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Catalytic asymmetric transfer hydrogenation of ketones: recent advances

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ABSTRACT

In this review, we consider the main processes for the asymmetric transfer hydrogenation of ketones from 2008 up today. The most effective organometallic compounds (derived from Ru, Rh, Ir, Fe, Os, Ni, Co, and Re) and chiral ligands (derived from amino alcohols, diamines, sulfur- and phosphorus-containing compounds, as well as heterocyclic systems) will be shown paying special attention to functionalized substrates, tandem reactions, processes under non-conventional conditions, supported catalysts, dynamic kinetic resolutions, the use of water as a green solvent, theoretical and experimental studies on reaction mechanisms, enzymatic processes, and finally applications to the total synthesis of biologically active organic molecules.

Contents

Abbreviations: Alloc, allyloxycarbonyl; $[bmim]^+$, *N*-butyl-*N*-methylimidazolium; Bn, benzyl; Boc, *tert*-butoxycarbonyl; BRu, $[RuCl_2(benzene)]_2$; Bz, benzoyl; cat, catalyst; Cbz, benzyloxycarbonyl; COD, 1,5-cyclooctadiene; COE, cyclooctene; conv, conversion; Cp^*, pentamethylcyclopentadienyl; CRu, $[RuCl_2(p\text{-cymene})]_2$; CTAB, cetyltrimethylammonium bromide; Cy, cyclohexyl; DMSO, dimethyl sulfoxide; dr, diastereomeric ratio; DTAB, dodecyltrimethylammonium bromide; DVB, 1,4-divinylbenzene; ee, enantiomeric excess; equiv, equivalent(s); Et, ethyl; HRu, $[RuCl_2(Me_6C_6)]_2$; *i*-Bu, isobutyl; *i*-Pr, isopropyl; L, ligand; Me, methyl; MRu, $[RuCl_2(mesitylene)]_2$; *n*-Pr, *n*-propyl; PEG, polyethylene glycol; Ph, phenyl; PS, polystyrene; SBA, Santa Barbara University at California; TBAI, tetrabutylammonium iodide; *t*-Bu, *tert*-butyl; Tf, trifluoromethylsulfonyl; THF, tetrahydrofuran; Ts, 4-methylphenylsulfonyl; TsDPEN, *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylene diamine.

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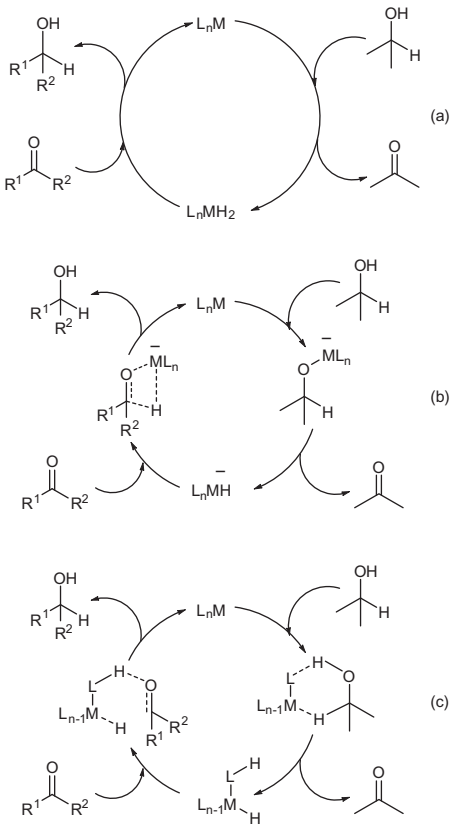
1. Introduction

The reduction of carbon–oxygen double bonds (carbonyl compounds) is an important transformation in synthetic organic chemistry because it is a general entry to alcohols.[1] Apart from some procedures that are not generally applied (electrochemical, photochemical or biochemical reactions), this methodology normally involves the use of molecular hydrogen under catalytic conditions, the use of a metal hydride, and transfer hydrogenation. The last method, also called hydrogen transfer,[2] has several advantages compared to the use of hydrogen or hydrides, such as (a) simple equipment; (b) low catalyst loading; (c) safe manipulation; (d) environmentally friendly solvents; (e) volatile by-products that can be easily removed; and (f) it can be applied to industrial processes.[3] Particularly significant is the asymmetric version of this reaction, namely the asymmetric transfer hydrogenation,[4] for which asymmetric information in the form of a chiral ligand is needed, together with a transition metal catalyst, such as those derived from ruthenium, rhodium, iridium, iron, and to a lesser extent osmium, cobalt, nickel and rhenium. Concerning the general mechanism accepted for the transfer hydrogenation, shown in Scheme 1 by using a secondary alcohol as the hydrogen source, it can involve a dihydride intermediate (Eq. a) or a monohydride one, in this second case with two possible variants: the inner sphere without ligand assistance (Eq. b) or the outer sphere with participation of the ligand (Eq. c) (Scheme 1).[5] More details on mechanistic aspects will be given later on in the corresponding section.



Scheme 1. Mechanism for transfer hydrogenation: (a) dihydride route; (b) monohydride inner sphere mechanism; (c) monohydride outer sphere mechanism.[5]

In the next section, the most significant information about the asymmetric transfer hydrogenation of ketones from 2008 up today will be given, considering different metal catalysts, ligands and reaction conditions, paying special attention to the best enantioselective methodologies and their application to synthetic organic chemistry.

2. Reaction scope: catalysts and chiral ligands

The asymmetric transfer hydrogenation of alkyl aryl ketones has been performed using different transition metals (Ru, Rh, Ir, Fe, Os, Ni, Co, Re) in combination with chiral ligands containing coordinating atoms (oxygen, nitrogen, sulfur and phosphorus).

2.1. Ruthenium catalysts

2.1.1. Aminoalcohols as ligands

Different chiral 1,2-amino alcohols have been used in combination with Ru catalysts for the asymmetric transfer hydrogenation of prochiral ketones (Table 1). For instance, ligand **1** was used for the enantioselective reduction of several phenones with a *p*-cymene derived complex $[RuCl_2(p\text{-cymene})]_2$ (CRu) in KOH as the base with good results (Table 1, entry 1).[6] The isosorbide derivative **2** gave variable data in combination with the benzene complex $[RuCl_2(benzene)]_2$ (BRu) and *t*-BuOK as base (Table 1, entry 2).[7] Another isosorbide derivative **3** was studied only for acetophenone and *p*-CRu with *t*-BuOK (Table 1, entry 3).[8] Aminoalcohol **4** was active in the same process with CRu and KOH giving variable results (Table 1, entry 4).[9] Ethanol was the hydrogen source used in combination with ligand **5** and CRu to get variable results in terms of conversion, but excellent enantioselectivities (Table 1, entry 5).[10] Several ketones were satisfactorily reduced with CRu and aminoalcohol **6**, with the obtained enantioselectivities being explained by calculations (Table 1, entry 6).[11] From a series of 1,2-aminoalcohols, ligand **7** proved to be the most active in collaboration with CRu working in aqueous sodium formate, although variable results were achieved (Table 1, entry 7).[12] Based on the α-pinene skeleton, several ligands mainly of type **8** (but also their corresponding dimers) were prepared and used in the asymmetric transfer hydrogenation with CRu and KOH as the base (Table 1, entry 8).[13] Finally, *Cinchona* derivatives were also used as ligands for the asymmetric transfer hydrogenation of aromatic ketones reaching up to 90% ee.[14] One special case, that really did not use an aminoalcohol, was reported by employing amino acids as ligands and BRu or its hexamethyl derivative $[RuCl_2(Me_6C_6)]_2$ (HRu) for the asymmetric transfer hydrogenation of acetophenone, with good conversions (up to 95%) but modest enantioselectivities (24–68% ee).[15]

2.1.2. Diamines as ligands

Since the pivotal introduction of *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine **9** (TsDPEN) as a chiral ligand for the Ru(II)-catalyzed asymmetric transfer hydrogenation of ketones,[16] several ligands of this type have been reported. In general, two