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NOTE

Kinetic resolution of chiral racemic alcohols by BITIANP–ruthenium(II)-catalysed hydrogenation†

S. R. Araneo,[1] E. Cesarotti[1]* and D. Berta[2]
[1]Università di Milano, Dipartimento di Chimica Inorganica, Metallorganica ed Analitica, Centro CNR, via G. Venezian 21, 20133 Milan, Italy
[2]Università di Milano, Istituto di Chimica Farmaceutica e Tossicologica, viale Abruzzi 42, 20133 Milan, Italy

Chiral allylic secondary alcohols have been resolved efficiently by catalytic hydrogenation with ruthenium complexes derived from the new chiral atropisomeric (*R*)- and (*S*)-BITIANP. These catalytic sistems have been applied to the resolution of NCS-382, a selective antagonist of the γ-hydroxybutyric acid (GHB) receptors. NCS-382 may play a role as a central neuromodulator and possesses several neuropharmacological properties that can be investigated in detail only if both eutomer and distomer are available in bulk.

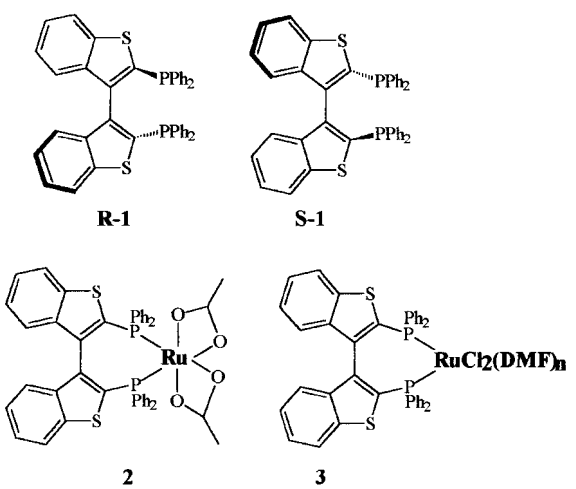
Keywords: asymmetric hydrogenation; kinetic resolution; ruthenium; chiral atropisomeric phosphine; BITIANP; allyl alcohols

Kinetic resolution is the result of a process in which one of the enantiomers of a racemic mixture reacts with a chiral catalyst more readily than the other to give the product with the consequence that, if the reaction is stopped at some stage before 100% conversion, either the starting material or the product can be enriched in one stereoisomer.[1]

Chemical kinetic resolution by transition-metal complexes is a well-established tool to obtain optically active compounds and it can now compete with the other chirotechnologies based on classical resolution methods or on enzymic and microbial techniques.

Examples of extremely successful chemical kinetic resolution are the epoxidation of secondary allylic alcohols by titanium complexes[2] or the homogeneous hydrogenation of unsaturated substrates with coordinating groups in the α-position catalysed by optically active phosphine–Rh[3] or –Ru[4] complexes.

We have recently developed a new class of chiral chelating phosphines characterized by an atropisomeric backbone composed of two interconnected five-membered heteroaromatic rings;[5,6] the ruthenium complexes derived from these ligands give very promising results in asymmetric homogeneous hydrogenation[7] of carbon–carbon and carbon–oxygen double bonds and show an enantioselection ability quite similar to that exhibited by more popular ligands, such as BINAP,[8] but with easier synthetic access.



Scheme 1

* Correspondence to: E. Cesarotti, Università di Milano, Dipartimento di Chimica Inorganica, Metallorganica ed Analitica, Centro CNR, via G. Venezian 21, 20133 Milan, Italy.
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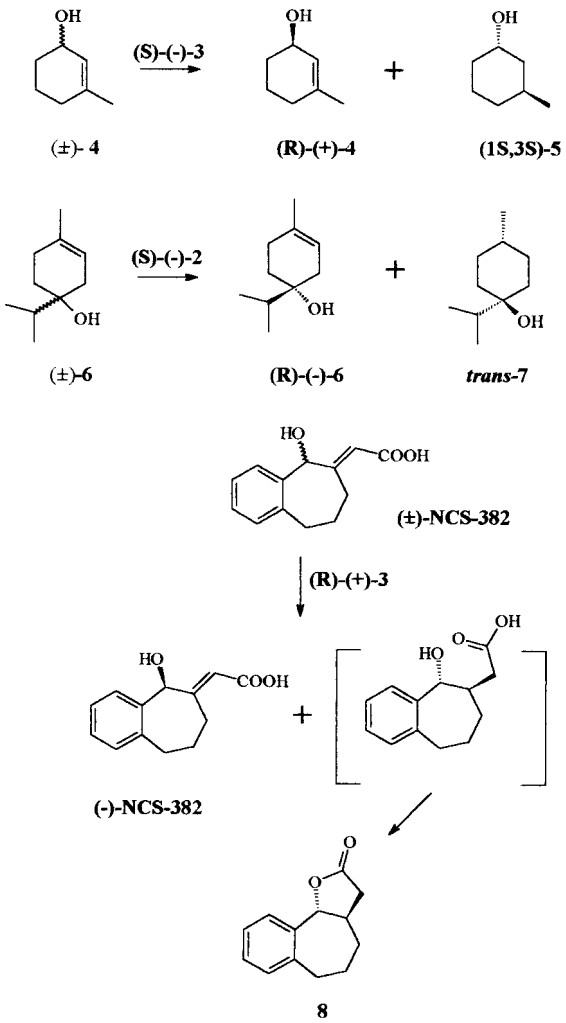

Scheme 2

The results in asymmetric hydrogenation have induced us to extend the investigations to the kinetic resolution of other substrates of considerable interest and applicability.

Here we report on the use of the new chiral ligands (*R*)−(+)- and (S)-(−)-2,2′-bis(diphenylphosphino)-3,3′-bis(benzo[*b*] thiophene) {[(*R*)-BITIANP], **R-1**, and [(*S*)-BITIANP], **S-1**} (Scheme 1) in the catalytic kinetic resolution by asymmetric hydrogenation of the well-known cyclic substrates (±)-3-methyl-2-cyclohexen-1-ol **4** and (±)-terpinen-4-ol **6** (Scheme 2, top) and, due to the encouraging results, of the substrate (5-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ylidene)-acetic acid NCS-382 (Scheme 2, bottom).

The asymmetric hydrogenations are performed with BITIANP–$Ru(OCOCH_3)_2$ **2**,[7] or with BITIANP-$RuCl_2(DMF)_n$ **3**,[7] with methanol as solvent at different temperatures with a substrate/catalyst mole ratio (S/C) of 300:1 or 600:1.

The results of the asymmetric hydrogenation and of the kinetic resolution are reported in Table 1.

When the racemic **4** is hydrogenated with (*R*)−(+)-**3** at 30 °C, at 21% conversion the unreacted substrate **4** shows a 26% ee (enantiomeric excess); at 70% conversion the (*S*)−(−)-3-methyl-2-cyclohexenol **4** can be recovered almost optically pure due to an enantiomer differentiation *s* higher than 70 (Table 1, entry 1).

The hydrogenation of **4** affords (1*R*,3*R*)- and (1*R*,3*S*)-3-methylcyclohexanol **5** in a ratio higher than 99:1. This very high diastereoselectivity confirms that the hydrogenation of allylic alcohols occurs via chelation to the metal of the hydroxy group.

When the catalyst (*S*)-(−)-**3** is employed (*R*)-(+)-3-methyl-2-cyclohexenol **4** is recovered (Table 1, entry 2).

The degree of kinetic resolution is largely influenced by the temperature of the reaction; thus the rise of the temperature to 60 °C reduces the enantiomer differentiation parameter *s* to 13 (Table 1, entry 2).

The cyclic homolallylic (±)-terpinen-4-ol **6** is reduced to the *trans*-1-isopropyl-4-methylcyclohexan-1-ol **7** (Scheme 2) with a selectivity higher than 100:1. The enantiomer differentiation, however, is lower compared with that obtained in the hydrogenation of the allylic alcohol **4**; (*R*)-(−)-terpinen-4-ol **6** can be recovered with a 15% *ee* at 70% conversion, indicating a stereoselectivity factor *s* of 1.2 (Table 1, entry 3).

These encouraging results prompted us to investigate the kynetic resolution by asymmetric hydrogenation of (5-hydroxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-6-ylidene)acetic acid, hereafter called NCS-382.

NCS-382[10] is a selective antagonist of the γ-hydroxybutyric acid (GHB) receptor and constitutes a major tool in the investigation on the GHB system. GHB is an endogenous constituent of mammalian brains synthesized locally from γ-aminobutyric acid (GABA),[11–13] it might play a role as a central neuromodulator and possesses several neuropharmacological properties. It has been used in anaesthesia,[14] sleep disorders[15] and recently in alcohol dependence where it reduced voluntary ethanol intake and suppressed withdrawal symptomatology in both selectively bred,

Table 1 A symmetric hydrogenation and kinetic resolution of unsaturated alcohols by BITIANP–Ru complexes[a]

Entry	Substrate	Catalyst	S/C	Temp. (°C)	Substrate		s^g
					Recovery (%)[b]	ee (%)[c]	
1	(±)-**4**	(*R*)-(+)-**3**	300	30	79	26[d]	76
					30	>99	
2	(±)-**4**	(*S*)-(−)-**3**	300	60	62	48[d]	13
					50	70	
3	(±)-**6**	(*S*)-(−)-**2**	600	30	21	15[d]	1.2
4	(±)-NCS-382	(*R*)-(+)-**3**	300	30	29	75[e]	3.9
5	(±)-NCS-382	(*S*)-(−)-**3**	300	60	32	43[e]	2.2
6	(±)-NCS-382	(*S*)-(−)-**2**	300	30	30	83[e]	5.0
7	(±)-NCS-382[f]	(*R*)-(+)-**3**	300	15	53	57[e]	8.3
					28	92	

[a] The reactions are carried out in 0.03 M methanol solutions at 10.1 MPa (100 atm).
[b] Determined by 300 MHz ^{1}H NMR and/or GC analysis.
[c] The enantiomeric excess is determined by GC or HPLC with chiral stationary phases.
[d] GC: MEGA DacTbuSilBETA, 25 m, i.d. 0.25 mm., 0.25 μm, He.
[e] HPLC: DAICEL Chiralcel OD; hexane/2-propanol/CF_3COOH = 90: 10:1.
[f] The concentration of the substrate is 0.15 M in methanol.
[g] *s* is the stereoselectivity factor k_R/k_S, where k_R and k_S are the overall rates with which the chiral catalyst reacts with the *R* and *S* enatiomers; it is calculated according to Refs[1] and [9].

Sardinian alcohol-preferring rats[16] as well as in alcoholics.[17]

However, high doses of GHB are needed to exert its pharmacological effects and, according to recent experimental data, it appears to be a risk for addiction. It has become a popular new drug of abuse, which implicates repeated self-administration, tolerance, craving, compulsive drug seeking and withdrawal.[18,19]

The demonstrated ability of NCS-382 to block GHB effects *in vivo* and *in vitro* suggests the possibility of using it both in alcoholism, compared with naloxon in heroine abuse, and in the prevention of recreational GHB use.

In order to deepen our knowledge of the eutomer and distomer of NCS-382 and their behaviour in GHB, a practical method of resolution of its racemic mixture is needed. The (*R*)-(+)- or (*S*)-(−)-**3** catalysed hydrogenation of (±)-NCS-382 at 10.1 MPa in methanol affords the γ-hydroxyacid, which spontaneously evolves to the cyclic lactone 3,3′,4,5,-tetrahydro-6*H*-benzo[6,7]cyclohepta[1,2-*b*]furan-2-one **8** (Scheme 2) with a *trans/cis* ratio higher than 80:20. The diastereoselectivity should be related, as in the other allylic substrates, to the coordination of the hydroxyl group to the metal atom during the hydrogen transfer to the double bond. The higher enantiomer differentiation is 8.3 with the catalysts (*R*)-(+)-**3** at 15 °C; *s* is strongly influenced by the reaction temperature (Table 1, entries 4, 5 and 7) and, to a lesser extent, by the nature of the catalyst (Table 1, entries 4 and 6).

At 15 °C the enantiomer differentiation is high enough to obtain NCS-382 optically pure and in sufficient quantities to allow pharmacological assays. Entry 7 (Table 1) describes a kinetic resolution performed on the scale of grams; after 15 h (*R*)-(+)-**3** gives a conversion higher than 72%. After preparative flash chromatography (silica gel; hexane/ethyl acetate = 1:1), (−)-NCS-382 is obtained optically pure in 25% yield. The same results are obtained with (*S*)-(−)-3, which affords optically pure (+)-NCS-382. The pharmaceutical properties of (+) and (−)-NCS-382 are currently under investigation and the results will be published elsewhere; however this new class of ligands has proved to give very effective catalysts able to perform kinetic resolution by homogeneous hydrogenation of chiral racemic substrates; work is in progress to investigate the enantiomer differentiation ability of these catalytic systems on other substrates of great relevance and industrial interest.

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