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[10] A series of compounds with different R groups, such as aliphatic and aromatic amides, carbamates, sulfonamides, and ureas, has been tested and all of the compounds showed very similar affinities to E-selectin. Compounds **3b–d** were selected as representative examples. See: R. Bänteli, P. Herold, C. Bruns, J. T. Patton, J. L. Magnani, G. Thoma, *Helv. Chim. Acta* **2000**, *83*, 2893.

[11] Compound **4**: ^{1}H NMR (600 MHz, D_2O, 25 °C, DSS): $\delta = 5.03$ (H1^F), 3.78 (H2^F), 3.88 (H3^F), 3.80 (H4^F), 4.77 (H5^F), 1.19 (H6^F), 4.49 (H1^G), 3.60 (H2^G), 3.38 (H3^G), 3.89 (H4^G), 3.60 (H5^G), 3.72 (H6^G), 3.47 (H1a^S), 3.94 (H1e^S), 1.62 (H2a^S), 2.21 (H2e^S), 3.98 (H3^S), 3.27 (H4^S), 3.43 (H5^S), 1.35 (H6^S). Compound **5**: ^{1}H NMR (600 MHz, D_2O, 25 °C, DSS): $\delta = 4.96$ (H1^F), 3.74 (H2^F), 3.88 (H3^F), 3.79 (H4^F), 4.42 (H5^F), 1.19 (H6^F), 4.49 (H1^G), 3.58 (H2^G), 3.38 (H3^G), 3.90 (H4^G), 3.62 (H5^G), 3.72 (H6^G), 3.55 (H1a^S), 3.90 (H1e^S), 1.67 (H2a^S), 2.15 (H2e^S), 4.01 (H3^S), 3.66 (H4^S), 3.46 (H5a^S), 3.99 (H5e^S). Compound **6**: ^{1}H NMR (600 MHz, D_2O, 25 °C, DSS): $\delta = 4.91$ (H1^F), 3.76 (H2^F), 3.87 (H3^F), 3.78 (H4^F), 4.12 (H5^F), 1.20 (H6^F), 4.44 (H1^G), 3.59 (H2^G), 3.40 (H3^G), 3.91 (H4^G), 3.66 (H5^G), 3.75 (H6^G), 3.88, 3.70 (H1^S), 4.08, 3.86 (H2^S). F = fucose, G = galactose, S = spacer between F and G.

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[20] NMR spectroscopic measurements were carried out on a Varian UnityPlus 600 spectrometer operating at a frequency of 600 MHz. All experiments were carried out at 25 °C with compound concentrations of approximately 10 mM in D_2O solutions. ROESY experiments were carried out with mixing times of 150 ms. For some compounds, ROESY spectra were recorded using 50 ms and 100 ms mixing times, and the results were indistinguishable. Typical acquisition times in the direct and indirect dimensions were 340 ms and 64 ms, respectively. The data were zero-filled to yield a digital resolution of 1.46 Hz and 2.92 Hz, respectively. For bound **2**, NOE values were extracted from transfer NOE spectra (see ref. [7b]). Signal integration was performed using Varian VNMR software. All NOEs were normalized using intraglycosidic NOE enhancements such as H1^G–H3^G and H4^F–H5^F. The distances between these hydrogens are given by the chair conformations of fucose and galactose and should be very similar for compounds **2**, **4**, **5**, and **6**. It should be noted that the measured NOE values do not refer to a distinct conformation of the molecule but represent the weighted mean distance over several coexisting low energy conformations.

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Benzene-Free Synthesis of Phenol**

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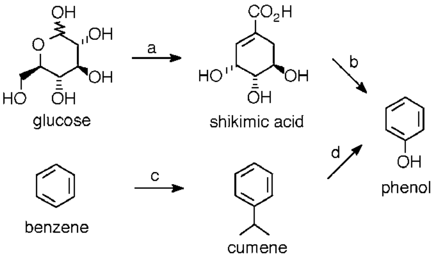
Although phenol has been synthesized by a succession of processes, the Hock oxidation of benzene-derived cumene (Scheme 1) is currently the predominant method used in the production of phenol, which amounts to 5×10^9 kg annually.[1] Most of the past and currently employed phenol syntheses use benzene,[1] a volatile organic carcinogen, as the starting



Scheme 1. Synthesis of phenol. Conditions: a) *E. coli* SP1.1PTS$^-$/pSC6.090B; b) 1) H_2O, 350 °C, 2) Cu^0, H_2O, 350 °C; c) propene, $AlCl_3$; d) 1. O_2, 100 °C, 2. △, H_2SO_4.

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material. Approximately 20% of the global benzene production is directed into the manufacture of phenol.[2] As part of an effort to elaborate alternatives to benzene,[3] the aromatization of shikimic acid in near-critical water has been examined, in which phenol is the primary reaction product. In parallel efforts, shikimic acid was synthesized in concentrations of 71 $g L^{-1}$ by altering the mechanism for glucose transport in *E. coli*. The chemistry of shikimic acid in near-critical water and its high-titer synthesis from glucose establish a benzene-free route to phenol.

An aqueous solution of shikimic acid was heated to 350 °C and maintained at this temperature for 30 min. Phenol, *m*-hydroxybenzoic acid, and *p*-hydroxybenzoic acid were produced in yields of 53%, 18%, and 1%, respectively. The extraction of the reaction mixture with diethyl ether and the distillation of the concentrated residue afforded white, crystalline phenol in a yield of 45%. The residue that remained from the distillation was dissolved in water and heated at 350 °C with Cu^0 powder. After extraction and distillation, additional phenol (6%) was obtained.

The overall yield of phenol that was obtained when shikimic acid was heated in near-critical water (51%) was significantly different from that found in the acid-catalyzed reaction.[4] When shikimic acid was heated at reflux in HCl (12 M) for 14 h, *p*-hydroxybenzoic acid and *m*-hydroxybenzoic acid were produced in yields of 40% and 13%, respectively. Similar yields were obtained when shikimic acid was heated at reflux in aqueous H_2SO_4 (8 M). The concentration of the acid catalyst could be lowered when solutions of shikimic acid in acetic acid were used: when shikimic acid was heated at 120 °C for 16 h in acetic acid that contained H_2SO_4 (1 M), *p*-hydroxybenzoic acid and *m*-hydroxybenzoic acid were obtained in yields of 57% and 9%, respectively.

Although phenol was formed in aqueous solutions of shikimic acid at temperatures as low as 250 °C, the dominant product was 3-*epi*-shikimic acid (Figure 1). At higher temperatures, the yield of 3-*epi*-shikimic acid declined and the yield of phenol increased. The yield of *p*-hydroxybenzoic acid was never higher than 6%, and only traces were detected at higher temperatures, whereas the yield of *m*-hydroxybenzoic acid was always approximately 20%. When *m*-hydroxybenzoic acid was heated in water at 350 °C for 3 h, the yield of phenol was only 5%. In contrast, the reaction of *m*-hydroxybenzoic acid at 350 °C for 3 h in the presence of one equivalent of Cu^0 or Cu^IOAc resulted in phenol in yields of 96% and 95%, respectively.[5]

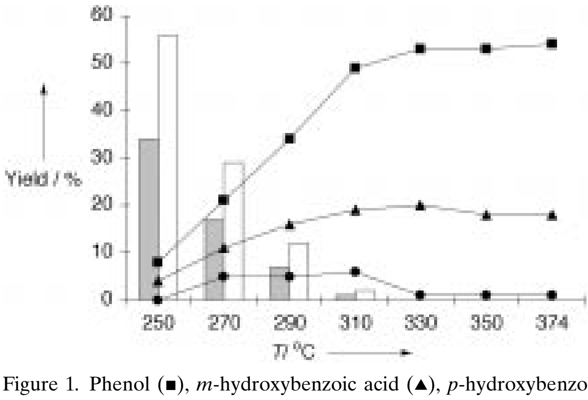
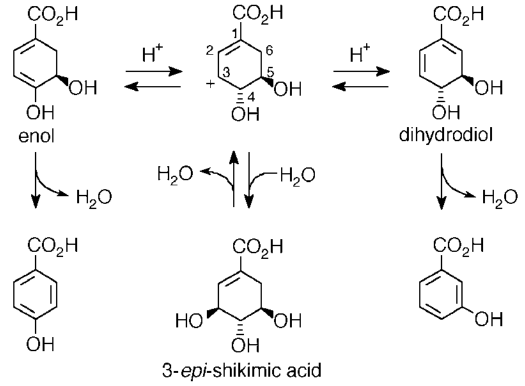


Figure 1. Phenol (■), *m*-hydroxybenzoic acid (▲), *p*-hydroxybenzoic acid (●), and 3-*epi*-shikimic acid (▭), formed in aqueous solutions of shikimic acid (▨) as a function of temperature. The indicated temperatures were maintained for 30 min in a Parr (Model No. 4742) high-pressure reaction vessel.

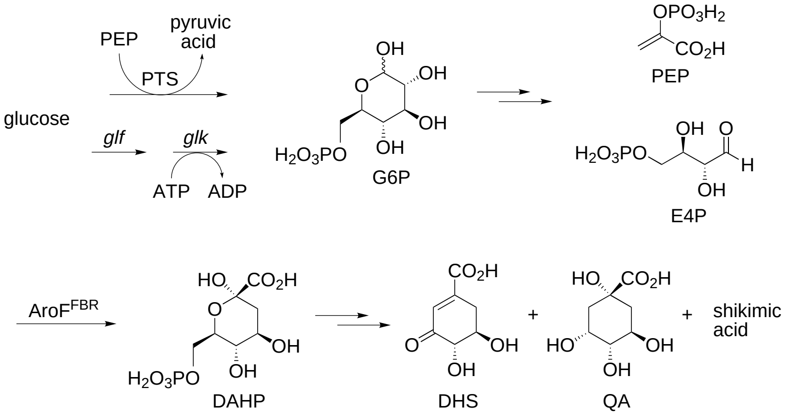
The formation of 3-*epi*-shikimic acid is possibly the result of a C3 carbocation intermediate (Scheme 2). The deprotonation of the C3 carbocation would generate enol and dihydrodiol reactive intermediates (Scheme 2) whose subsequent dehydration would produce *p*-hydroxybenzoic and *m*-hydroxybenzoic acids, respectively. Relatively little phenol is likely to be produced from the decarboxylation of *m*-hydroxybenzoic acid. The decarboxylation of *p*-hydroxybenzoic acid provides one route to phenol although decarboxylation and dehydration of a conjugated δ-keto carboxylate derived from enol tautomerization (Scheme 2) could lead to phenol without the intermediacy of *p*-hydroxybenzoic acid.



Scheme 2. Possible mechanisms for the reaction of shikimic acid in water heated from 250–374 °C.

Shikimic acid has historically not been used in synthesis owing to the expense of its isolation from *Illicium* plants.[6] With the elaboration of a microbe-catalyzed synthesis from glucose,[7] shikimic acid is now used to synthesize the antiinfluenza drug Tamiflu.[8] Microbes such as *E. coli* rely on the carbohydrate phosphotransferase (PTS) system, which catalyzes the transfer of the phosphoryl group from phosphoenolpyruvic acid to promote the transport of glucose and generate glucose 6-phosphate (Scheme 3).[9] Because the byproduct, pyruvic acid, is oxidized to CO_2, the maximum theoretical yield for the synthesis of shikimic acid is 43% (mol/mol) when a microbe that relies on the PTS-mediated transport of glucose is used.[3c, 10]

The PTS system in shikimate-synthesizing *E. coli* SP1.1 was therefore inactivated by using the mutation *Δ(ptsH ptsI crr)::Kn*^{R} to generate *E. coli* SP1.1PTS$^-$.[7, 11] The diffusion of glucose into *E. coli* SP1.1PTS$^-$/pSC6.090B was mediated by the *glf*-encoded glucose facilitator whereas the reaction of glucose with adenosine triphosphate was catalyzed by *glk*-encoded glucokinase (Scheme 3).[12] Both *glf* and *glk* genes, isolated from *Zymomonas mobilis*,[12a] were plasmid pSC6.090B inserts (Figure 2). Improved phosphoenolpyru-



Scheme 3. Glucose transport and biosynthesis of shikimic acid and metabolically related by-products. Abbreviations: PEP = phosphoenolpyruvic acid, PTS = carbohydrate phosphotransferase system, ATP = adenosine triphosphate, *glf* = glucose facilitator protein, *glk* = glucokinase, G6P = D-glucose 6-phosphate, E4P = D-erythrose 4-phosphate, *AroF*^{FBR} = DAHP synthase, DAHP = 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate, DHS = 3-dehydroshikimic acid, QA = quinic acid.

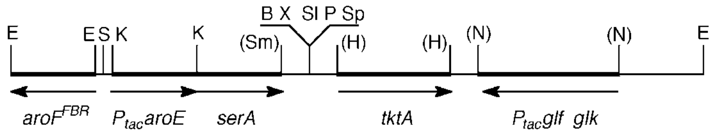


Figure 2. Restriction enzyme map of plasmid pSC6.090B.

vate availability does not increase the biosynthesis of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate, a precursor of shikimic acid, unless the availability of D-erythrose 4-phosphate is increased (Scheme 3).[13] This was accomplished with the increase in transketolase activity attendant with the expression of the *tktA* insert (Figure 2) of plasmid pSC6.090B.[14]

E. coli SP1.1PTS$^-$/pSC6.090B was cultured on a 1 L scale in minimal salts medium under controlled fermentor conditions: the culture was maintained at pH 7, 33 °C, and with a dissolved oxygen level of 10 % air saturation.[15] SP1.1PTS$^-$/pSC6.090B produced (Figure 3) shikimic acid (71 gL^{-1}, 27 % mol/mol yield) from glucose after cultivation for 60 h along with 3-dehydroshikimic acid (15 gL^{-1}) and quinic acid (5 gL^{-1}). In comparison, *E. coli* PTS$^+$ strains, which lack the expression of the *glf*-encoded glucose facilitator, produced less shikimic acid (52 gL^{-1}, 18 % mol/mol yield). The addition of ethanol to the clarified, decolorized fermentation broth followed by continuous liquid–liquid extraction with ethyl acetate provided shikimic acid (97 % recovery).

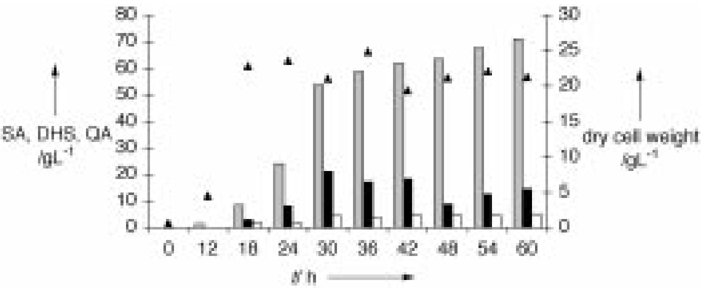


Figure 3. Growth of *E. coli* SP1.1PTS$^-$/pSC6.090B (dry cell weight: ▲) and synthesis of shikimic acid (SA: ▨), by-products 3-dehydroshikimic acid (DHS: ■), and quinic acid (QA: ▭) under fed-batch fermentor conditions.

The reactivity of shikimic acid in near-critical water circumvents the potent antimicrobial activity of phenol. The employment of near-critical water also establishes a unique reaction manifold which connects hydroaromatic compounds with aromatic products, while avoiding the use of high concentrations of strong acids. This is probably a result of the 1000-fold increase in the dissociation constant of water as its critical-point temperature is approached.[16] Shikimic acid can become more readily available, given a predicted 86 % (mol/mol) theoretical maximum yield for its synthesis in lieu of PTS-mediated glucose transport.[3c, 10] The chirality of shikimic acid could thus become essentially disposable as a previously scarce natural product evolves into an abundantly available commodity chemical that is used primarily for its cyclic assemblage of carbon atoms.

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Highly Efficient Catalytic Synthesis of α-Amino Acids under Phase-Transfer Conditions with a Novel Catalyst/Substrate Pair**

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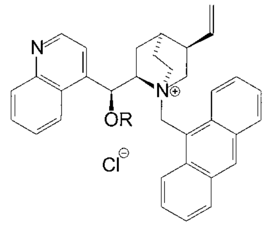
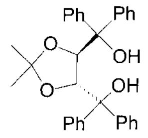
Asymmetric phase-transfer catalysis (PTC) reactions constitute one of the most challenging fields of contemporary organic synthesis.[1] Following the seminal work by O'Donnell et al.[2a] and Grabowski et al.[2b] dramatic improvements in the asymmetric efficiency of PTC reactions were achieved by introducing (9-anthracenylmethyl)cinchonidinium (**1a**, R = allyl, benzyl, H) and other cinchoninium salts as catalysts for the enantioselective alkylation of *N*-(diphenylmethylene)glycine esters with electrophiles.[2c–e] Purely synthetic, chiral, C_2-symmetrical ammonium salts were recently prepared and shown to be highly efficient in the same set of reactions.[3] Thus, preparative catalytic asymmetric syntheses of very important synthetic targets such as amino acids were developed, and enantioselectivities of up to 92-98 % for the final product were achieved.[2c–e, 3]

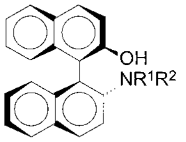


1a



TADDOL **1b**

Unfortunately, *N*-(diphenylmethylene)glycine esters are expensive, and quaternary ammonium salts are sometimes unstable under basic conditions. Hence, the search for novel types of substrates and catalysts for the asymmetric PTC synthesis of amino acids deserves further effort. Recently, we reported on the use of 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN, **2a**) as a novel type of PTC catalyst in the alkylation of *N*-(phenylmethylene)alanine esters and thus the synthesis of α-methyl-α-amino acids with a modest *ee* of 68 %.[4] Our attempts to use **2a** as a catalyst for the asymmetric alkylation of *N*-(diphenylmethylene)glycine esters failed to give any asymmetric induction. We reasoned, however, that other types of achiral glycine derivatives capable of stronger interactions with NOBIN would be more suitable substrates.



R^1=R^2=H, **2a**, (*R*)-NOBIN
R^1=Ph, R^2=H, **2b**
R^1= R^2=Me, **2c**

Earlier, we reported on the synthesis and application of substrate **3** (see Scheme 1) in an asymmetric Michael reaction, catalyzed by (*R*,*R*)-TADDOL (**1b**), that led to 4-methylglutamic acid with a low *ee* (28 %).[5] Substrate **3** seemed to be a suitable model for use in other alkylation reactions with catalyst **2a**, as there are several potential centers of substrate – catalyst interaction by formation of a hydrogen bond or a metal complex. Here we report new results on the alkylation of substrate **3** (Scheme 1) with catalysis by **2a** under phase-transfer conditions, which led to a fast (as little as 5 min), efficient synthesis of α-amino acids at ambient temperature and with *ee* values of up to 93 – 98 %.

Substrate **3** was readily prepared by the templated condensation of *N*-(2-benzoylphenyl)pyridine-2-carbamide (PBP, **4**) with glycine (Gly) and $Ni(NO_3)_2$ in MeOH in the presence of MeONa (Scheme 1). Complex **3** is a red, crystalline compound, easily purified by chromatography on SiO_2 and poorly soluble in most organic solvents and water. The solubility of the complex in organic solvents such as CH_2Cl_2 or $(CH_2Cl)_2$ was greatly increased by adding **2a**.

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