molecular systems could lead to new phase structures with useful macroscopic properties.

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Catalytic Asymmetric Aminohydroxylation with Amino-Substituted Heterocycles as Nitrogen Sources**

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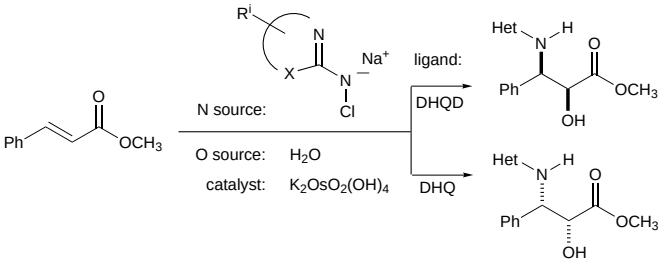
Dedicated to Professor Theodore Cohen on the occasion of his 70th birthday

The β-amino alcohol moiety appears in numerous biologically active compounds,[1] and the osmium-catalyzed asymmetric aminohydroxylation (AA) of olefins provides an efficient method for the enantioselective creation of this important functionality.[2] Sulfonamides,[2a, 3] amides,[4] and carbamates[5] have been utilized as nitrogen sources for the AA, and there has been rapid improvement in both scope and selectivity since the initial report.[2a] The *N*-protected amino alcohols obtained were usually converted into free amino alcohols, so that the development of a set of orthogonally cleavable protecting groups had been our major concern.[2–5] Current developments in combinatorial chemistry stimulated us to exploit this reaction for the direct introduction of biomedically relevant heterocyclic substructures to olefins.[6] We now report an enantioselective procedure for the vicinal addition of a hydroxyl group and amino-substituted heterocycles to olefins (Scheme 1).



Scheme 1. Aminohydroxylation with amino-substituted heterocycles. R^i indicates the remaining portion of the heterocycle. Het = heterocycle, DHQ = dihydroquinine, DHQD = dihydroquinidine.

Attempts to extend the scope of the nitrogen sources in the AA to heterocyclic substituted amines had long been frustrated by very poor turnover and side reactions (e.g. ring chlorinations)[7] until Jerina et al. achieved a breakthrough with the use of an adenine derivative as nitrogen source in the aminohydroxylation of a unique olefin.[8] Then, in collabo-

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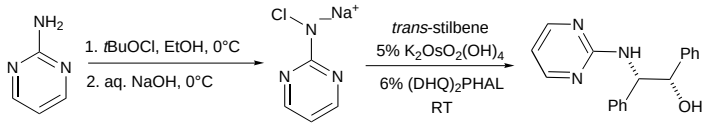
ration with the Jerina group, we developed a general procedure for this kind of transformation;[9] however, no asymmetric induction was achieved. We reasoned that the size and particular placement of the heteroatoms in the adenine moiety favor "second cycle turnover",[3] precluding the desired chirality transfer from the alkaloid ligand. Fortunately, we have since found that simple aminopyrimidines and aminotriazines function as excellent reagents for the AA. With a few modifications to the original procedure, stilbene is converted into either enantiomer of the corresponding amino alcohol with high enantiomeric excesses with 2-aminopyrimidine as the nitrogen source (Scheme 2).

Scheme 2



Scheme 2. Aminohydroxylation of *trans*-stilbene with 2-aminopyrimidine. $(DHQ)_2PHAL$ = 1,4-bis(dihydroquininyl)phthalazine.

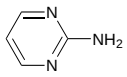
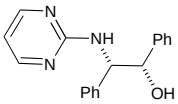
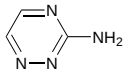
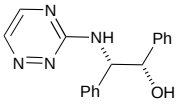
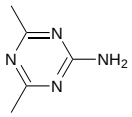
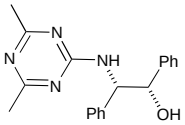
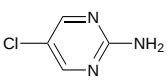
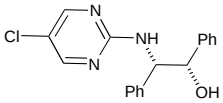
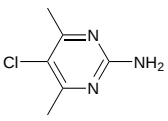
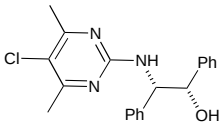
It is imperative that the N-chlorination be performed in the absence of water to retard the electrophilic aromatic substitution. Deprotonation with aqueous NaOH affords the chloramine salts, which are relatively stable, especially under an inert atmosphere. A slight deficit of NaOH ensured the absence of excess OH^- even if some chloramine had been consumed by side reactions. The only suitable solvent systems proved to be mixtures of primary alcohols and water (approx. 2:1 ratio). No turnover was observed for mixtures of water and acetonitrile or *tert*-butyl alcohol. The use of highly polar protic solvents appears crucial to facilitate the rate of hydrolysis of the relatively electron rich osmium azaglycolate intermediate.

Stilbene was chosen as an ideal test olefin for probing the reactivity of other heterocycles because of the mediocre enantioselectivities observed with standard nitrogen sources. The results are documented in Table 1.

The enantiomeric excesses of 56 to 97% observed with these heterocyclic nitrogen sources are quite impressive when compared to those obtained with earlier nitrogen sources for the AA.[10] Obviously, the *ee* value depends on both steric and electronic characteristics of the heterocycles. Smaller nitrogen sources seem to provide higher enantiomeric excesses than the more sterically demanding systems (entries 1, 2 versus 3, 5). There seems to be a modest *ee* advantage for less electron withdrawing substituents on nitrogen (entries 1, 3 versus 2, 5). The chemical yields are reasonable to good, with ring-chlorinated amino alcohols as the major contaminants (entry 1).[11]

To map out the scope of this reaction on the olefin side, we screened a number of representative olefins with 2-amino-4,6-dimethyl-1,3,5-triazine as nitrogen source, for the simple reason that it had shown midrange enantioselectivity with stilbene (Table 1, entry 3). A remarkably broad range of olefins gave good yields and enantioselectivities when subjected to the reaction conditions (Table 2). Cinnamate and fumarate (entries 1 and 2) are among the best substrates, whereas the enantioselectivity for the trisubstituted olefin remains poor (entry 5). In contrast to the highly regioselective adenine derivatives,[9] the simple heterocyclic nitrogen sources give modest regioselectivities, comparable to that of the earlier versions of the AA. For all unsymmetrical olefins, a strong preference for the isomer with nitrogen in the benzylic position was observed; isopropyl cinnamate gave only a single

Table 1. Aminohydroxylation of stilbene with various amino-substituted heterocycles.

Entry	Substrate	Product[a]	Yield [%][b]	% *ee*[c]	M.p. [°C]	$[\alpha]_D^{20}$[d]
1			45	97	132 (decomp)	−0.7 (c = 0.59)
2			50	88	190 (decomp)	−0.7 (c = 1.14)
3			86	87	–[e]	+19.8 (c = 0.98)
4			60	56	119 (decomp)	−11.2 (c = 0.13)
5			65	67	130 (decomp)	−3.2 (c = 0.29)

[a] Major product from the reaction using $(DHQ)_2PHAL$. [b] Yields of isolated pure products after chromatography on silica gel. [c] Determined by chiral HPLC. [d] Concentration in grams per 100 mL of EtOH/$CHCl_3$ (1/1). [e] Not applicable.

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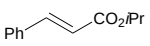
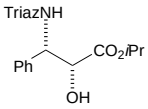
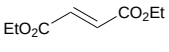
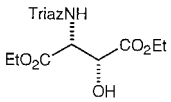
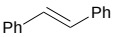
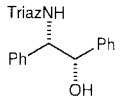
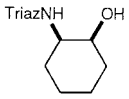
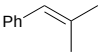
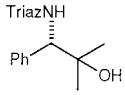
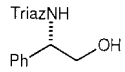
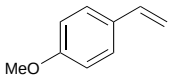
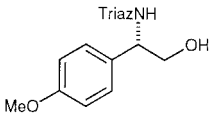
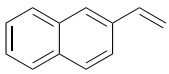
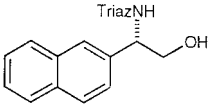
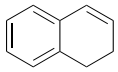
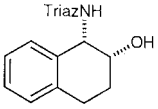
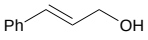
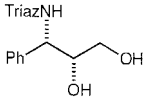
Table 2. Aminohydroxylation of various olefins with 2-amino-4,6-dimethyl-1,3,5-triazine ($TriazNH_2$).

Entry	Substrate	Product[a]	Regioselectivity[b]	% *ee*[c] $(DHQ)_2PHAL$	% *ee*[c] $(DHQD)_2PHAL$	Yield [%][d]
1			> 20:1	99	98	97
2			–	92	81	94
3			–	87	87	86
4			–	79	71	92
5			> 20:1	41	37	60
6			5:1	86	80	74
7			6:1	95	95	79
8			6:1	98	96	80
9			2:1	46	48	75
10			7:1	45	38	81

[a] Major product from the reaction using $(DHQ)_2PHAL$. [b] Determined by ^1H NMR spectroscopy. [c] Determined by HPLC on a chiral stationary phase. [d] Yields of isolated products from the reaction using the $(DHQ)_2PHAL$ ligand, where regioisomers are possible, of a mixture of both regioisomers. Similar yields and regioselectivities were obtained with the $(DHQD)_2PHAL$ ligand.

regioisomer. The regioisomers were separable by preparative thin-layer chromatography (TLC).

In summary, this new generation of nitrogen sources greatly extends the scope of the osmium-catalyzed AA. Of additional interest, the AA can now be considered as a means for introducing complex heterocyclic fragments into hydrocarbon backbones when appropriate olefinic functionality is present.

Experimental Section

Representative procedure for the aminohydroxylations: reaction of 2-aminopyrimidine with *trans*-stilbene: All solvents were deoxygenated by three freeze – pump – thaw cycles under nitrogen; all reactions were performed under an argon atmosphere. 2-Aminopyrimidine (166 mg, 1.75 mmol) was dissolved in dry ethanol (20.0 mL). The solution was cooled in an ice bath. *tert*-Butyl hypochlorite (190 mg, 1.75 mmol) was added. The solution was allowed to warm up to room temperature (RT) and stirred for 30 min. Then it was cooled again to 0 °C, and aqueous NaOH (1.00 M, 1.50 mL, 1.50 mmol) was added. The solution was again warmed to RT in a water bath, and water (8.5 mL) was added. Finely divided *trans*-stilbene (90.1 mg, 0.50 mmol), $(DHQ)_2PHAL$ (23.3 mg, 30 μmol, 6 mol %), and $K_2OsO_2(OH)_4$ (9.2 mg, 25 μmol, 5 mol %) were added. The mixture was stirred at RT for 12 h. A saturated solution of $NaHSO_3$ (4 mL) and water (10 mL) was added, and the mixture was stirred for 1 h at RT. The mixture was then placed in a separatory funnel, and EtOAc (80 mL) was added. The organic phase was separated and washed with water (40 mL) and brine (40 mL). After the mixture was dried over $MgSO_4$, the solvent was evaporated to leave a brownish residue. The product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH, 1/99 – 5/95) yielding 66 mg (45 %) of product as an off-white solid. As a second band, small quantities of the corresponding ring-chlorinated product were isolated. M.p. 132 °C (decomp); HR-MS (FAB) for $C_{18}H_{17}N_3O$: calcd for MH^+: 292.1450, found: 292.1460; ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.12$ (d, $^3J(H,H) = 8$ Hz, 2H, N=CH), 7.37 – 7.21 (m, 10H, Ph), 6.45 (t, $^3J(H,H) = 8$ Hz, 1H, py), 6.28 (br d, $^3J(H,H) = 13$ Hz, 1H, NH), 5.29 (dd, $^3J(H,H) = 13$, 7 Hz, 1H, CHN), 5.07 (d, $^3J(H,H) = 7$ Hz, 2H, CHO), 4.08 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.2$, 157.9, 141.4, 140.5, 128.5, 128.1, 127.5, 127.4, 127.1, 126.4, 111.0, 78.0, 61.7; $[\alpha]_D^{20} = -0.7$ ($c = 0.59$, in EtOH/$CHCl_3$ (1/1),

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$\alpha = -0.4^\circ$); HPLC (Chiralpak AS, *i*PrOH/hexane 3/7, 1 mL min^{-1}): $t_r = 5.1$ (1*S*,2*S*), 7.2 min (1*R*,2*R*).

Assignment of the absolute configuation: (1*S*,2*S*)-2-Amino-1,2-diphenylethanol was converted into an authentic sample of the 1*S*,2*S* enantiomer mentioned above by reaction with 2-bromopyrimidine.[12]

All other compounds were produced similarly. Regioisomers were usually separable by preparative TLC. It is advisable to keep the solvent polarity as high as possible; however, for some nonpolar olefins the addition of a small quantity of *n*-propanol was necessary to ensure the formation of homogeneous mixtures. A catalyst loading of 5% is sufficient for converting even heterocycles prone to electrophilic aromatic substitution. In most cases, however, it is possible to reduce the catalyst content to 1% without significant loss of *ee*; for example isopropyl cinnamate (Table 2, entry 1) gave 96% *ee* and 51% yield after 24 h. It is also usually possible to reduce the excess of the chlorinated salt of the heterocyclic amine to two equivalents.

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[10] For instance, 62% *ee* with Chloramine-T;[2a] 75% *ee* with Chloramine-M;[3] 94% *ee* with *N*-bromoacetamide;[4] 91% *ee* with *N*-halocarbarmate.[5]

[11] A total of 23% of amino alcohol derived from 2-amino-5-chloropyrimidine was isolated.

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High-Resolution Calorimetry: New Perspectives for the Study of Phase Transitions**

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New developments in the area of microcalorimetry permit the thermal investigation of materials in sub-μg quantities.[1] The thermal investigation of masses in the picogram range is also of interest, for example, for the analysis of surfaces, and still represents a large experimental challenge. King and coworkers recently reported methods to perform the thermal analysis of adsorption phenomena,[2] but practical limits still exist that prevent these high-resolution methods, with a sensitivity in the nanojoule range, from having a wide application under simple laboratory conditions.

Presented herein is a calorimeter whose efficiency enables the thermal analysis of substances on the nano- and picogram scale and with a picojoule sensitivity by using simple experimental equipment. The calorimeter[3] is based on techniques well known in scanning probe microscopy and formed on a concept that was used to prove a surface reaction under high vacuum conditions.[4] We were able to quantify a solid – solid phase transition in *n*-alkanes in air. Only 7 pg of substance were needed. This corresponds to a released heat of a mere 500 pJ. The calorimeter furthermore has a time resolution of 0.5 ms, and dynamic effects can also be studied. This enables us to determine differences in the solid – solid phase transition of the *n*-alkanes while different phases are being formed. Differences in the phase dynamics of odd and even-numbered *n*-alkanes were also studied.

The essential item of the calorimeter (Figure 1) is a microfabricated composite cantilever in the form of a bimetallic

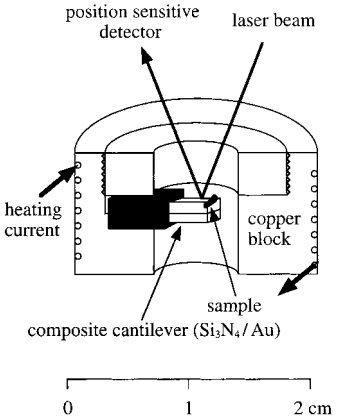

Figure 1. Schematic arrangement of the calorimeter. The heating block with the bimetallic cantilever are accommodated in a closed housing to avoid any disturbing air turbulence.

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