measured ($4.0 < 2\theta < 55.6^\circ$), of which 13778 were unique ($R_{int} = 0.0862$). Refinement against F^2 to $wR_2 = 0.2438$, $S = 1.068$ (all data), R_1 (9753 reflections with $I > 2\sigma(I)$) $= 0.0916$. 858 parameters, 18 restraints; all non-H atoms were anisotropic apart from some of the disordered solvent molecules; hydroxy hydrogen atoms were located and refined. The unit cell was close to tetragonal ($P4_2/ncm$) but no twinning was observed. **1b**: ($C_{48}H_{133}Al_{15}N_{10}O_{83}$ 2583.34 g mol^{-1}): colorless octahedron $0.35 \times 0.30 \times 0.30$ mm, orthorhombic, space group $Pccn$, $a = 26.871(3)$, $b = 28.001(3)$, $c = 15.5309(17)$ Å, $V = 11686(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.47$ g cm^{-3}, $F(000) = 5400$, $\mu(Mo_{K\alpha}) = 0.238$ mm^{-1}. 56757 reflections were measured ($4.2 < 2\theta < 56.1^\circ$), of which 13542 were unique ($R_{int} = 0.0733$) The crystal quality was significantly poorer than for **1a**. Refinement against F^2 to $wR_2 = 0.3459$, $S = 1.101$ (all data), R_1 (9859 reflections with $I > 2\sigma(I)$) $= 0.1237$. 776 parameters, 10 restraints; all non-H atoms in the cluster and counterions were anisotropic. Some disordered solvent waters were assigned partial occupancies.

Crystal data for **2**: ($C_{58}H_{84}Al_{15}N_{24}O_{74}$; 2706.19 g mol^{-1}): colorless octahedron $0.14 \times 0.07 \times 0.06$ mm, tetragonal, space group $P4_2/ncm$, $a = 27.979(3)$, $c = 15.623(2)$ Å, $V = 12230.1(24)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.47$ g cm^{-3}, $F(000) = 5548$, $\mu(Mo_{K\alpha}) = 0.230$ mm^{-1}. Data were collected at 293 K on a Rigaku R-Axis IIc area detector diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation. 56705 reflections were measured ($4.1 < 2\theta < 50.8^\circ$), of which 5737 were unique ($R_{int} = 0.2335$). Structure solution by direct methods; refinement against F^2 (SHELXTL[10]) to $wR_2 = 0.1886$, $S = 1.125$ (all data), R_1 (2450 reflections with $I > 2\sigma(I)$) $= 0.0604$. 484 parameters; all non-H atoms in the cluster and counterions were anisotropic. The solvent molecules were heavily disordered, and only those directly H-bonded to the cluster could be modeled realistically; the solvent content is likely to be similar to that in **1a** and the parameters given here only refer to the atoms which were located during the refinement.

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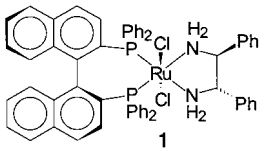
Noyori's Hydrogenation Catalyst Needs a Lewis Acid Cocatalyst for High Activity**

Rudolf Hartmann and Peter Chen*

The asymmetric hydrogenation of simple ketones[1] in isopropyl alcohol by using *trans*-$RuCl_2$[(*S*)-binap][(*S*,*S*)-dpen] **1** (binap = [1,1′-binaphthalene-2,2′-diylbis(diphenylphosphane)]; dpen = diphenylethylenediamine), an excess of an inorganic base, and 10 – 50 bar H_2 at 30 – 60 °C is remarkable in several respects: quantitative chemical yield within hours, enantiomeric excesses (*ee*) up to 99 %, high chemoselectivity for carbonyl over olefin reduction, and a substrate-to-catalyst ratio (S/C) > 100000. The combination of desirable features makes this catalytic reaction of great practical interest.[2] Moreover, the catalytic cycle is mechanistically novel, with most of the attention having been focussed on the step in which the ketone is reduced. Much less attention has been devoted to the cleavage of hydrogen to form the active ruthenium hydride. However, it is this step that differentiates the new class of hydrogen-cleaving Ru^{II} catalysts from the structurally similar transfer hydrogenation Ru^{II} complexes.[3, 4] We report herein an experimental study of the mechanism of catalytic hydrogenation with **1** which shows that the catalyst requires the presence of alkali metal cations, or more generally, a Lewis acid, as a cocatalyst for efficient turnover.



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The preparation and purification of Noyori's catalyst **1** as well as the other reagents used in this study is described in the Supporting Information. Solution-phase reactivity studies were performed in thick-walled Pyrex pressure tubes fitted with a Bourdon-tube manometer on a stainless-steel head fitted with high-pressure valves (Whitey SS-43MA-S4, specified up to 200 bar). The solution (typically 2.9 mL) was degassed by three freeze-pump-thaw cycles, and then magnetically stirred in a temperature-controlled oil bath. The apparatus was found to be leak-proof over 48 h with up to 6 bar H_2. Test reactions with **1** (3 mg), *t*BuOK (10 equiva-

[*] Prof. Dr. P. Chen
Laboratorium für Organische Chemie
ETH Zentrum, 8092 Zürich (Switzerland)
Fax: (+41) 1-632-12-80
E-mail: chen@org.chem.ethz.ch
and
Thales Technologies
Technoparkstrasse 1, 8005 Zürich (Switzerland)

R. Hartmann
Laboratorium für Organische Chemie
ETH Zentrum, 8092 Zürich (Switzerland)

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Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

lents), and acetophenone (660 mg, 2000 equivalents) in isopropyl alcohol (2.9 mL, 2.0 M with respect to the ketone) for 4 h under H_2 (5 bar) and at 50 °C afforded (*R*)-1-phenylethanol quantitatively with 90 % *ee*.[5] The rather low S/C value of 2000, which corresponds to a millimolar concentration of catalyst, was chosen to adjust the reaction rate to a convenient range. After confirmation that the hydrogenation proceeded as expected, kinetic studies were performed by monitoring the rate of H_2 consumption over several hours, with or without various additives.

Although the conversion of the pressure drop per unit time to turnover frequency (TOF) requires a precise cell volume, the pressure drops themselves do serve as a relative rate measurement.[6] For each measurement, an initial rate was recorded, which was defined as the rate within the first 15 min after temperature equilibration and saturation with H_2 to 5 bar (t_0). The second rate corresponds to the maximum rate of H_2 consumption (t_1). The results in Table 1 must be considered with a particular equilibrium in mind. If one considers the pK_a values of isopropyl alcohol (18)[7] and the conjugate acid of DBU (11.8; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene)[8], then one can calculate the protonated fraction of DBU, and hence the concentration of isopropoxide, as a function of DBU concentration in neat isopropyl alcohol. For a 1 mM solution of **1** in isopropyl alcohol, 100 equivalents of DBU would give approximately 1 mM isopropoxide (one equivalent with respect to **1**). Interestingly, for a thousandfold decrease in catalyst concentration to 1 μM, 100 equivalents of DBU would result in approximately 30 equivalents of isopropoxide relative to catalyst. Similarly, for a 1 mM and 1 μM solution of catalyst, 1000 equivalents of DBU would generate roughly 3 and 100 equivalents of isopropoxide, respectively. In other words, both DBU and isopropoxide are present as bases when DBU is added to isopropyl alcohol, so that even in the (hypothetical) limiting case in which DBU only promotes dehydrochlorination but does not participate further except through its contribution to the isopropoxide concentration, one has at least one equivalent of isopropoxide.

Table 1 shows several clear results: 1) although a base is needed for dehydrohalogenation of **1**, alkoxide alone is insufficient for high activity—an alkali metal cation is also necessary; 2) the experiments that involved crown ethers show that the alkali metal cation is needed for turnover, and not only for initiation; 3) the alkali metal cations influence the activity in the order K > Na ~ Rb > Li; 4) an increase in the alkali metal cation concentration with a constant amount of base results in a higher activity.

The above-mentioned properties of hydrogenation catalysts of the same family as **1** require an explanation. Noyori et al. have proposed a novel mechanistic explanation for the reversible hydride transfer from Ru^{II}–amine complexes to secondary alcohols. This mechanism rationalizes the activity and selectivity of the transfer hydrogenation catalysts, typically (arene)Ru(diamide) complexes and differs sharply from the accepted mechanism for rhodium- and iridium-catalyzed hydrogenations.[9] The proposed mechanism is supported by the isolation of the presumed intermediates,[10] as well as by computational evidence,[11,12] and is at least plausible for transfer hydrogenation. The proposal does not, however, explain why **1** and its close relatives can cleave hydrogen and why they have such a high activity with an S/C ratio in excess of 1 000 000.

Scheme 1 shows the mechanism for transfer hydrogenation as well as for hydrogen-cleaving routes, both with and without a Lewis acid cocatalyst, which is consistent with the experimental results in Table 1. The reaction depicted is the reduction of acetophenone in isopropyl alcohol with a potassium alkoxide as the inorganic base. Because even the hydrogenation reactions catalyzed by **1** are performed in isopropyl alcohol, and the hydride transfer from the activated form of **1** to acetophenone is the microscopic reversal of a putative dehydrogenation of a secondary alcohol, one can infer that **1** uses hydrogen rather than isopropyl alcohol as a

Table 1. Relative rate of H_2 consumption [bar h^{-1}] in the catalytic hydrogenation of acetophenone with **1** for various conditions and additives.[a]

Entry	Conditions [equiv]	Rate at t_0	t_1 [min]	Addition at t_1 [equiv]	Rate at t_1	t_2 [min]	Addition at t_2 [equiv]	Rate at t_2
1	10 *t*BuOK	2.8	30	–	3.6	–	–	
2	2 *t*BuOK	1.8	60	400 [18]crown-6	0.8	75	450 *t*BuOK	1.0 (at $t_2 = 135$)
3	100 DBU, 10 KBAF	0.45	180	10 [18]crown-6	0.00	240	10 KBAF	0.20
4	100 DBU, 10 NaBAF	0.20	165	10 [18]crown-6	< 0.05	315	10 KBAF	> 0.10
5	10 *t*BuOLi	1.40	60	–	2.00			
6	10 *t*BuONa	2.00	30	–	2.80			
7	10 *t*BuOK	2.80	30	–	3.60			
8	10 *t*BuORb	2.00	30	–	2.60			
9	100 DBU	0.00	150	–	0.00			
10	100 DBU, 10 LiBAF	0.00	120	–	0.00			
11	100 DBU, 10 NaBAF	0.20	60	–	0.30			
12	100 DBU, 10 KBAF	0.45	30	–	0.50			
13	100 DBU, 10 RbBAF	0.20	60	–	0.30			
14	100 DBU, 100 LiBAF	0.23	60	–	0.16			
15	100 DBU, 100 NaBAF	3.00	40	–	3.63			
16	100 DBU, 100 KBAF	3.33	30	–	6.00			
17	1000 DBU, 100 NaBAF	4.00	40	–	4.44			
18	1000 DBU, 100 KBAF	4.29	30	–	7.20			

[a] Each row describes an experiment which proceeds with the designated addition of a reagent or rate measurement at the marked time. Quantities of base and additives are expressed in mole equivalents relative to **1**. All reactions were performed at 5 bar H_2 pressure at 50 °C. BAF = tetrakis(3,5-bis(trifluoromethyl)phenyl)borate anion.

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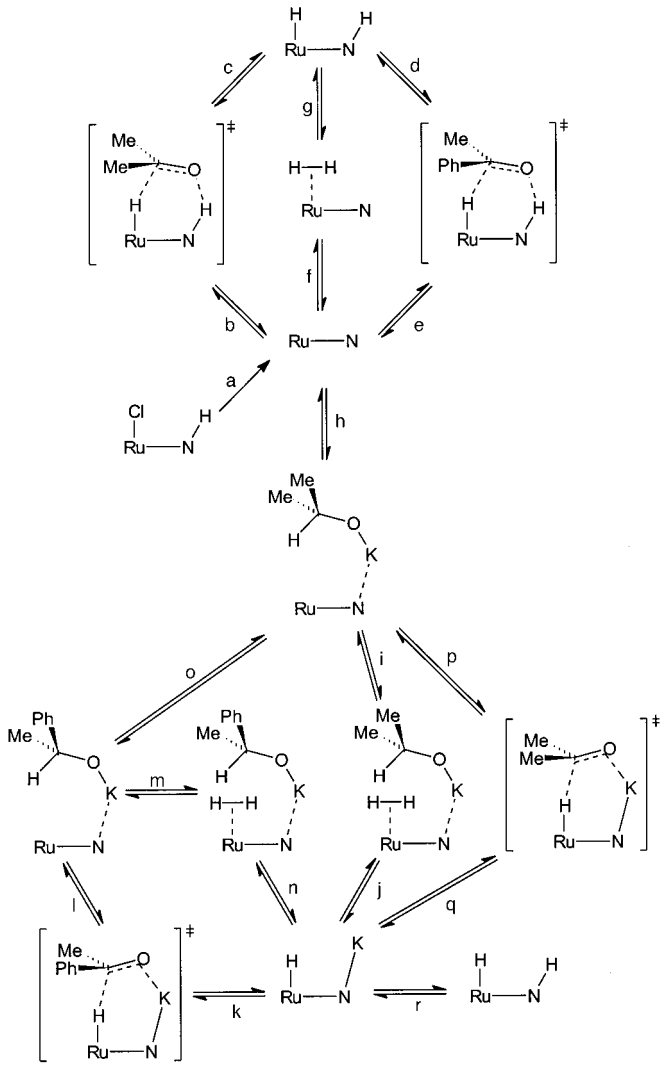

Scheme 1. Elementary steps in a unified mechanism for the reduction of acetophenone by both isopropyl alcohol (above) or H_2 (below), catalyzed by a ruthenium–amine complex: a) – HCl; b) + isopropyl alcohol; c) – acetone; d) + acetophenone; e) – 1-phenylethanol; f) + H_2; g) –; h) + *i*PrOK; i) + H_2; j) – isopropyl alcohol; k) + acetophenone; l) –; m) + H_2; n) – 1-phenylethanol; o) + isopropyl alcohol, – 1-phenylethanol; p) –; q) – acetone; r) + *i*PrOK, – isopropyl alcohol. The base is taken to be potassium isopropoxide, although the role of the potassium cation could be played by another suitable oxophilic Lewis acid.

hydride source,[13] because hydrogen cleavage is faster than dehydrogenation of isopropyl alcohol. In other words, for the catalytic cycle that involves the earlier transfer catalysts (upper half of Scheme 1), step g cannot compete with step b, even if the binding of H_2 (step f) is favorable. A process that accelerates hydrogen cleavage until it dominates the competing isopropyl alcohol dehydrogenation must lead to a catalyst such as **1**, which is more active than the previous transfer catalysts, as shown by the higher turnover frequency and S/C ratios.

The accelerated cleavage of hydrogen corresponds to a dominance of steps j and n over step p (Scheme 1). The key to understanding the acceleration lies in the activation of H_2 in related systems.[14] The reaction itself is presumably related to that in Wilkinson's ruthenium catalyst,[15] which is interestingly accelerated in aqueous solutions by alkali metal cations.[16] Whereas hydrogen typically binds only weakly to neutral 16-electron Ru^{II} complexes, some cationic complexes bind H_2 quite strongly, for example, $[CpRu(dmpe)(H_2)]^+$ is stable in hot THF, with H_2 being displaced only slowly in refluxing acetonitrile.[17] Moreover, hydrogen coordinated to Ru^{II} can be strongly activated to heterolysis if the metal center is made sufficiently electron deficient, that is, if the complex is mono- or dicationic, but nevertheless capable of back-donation into the σ^*_{H-H} orbital of hydrogen. The pK_a value of bound H_2 in $[CpRu(dmpe)(H_2)]^+$ was measured by Heinekey and co-workers[18] to be 5. Similarly, Morris and co-workers[19] found a pK_a value of 9.2 for $[Cp^*Ru(dppm)(H_2)]^+$. The variation of the pK_a values of H_2 in the complex $[CpRu(L)_2H_2]^+$ (L = phosphanes) correlates systematically with electron deficiency at the ruthenium center.[20] Dicationic Ru^{II} complexes[21] show even more extreme behavior with respect to H_2. The same effect has been suggested to be operative in certain hydrogenases.[22]

Given that the ruthenium amide complexes (Ru–N; Scheme 1) are neutral, one would expect them to bind H_2 substantially more poorly than their cationic congeners. Moreover, the bound hydrogen should be substantially less acidic than in $[CpRu(dmpe)H_2]^+$. Step g) in Scheme 1 shows the deprotonation of bound hydrogen by the amide ligand. How basic is the amide nitrogen? There are no quantitative data available, but one may make an estimate by using two procedures. First, one can model the coordination of the amine to a Ru^{II} center on the protonation of a primary amine to form the corresponding ammonium cation. A decrease in the pK_a value from ~30 to ~10 is observed—a change of 20 orders of magnitude,[23] which is consistent with the effect seen in other Ru– and Os–amine complexes.[24] Alternatively, if one observes that the activation of **1** requires 10 equivalents of potassium alkoxide when the concentration of **1** is 1 mM, but 10000 equivalents of base for a 1 μM solution of **1**, then, with the assumption that full activation is represented by approximately 90% deprotonation of the N–H moiety, one can calculate a pK_a value of 14 for the ruthenium–amine complex.[25]

The lack of significant hydrogen cleavage in the absence of alkali metal cations indicates that the ruthenium amide moiety (Ru–N) is not sufficiently basic to cleave hydrogen efficiently enough to compete with the alternative isopropyl alcohol dehydrogenation reaction.[26] On the other hand, the coordination of the alkali metal cation to the N atom of the ruthenium amide should withdraw electron density from the amide ligand, and hence from the ruthenium center, thus rendering the coordinated hydrogen more acidic. Moreover, the product of the previous cycle of reduction, a ruthenium amide with coordinated potassium alkoxide, places the basic alkoxide in an ideal position to deprotonate the coordinated hydrogen through a six-membered cyclic transition state (Scheme 1, step n).

As a last question, one may speculate as to why the alkali metal cation accelerated reaction occurs for **1**, but not for the structurally related transfer catalysts. The X-ray crystal structure of **1** and the MMX-optimized calculated structure (Figure 1) show that the N–H moiety that is almost *syn*-periplanar to the Ru–Cl (later Ru–H) bond has the amine proton situated between two face-to-face aryl rings. One of

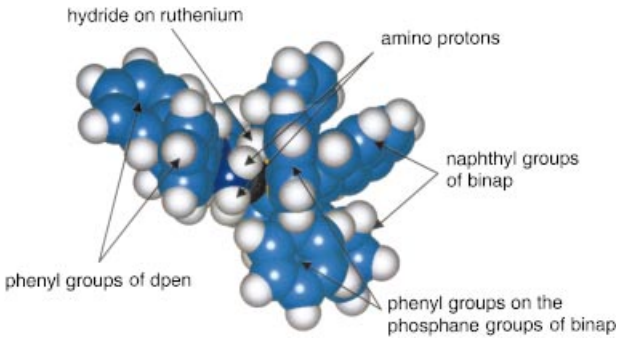

Figure 1. Structure of *trans*-[RuH_2{(*S*)-binap}{(*S*,*S*)-dpen}] calculated by using molecular mechanics with the MMX forcefield, viewed along a N–Ru bond. See text for details.

the aryl rings belongs to the dpen moiety and the other to the binap group. The center-to-center distance between the two rings is approximately 5.6 Å, and the midpoint between the rings lies around 2 Å from the nitrogen atom. When the amine ligand is deprotonated, the amide nitrogen and the two aryl rings form a preorganized cation binding site for potassium, based on cation–arene interactions.[27] Similar albeit not catalytic structures,[28] in which alkali metal cations are π-bound to aryl groups in Ru or Os complexes have been crystallographically characterized, thus supporting the plausibility of the present hypothesis in the Noyori-type complexes. The observed order for reaction acceleration, $K > Na \sim Rb > Li$, would also be explained by the conjecture that a potassium-specific binding site is coincidentally created in **1** by the aryl groups of the two ligands on the ruthenium. Lewis acidity alone would have predicted $Li > Na > K > Rb$. Interestingly, the crown ether experiments for hydrogenation catalyzed by **1**/*t*BuOK are less clearcut than the equivalent ones that use **1**/DBU/KBAF (Table 1, entries 2 and 3). A likely explanation is that crown ether sequestration of K^+ in the former case not only removes the alkali metal cation, but also breaks up the aggregation and ion-pairing[29] of *t*BuOK with a concomitant increase in the alkoxide basicity and partial compensation for the reduced H_2 consumption rate. The effect would be absent in the latter case.

The bimetallic, binuclear mechanism with a cooperative action of two metal centers is reminiscent of the role of bimetallic intermediates in the alkylation of ketones and in CO_2 fixation reactions investigated by Floriani and co-workers.[30] Also similar are the cross-coupling reactions of Grignard reagents with acyl chlorides in the presence of transition metal chelates studied by Uhlig and co-workers,[31] and the "flip-flop" mechanism for anionic coordination polymerization of epoxides by zinc and aluminum catalysts.[32] Perhaps the most interesting parallel is that between the key hydride transfer (step k) and the corresponding step in the asymmetric catalytic reduction of ketones by $BH_3 \cdot THF$ in the presence of chiral oxazaborolidine catalysts, reviewed by Corey et al.,[33] and other reductions with complex metal hydrides.[34] The major difference is that the present ruthenium systems can cleave hydrogen as well as deliver the hydride efficiently to the ketone substrate.

The combination of a nonionic base with an alkali metal salt (that is soluble in isopropyl alcohol and that contains a noncoordinating anion) allows the separation of base effects from those of the cations. The surprising dependence of catalytic turnover in Noyori's hydrogenation catalyst on the presence of alkali metal cations suggests a mechanism in which an accidental cation-binding site leads to an enhanced cleavage of the coordinated hydrogen. The resulting acceleration of direct hydrogenation relative to transfer hydrogenation gives **1** its remarkable activity. Further work to exploit this mechanism is underway.

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Bioreduction of $AuCl_4^-$ Ions by the Fungus, *Verticillium sp.* and Surface Trapping of the Gold Nanoparticles Formed**

Priyabrata Mukherjee, Absar Ahmad, Deendayal Mandal, Satyajyoti Senapati, Sudhakar R. Sainkar, Mohammad I. Khan, R. Ramani, Renu Parischa, P. V. Ajayakumar, Mansoor Alam, Murali Sastry,* and Rajiv Kumar*

The area of nanotechnology, which spans the synthesis of nanoscale matter, understanding/utilizing their exotic physicochemical and optoelectronic properties, and organization of nanoscale structures into predefined superstructures, promises to play an increasingly important role in many key technologies of the new millennium.[1] As far as the synthesis of nanoparticles is concerned, there is an ever-growing need to develop clean, non-toxic, and environmentally friendly ("green chemistry") synthetic procedures. Consequently, researchers in the field of nanoparticle preparation have been looking at biological systems for inspiration. The above factors, combined with academic curiosity, has lead to the development of biomimetic approaches for the growth of advanced materials. Many organisms, both unicellular and multicellular, are known to produce inorganic materials either intra- or extracellularly,[2] examples include magnetotactic bacteria (which synthesize magnetite nanoparticles),[3] diatoms (which synthesize siliceous materials),[4] and S-layer bacteria (which produce gypsum and calcium carbonate layers).[5]

Even though microbes have been used with considerable success in biotechnological applications, such as remediation of toxic metals,[6] reports on their use in the synthesis of nanomaterials are extremely limited. Beveridge and coworkers have demonstrated that nanoscale gold particles

[*] Dr. M. Sastry, Dr. S. R. Sainkar, Dr. R. Parischa
Materials Chemistry Division
National Chemical Laboratory
Pune, 411 008 (India)
Fax: (+91) 20-5893952/5893044
E-mail: sastry@ems.ncl.res.in

Dr. R. Kumar, Dr. P. Mukherjee, D. Mandal, S. Senapati
Catalysis Division
National Chemical Laboratory
Pune, 411 008 (India)
Fax: (+91) 20-5893761
E-mail: rajiv@cata.ncl.res.in

Dr. A. Ahmad, Dr. M. I. Khan
Biochemical Sciences Division
National Chemical Laboratory, Pune, 411 008 (India)

R. Ramani
Department of Pathology, Armed Forces Medical College, Pune, 411 001 (India)

P. V. Ajayakumar, Dr. M. Alam
Department of Microbiology and Plant Pathology
Central Institute of Medicinal and Aromatic Plants, P.O. CIMAP, Lucknow, 226 015 (India)

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