Homogeneous Asymmetric Hydrogenation

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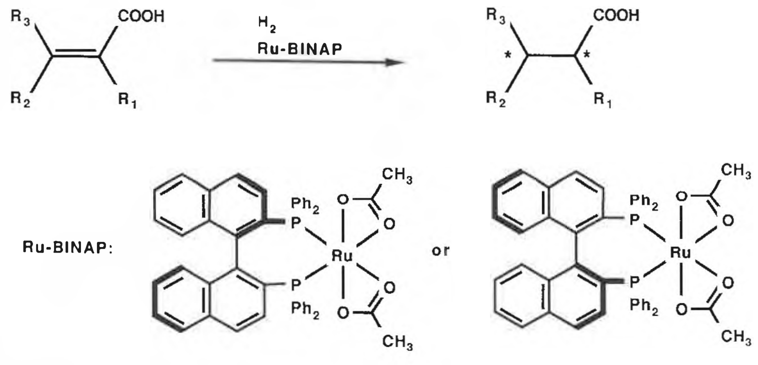
Scheme 1



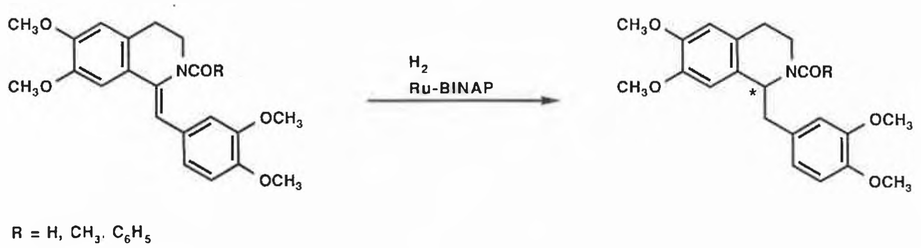
Asymmetric catalysis by chiral transition metal complexes in homogeneous phase, dating back to our first discovery of the copper-catalyzed asymmetric carbenoid reaction in 1966 (H. Nozaki, S. Moriuti, H. Takaya, and R. Noyori, *Tetrahedron Lett.* 7 (1966) 5239), is now recognized as an ideal, general chemical means to multiply chirality. This strategy has been successfully utilized for industrial production of L-DOPA (Monsanto, USA), L-phenylalanine (Anic, Italy), cilastatin (Sumitomo, Japan, and Merck Sharp & Dohme, USA), dispalure (J. T. Baker, USA, and Shanghai Institute for Organic Chemistry, China), (−)-menthol (Takasago, Japan), etc.

Asymmetric hydrogenation is one of the most fundamental organic reactions. The utility of the well-studied Rh-catalysis, however, is limited, with some exceptions, to the reaction of α-(acylamino)acrylic acids or esters. The devise of the BINAP-based ruthenium complexes has opened a new generation in this significant subject. First, hydrogenation of certain α,β- or β,γ-unsaturated carboxylic acids in the presence of $[Ru(OCOCH_3)_2(binap)]$ affords the saturated products in high enantiomeric excesses and in quantitative yields (Scheme 1). This hydrogenation has been applied to the asymmetric synthesis of naproxen, a 1β-methylcarbapenem precursor, and some methylated γ- and δ-lactones.

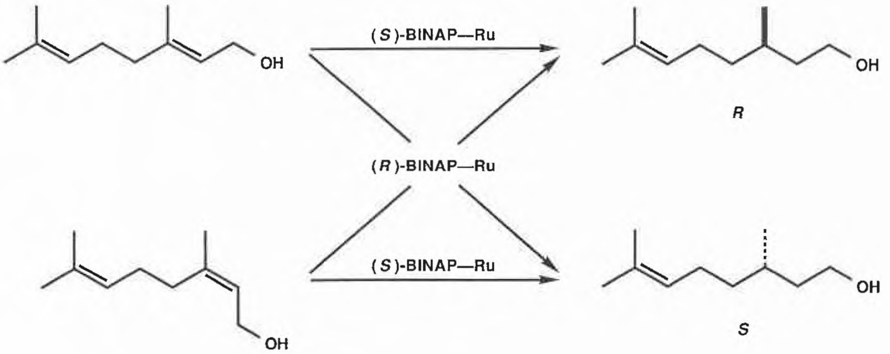
The hydrogenation of *N*-acyl-1-(*Z*)-alkylidenetetrahydroisoquinolines leads to the (1*R*)- or (1*S*)-alkyltetrahydroisoquinolines in 95 to 100% *ee*, providing a powerful tool in asymmetric construction of isoquinoline alkaloids (Scheme 2). The enantioselective reaction followed by removal and/or modification of the *N*-acyl groups gives tetrahydropapaverine, laudanosine, tretoquinol, norreticuline, salsolidine, etc. In addition to natural morphine, a variety of optically active benzomorphans including metazocine and pentazocine as well as dextrometorphan, are obtainable by using this reaction as key operation.

The BINAP-Ru complexes catalyze highly enantioselective hydrogenation of prochiral allylic and homoallylic alcohols (Scheme 3). Geraniol and nerol, for instance, are hydrogenated to give (*R*)- or (*S*)-citronellol in 96–99% *ee*. The substrate/catalyst mole ratio approaches 50000. The homogeneous catalysis is applicable to selective preparation of (3*R*,7*R*)-3,7,11-trimethyldodecanol, a versatile synthetic intermediate of α-tocopherol, vitamin K_1, etc. Chiral allylic secondary alcohols can be resolved by the BINAP-Ru catalyzed hydrogenation. The combined effects of intramolecular and intermolecular asymmetric induction give up to 76:1 differentiation between the enantiomeric unsaturated alcohols.

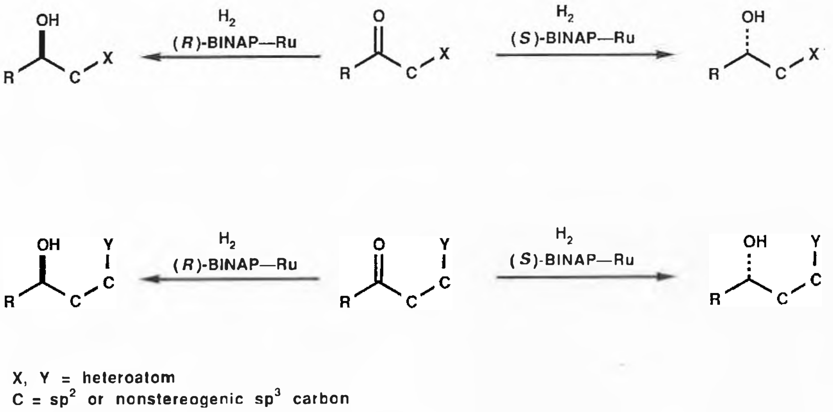
Scheme 2



Scheme 3



Scheme 4



The asymmetric hydrogenation has been extended to the previously unexploited synthesis of functionalized alcohols (Scheme 4). Thus under the influence of $[RuX_2(binap)]$ (X = OCOR, Cl, Br, I), a wide range of functionalized ketones are hydrogenated in a highly enantioselective and predictable manner. Various functionalities including dialkylamino, hydroxy, keto, alkoxycarbonyl, alkylthiocarbonyl, dialkylaminocarbonyl, carboxy, etc., can act as the efficient directive groups. Neighboring halogen atoms also affect the stereochemical outcome. Certain α- and β-diketones are hydrogenated to give isomeric diols by double stereodifferentiation. This chemical procedure compares well with the biochemical transformations, whose chemical and optical yields are often variable.