivative. Propiophenone was less reactive, but 1-phenylacetone showed higher reactivity; however, the percent de was lower. The 4-Cl and 4-Br acetophenone derivatives were dehydrohalogenated to yield a combination of

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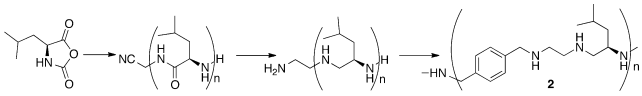
the direct amination product, acetophenone and 1-phenylethanol.

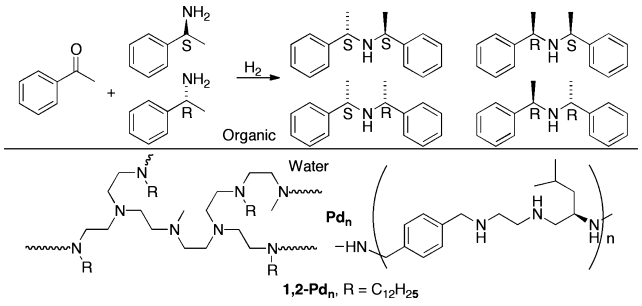
After succeeding in carrying out the direct amination reaction in water by hydrogenation with high diasteroselectivity, we wished to test the possibility of carrying out enantiospecific reactions by kinetic resolution. For this purpose, a homochiral polyethylenimine compound is needed. This can be prepared, as previously reported,[8] by *N*-carboxyanhydride polymerization of L-leucine using 2-aminoacetontrile as a polymerization initiator. Upon reduction, a homochiral polyethylenimine oligomer is formed with repeating chiral centers and *i*-butyl side chains. The polymer chain can be extended by reaction of the terminal amines with terephthaldehyde followed by reduction of the intermediate imine to yield the homochiral polyethylenimine, **2** (Scheme 2). Since this compound is not

Scheme 2. Preparation of the Homochiral Polyethylenimine Derivative, 2



sufficiently water-soluble, it was mixed with **1**. This combination allowed the preparation of stable palladium nanoparticles, **1,2-Pd$_n$** (see the Supporting Information) that were used as hydrogenation catalysts for the aqueous biphasic enantiospecific direct reductive amination of acetophenone with (*R*,*S*)-1-aminoethylbenzene (Scheme 3).

Scheme 3. Enantiospecific Aqueous Biphasic Direct Reductive Amination of Acetophenone Derivatives with (*R*,*S*)-1-Phenylethanamine



Representative results for the direct reductive amination of acetophenone with (*R*,*S*)-1-phenylethanamine catalyzed by **1,2-Pd$_n$** are presented in Table 3. Analysis of the results shows that

Table 3. Aqueous Biphasic Direct Reductive Amination of Acetophenone with (*R*,*S*)-1-Phenylethanamine[a]

$MgCl_2$, mg (*T*, °C)	conversion mol %[b]	DRA yield, mol %	% ee[c]	% de
none (22)	92	15	16	96
300 (22)	69	38	20	93
300 (50)	96	44	9	91

[a](*R*,*S*-1)-phenylethanamine (0.4 mmol), acetophenone (0.2 mmol), **1,2-Pd$_n$** (1 mL of H_2O, 2 mg of **1**, 3 mg of **2**, 0.87 mg of Pd$_n$), 3 bar H_2, 21 h. [b]The conversion was determined by GC–FID, and the % de, by GC–MSD. [c]The % ee was determined by HPLC by measuring the ratio of the remaining (*R*,*S*)-1-phenylethanamine. The results showed a preference for the reaction of the *R* isomer. The imine was observed in trace amounts. The results are an average of three experiments.

the direct reductive amination of chiral 1-phenylethanamine with acetophenone proceeded enantiospecifically with a preference for reaction of (*R*)-1-phenylethanamine. In addition the following results were obtained. (i) A prochiral imine such as one prepared from acetophenone and achiral benzylamine, prepared either in situ or directly used as substrate, yielded *N*-benzyl-1-phenylethanamine without any discernable enantiomeric excess. (ii) The partial reduction of acetophenone to 1-phenylethanol also proceeded without any enantioselectivity. All these results support the idea that the kinetic resolution is likely due to a "solvent" effect of the homochiral polyethylenimine that allows preferred access of (*R*)-1-phenylethanamine to the achiral Pd nanoparticulate catalyst. It would appear that the chiral polyethylenimine *does not* act as a chiral modifier of Pd nanoparticles, as has been observed in the past, notably for hydrogenation catalyzed by platinum modified with a cinchona alkaloid.[52−54]

Counterintuitively, in this research, we have shown that direct reductive amination of a ketone and chiral amine via an intermediate imine is possible in an aqueous reaction medium by hydrogenation over a Pd nanoparticulate catalyst stabilized by an alkylated polyethylenimine. Salts such as $MgCl_2$ can increase the yield through salting out of the amine into the hydrophobic regions of the alkylated polyethylenimine that stabilizes the Pd nanoparticles. The reaction proceeds with high diasteroselectivity. Stabilization of achiral Pd nanoparticles by addition of a homochiral polyethylenimine can lead to enantiospecificity by kinetic resolution.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details including syntheses and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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