Jean-Pierre Changeux and I proposed some 10 years ago (*9*). The model, which was implemented as a working neural network simulation, supposes that number is extracted by pooling activation of neural maps of the locations of salient objects, computed preattentively in the parietal lobe. The model correctly predicts the fixed firing latency of the neurons and the linear increase of their tuning curves as the numbers get larger. It even helps make sense of fine details, such as the fact that the tuning curves assume a symmetrical Gaussian shape only when plotted on a logarithmic scale, not a linear scale of number; this is predicted if the internal "number line" is compressed and logarithmic, a coding scheme that may be optimal given the increasing imprecision associated with larger numbers.

The model predicts that numerical information is first computed in parietal cortex, and only then is it transmitted to prefrontal cortex neurons. Currently, however, the respective contributions of parietal and prefrontal cortices cannot be assessed from the existing data. There is even some inconsistency, with Sawamura *et al.* observing 31% numerical neurons in parietal cortex and 14% in prefrontal cortex, and Nieder *et al.* reporting the reverse. To resolve this discrepancy and to map out the entire circuit for number detection, more extensive electrophysiological surveys will be required, perhaps combined with functional imaging and reversible lesion experiments.

On a broader scale, the finding of a parietofrontal circuit for number in the monkey fits well with neuroimaging studies that reveal a homologous network in humans performing simple arithmetic tasks (*10*) (see the figure). The new findings in numerical neuroscience compel us to accept that our mathematics, sometimes heralded as the pinnacle of human activity, is really made possible by conceptual foundations laid down long ago by evolution and rooted in our primate brain (*11*). We are clearly not the only species with a knack for numbers.

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PERSPECTIVES: CHEMICAL SYNTHESIS

Raising the Bar for the "Perfect Reaction"

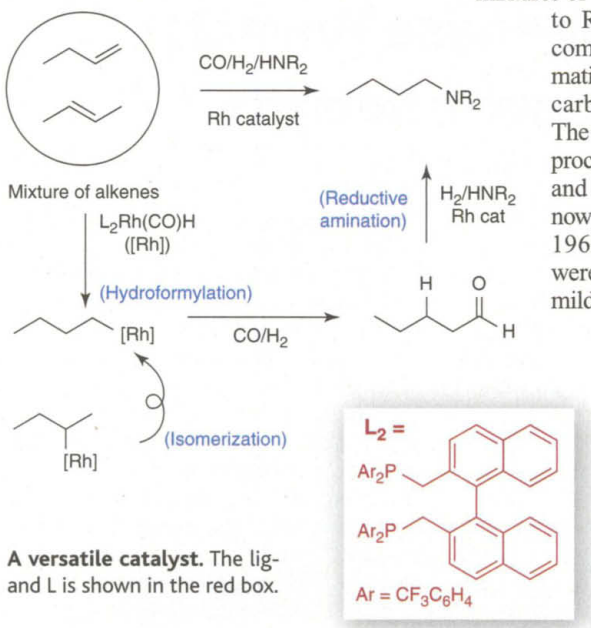
John F. Hartwig

Amines pervade our body and the world around us. They are found on the termini and side chains of amino acids, are components of common pharmaceuticals, and are behind the stench of rotting fish. They link the monomer units in most carpeting, help foam our shampoo, and soften our clothes. Fifteen to 20 billion kilograms of ammonia are produced per year, and amines are produced from ammonia in similarly staggering amounts (*1*). On page 1676 of this issue, Seayad *et al.* (*2*) report on a synthetic method that may ultimately make the production of amine cleaner and more efficient.

Amines are derivatives of ammonia that contain three single bonds between nitrogen and carbon or hydrogen. There are several classic methods to prepare amines, but most of them are inappropriate for large-scale production. For example, the reactions of amines with alkyl halides are taught in introductory organic chemistry courses. But the large amounts of halide by-product, the need for blocking groups to address poor selectivity, and the cost of the alkyl halide reagent make this method unsuitable for commodity chemical production.

The author is in the Department of Chemistry, Yale University, New Haven, CT 06422, USA. E-mail: john.hartwig@yale.edu

Instead, amines are generally produced from alcohols with a solid-acid catalyst by elimination of water (*3*). The alcohols in these reactions are often produced from alkene hydrocarbons, which contain a reactive carbon-carbon double bond. A synthetic route to amines directly from alkenes would eliminate the need for the alcohol intermediate, thereby avoiding the cost and energy consumption of the separation and purification of the alcohol. This is what Seayad *et al.* report. The yields are not yet 100%, but the reaction transcends the criteria typically assigned to the "perfect reaction."



A versatile catalyst. The ligand L is shown in the red box.

A perfect reaction is generally thought to occur with inexpensive reagents, run with fast rates, form 100% yield of product, require no added heat, and generate no waste (*4*–*5*). Because impure reactants usually form even less pure products, synthetic chemists are usually taught to start with clean reagents. The remarkable feature of the reaction reported by Seayad *et al.* is that predominantly a single terminal amine is made from a mixture of alkenes.

Most new reaction processes build on a long history of related reactions. The history that led to amine synthesis from an isomeric mixtures of alkenes began in 1938, when Otto Roelen discovered that cobalt compounds could catalyze the formation of aldehydes from hydrogen, carbon monoxide, and an alkene. The aldehyde was a side product of a process for generating hydrocarbons and alcohols. Roelen's discovery is now called hydroformylation. In the 1960s, soluble rhodium catalysts were discovered that operate under milder conditions than the cobalt catalysts. Today, 5 to 10 million tons of aldehydes and alcohols are produced annually by this reaction worldwide (*1*).

The link between hydroformylation and the amine synthesis of Seayad *et al.* is reductive amination. In a reductive amination, an aldehyde reacts

with an amine in the presence of hydrogen or another reducing agent to form an alkylated amine. The rhodium complexes that catalyze hydroformylation also catalyze reductive amination (*6*). Sequential hydroformylation and reductive amination of the intermediate aldehyde in the same reaction pot—called hydroaminomethylation—was discovered by Walter Reppe at BASF in the 1940s. A version of this reaction catalyzed by rhodium complexes has been studied more recently in the context of small-scale synthesis (*7*). The reaction starts with inexpensive reagents and generates valuable products, but the potential for commercial chemical synthesis has not been exploited.

The work of Seayad *et al.* begins to demonstrate even greater potential for this reaction, which brings us back to the formation of a single product from a mixture of reactants. Some commercial hydroformylations start from mixtures of isomeric alkenes and generate mostly terminal alcohols or aldehydes (*8–10*). Several new transition metal complexes that catalyze both isomerization and hydroformylation have been reported recently (*11–13*). But most catalysts for the hydroformylation of internal alkenes are ineffective for hydroaminomethylation because amines poison their isomerization activity. The poisoning is probably caused by amines displacing ligands from the metal center of the catalyst.

Seayad *et al.* have found a catalyst composition that is immune to this poisoning, allowing isomerization and hydroformylation to be linked to reductive amination. The soluble compound isomerizes alkenes, catalyzes hydroformylation to form terminal aldehydes, and catalyzes reductive amination to convert the terminal aldehyde to a terminal amine (see the figure).

The catalyst has a simple composition that emerged from modification of structures used previously for hydroformylation and from consideration of a fundamental principle of transition metal chemistry: Ligands with two donor atoms tethered to each other (chelating or bidentate ligands) resist displacement by monodentate ligands (*14*). The catalyst of Seayad *et al.* makes use of this principle of chelation to prevent coordination of amine.

The Seayad *et al.* group, led by Beller, recently modified a ligand used by Eastman Chemicals for hydroformylation (*15*) to create a catalyst for the hydroformylation of internal alkenes to terminal aldehydes (*15*). The modified ligand contains two phosphorus donors that chelate the metal. The rhodium complex with the modified ligand therefore resists coordination of amine and catalyzes both alkene isomerization and the final reductive amination. By luck or design, the catalyst that most effectively isomerizes olefins is also the most active for the final reductive amination.

As exciting as this work is, high hurdles remain before the process can be used to produce millions, thousands, or even hundreds of kilograms of amines. First, the ratio of terminal to internal amine produced by the reaction is much lower than the best ratios of terminal to internal aldehyde produced from commercial hydroformylations, and the rates are slower than would be needed for a commercial process. Second, the most useful amines are terminal primary amines. Beller and co-workers recently reported the selective hydroaminomethylation of terminal alkenes with ammonia (*16*), but the current system apparently does not catalyze additions of ammonia. Finally, diamines, such as those used to generate nylon, are produced on the largest scale. Hydroaminomethylation of dienes, particularly butadiene, will pose additional challenges for the catalyst.

Nonetheless, the work of Seayad *et al.* points the way to useful hydroaminomethylations. It should therefore generate a flurry of activity on this reaction. A commercially viable production of terminal amines from hydrogen, carbon monoxide, and ammonia would constitute a spectacular achievement for homogeneous catalysis and transition metal chemistry.

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PERSPECTIVES: STRUCTURE

Nitrogenase Reveals Its Inner Secrets

Barry E. Smith

Given sufficient water, plant growth and therefore agricultural productivity is usually limited by the amount of bioavailable (fixed) nitrogen. Biological nitrogen fixation still contributes about half of the total nitrogen input to global agriculture, the rest principally coming from nitrogenous fertilizer produced chemically from the Haber-Bosch synthesis of ammonia. To produce the hydrogen gas together with the high temperatures and pressures needed for this chemical process, about 1% of the world's total annual energy supply has to be consumed. In marked contrast, a similar chemical process requiring only atmospheric temperature and pressure is carried out by nitrogen-fixing bacteria, many of which live in symbiotic association with legume plants. The secret of their success is the enzyme nitrogenase, which transforms atmospheric nitrogen gas (dinitrogen) into ammonia that plants can then use for growth. Many groups have tried for decades to determine how nitrogenase catalyzes this essential process. Now, a high-resolution structure of part of bacterial nitrogenase reported by Einsle *et al.* (*1*) on page 1696 of this issue yields some surprises about the biosynthesis and catalytic activity of this crucial metalloenzyme.

Nitrogenase (*2*) consists of two essential metalloproteins: one, the iron (Fe) protein, is a very specific ATP-activated electron donor to the other, the molybdenum-iron (MoFe) protein. The MoFe protein contains two unique metallosulfur clusters: the P cluster [8Fe-7S] and the [Mo:7Fe:9S]:homocitrate iron-molybdenum (FeMo) cofactor cluster. About a decade ago, the first, relatively low-resolution (2.8 Å) crystal structure of the MoFe protein was reported (*3*). At this level of resolution, there were still some uncertainties about the structures of the metalloclusters. However, subsequent improvements in resolution to 2.0 Å (*4*) and then to 1.6 Å (*5*) yielded what seemed to be the accurate structure of the FeMo cofactor (see the figure). The FeMo cofactor

The author is at the John Innes Centre, Colney, Norwich NR4 7UH, UK. E-mail: barry.smith@bbsrc.ac.uk