Use of the Trost Ligand in Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones

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Abstract: The Trost ligand (1*S*,2*S*)-1,2-diaminocyclohexane-*N*,*N*′-bis(2'-diphenylphosphinobenzoyl) **L** is reported for the first time as ligand in the asymmetric hydrogenation (AH) of ketones. Ligand (*S*,*S*)-**L** was screened in the presence of several metal salts and found to form active catalysts when combined with ruthenium sources in the presence of hydrogen and a base. Reaction optimization was carried out by screening different Ru sources, solvents and bases. Under the optimized conditions, the complex formed by combination of (*S*,*S*)-**L** with $RuCl_3(H_2O)_x$ in the presence of Na_2CO_3, is able to promote the AH of several ketones at r.t. with good yields and up to 96% *ee*. The reaction kinetics measured under the optimized conditions revealed the presence of a long induction period, during which the initially formed Ru species is transformed into the catalytically active complex by reaction with hydrogen. Remarkably, ketone **S8**, precursor of the antiemetic drug Aprepitant, was hydrogenated with excellent yield and good *ee*.

In spite of the enormous advancements in the development of asymmetric catalysis over the past half a century, its industrial application is still in its early stages.[1] Indeed, at present the classical resolution of diastereoisomeric salts is still the most widely exploited methodology to obtain enantiomerically pure compounds, despite its intrinsically poor atom economy. Among the enantioselective catalytic methodologies, asymmetric hydrogenation (AH) is probably the most appealing one from the industrial point of view, due to its practicality and to the use of a cheap and clean reducing agent such as H_2.[2] Despite this, the number of industrially implemented AH processes is still fairly limited.[1,2] One of the main reasons for this paradox is the high cost of the catalysts, which often contain expensive metals and/or ligands. For this reason, replacement of the precious metals traditionally used in AH (e.g., Rh, Ir, Ru) with cheap base metals (e.g., Fe, Co, Ni) has recently become an important research goal.[3,4] However, much less attention has been paid to the cost of the chiral ligand, which is often comparable or even higher than that of the metal. For a successful industrial application of AH, the availability on short notice of gram and kilogram amounts of chiral ligands is often a key issue.[5] Actually, noble metals can still be an economically viable option, provided that the chiral ligand is sufficiently cheap, readily available and robust. The "Trost ligand" (1*S*,2*S*)-1,2-diaminocyclohexane-*N*,*N*′-bis(2'-diphenylphosphinobenzoyl) **L** (Figure 1) meets these requirements to a large extent, as it is commercially available at a reasonable price or, alternatively, can by synthesized in one step from *trans*-1,2-diaminocyclohexane, readily available in both the enantiomeric forms. Ligand **L** was developed in 1992 by Trost and Van Vranken for Pd-catalyzed asymmetric allylic alkylations (AAA),[6] and it was soon recognized as one of the most effective ligands for this kind of transformation.[7] Quite surprisingly, despite this success, the use of the Trost ligand has remained mostly restricted to Pd-catalyzed AAA,[8] and – to the best of our knowledge – no successful application in AH has been reported so far.[9] The AH of ketones is an important transformation providing access to chiral alcohols, which are valuable building blocks for the synthesis of fine chemicals and active pharmaceutical ingredients. Over the past decade, the AH of ketones has been predominantly investigated with chiral ruthenium complexes containing various ligand combinations of mono- or bidentate phosphines and diamines, analogous to the original Noyori's BINAP–Ru–diamine complexes.[10,11,12] Ruthenium catalysts based on PNNP ligands (in which N = imine or amine) have also been reported in AH and transfer hydrogenation of ketones.[13]

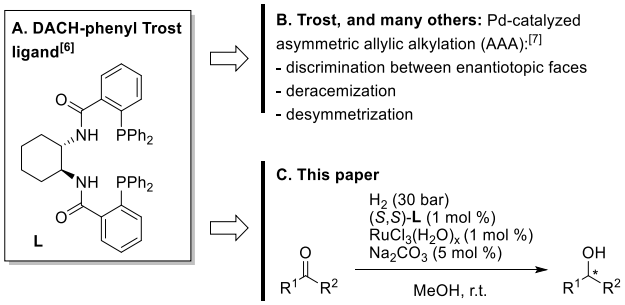

Figure 1. *Trans*-1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphino-benzoyl), better known as Trost ligand (A),[6] its best known applications (B),[7] and its new application described in this paper (C).

We thus set out to investigate the potential of Trost's diphosphine ligand (**L**) for the AH of ketones. Using acetophenone (**S1**) as model substrate and KO*t*Bu as base, we screened different metal precursors in the presence of the Trost ligand under 30 bar of H_2 at 80 °C (Table 1, entries 1-12). No or trace conversions were obtained using Ni, Co and Fe salts (Table 1, entries 2-9), with the exception of $NiCl_2$ (Table 1, entry 1, conversion = 98%) which, however, led to racemic product (**P1**). In sharp contrast, several Ru sources led to good activity and promising enantioselectivity (Table 1, entries 10-18). Lowering the reaction temperature from 80 °C to 60 °C led to a significant improvement of the enantioselectivity without eroding

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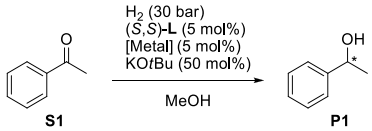
the yield (Table 1, entry 14 vs. 11), and for this reason additional Ru sources were screened at 60 °C (Table 1, entries 15-18). As a general trend, the Ru complexes containing PPh_3 gave the product with opposite absolute configuration compared to the others (Table 1, entries 10, 12-13, 16, 18 vs. 11, 14-15, 17). In absolute terms, the best *ee* values were obtained with anhydrous or hydrated $RuCl_3$ (Table 1, entries 11, 14 and 15).[14] As $RuCl_3(H_2O)_x$ is remarkably cheaper than anhydrous $RuCl_3$, the hydrated salt was selected as Ru source for further reaction optimization.

A solvent screening was then performed, the results of which are shown in Table 2.

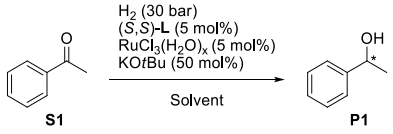
Table 1. Screening of different metal sources in the AH of acetophenone (**S1**) in the presence of the Trost ligand (*S*,*S*)-**L**.[a]



Entry	Metal source	*T* (°C)	Conv. (%)[b]	*ee* (%),[b] abs. conf.[c]
1	$NiCl_2$	80	98	0
2	$Ni(NO_3)_2{\cdot}6\ H_2O$	80	0	-
3	$Ni(cod)_2$	80	0	-
4	$Ni(CO)_2(PPh_3)_2$	80	0	-
5	$CoCl_2$	80	1	29, *R*
6	$FeBr_2$	80	0	-
7	$FeBr_3$	80	0	-
8	$Fe(CO)_5$	80	0	-
9	$FeCl_2{\cdot}4\ H_2O$	80	1	23, *S*
10	$(PPh_3)_3RuCl_2$	80	96	44, *R*
11	$RuCl_3$	80	98	32, *S*
12	$(PPh_3)_3Ru(CO)H_2$	80	69	29, *R*
13	$(PPh_3)_3RuCl_2$	60	91	43, *R*
14	**$RuCl_3$**	**60**	**97**	**56, *S***
15	**$RuCl_3(H_2O)_x$**	**60**	**99**	**46, *S***
16	$(PPh_3)_4RuCl_2$	60	92	40, *R*
17	$[(C_6H_6)RuCl_2]_2$	60	98	23, *S*
18	$(PPh_3)_3Ru(CO)(Cl)H$	60	4	29, *R*

[a] Reaction conditions: **S1**/metal/(*S*,*S*)-**L**/KO*t*Bu = 100/5/5/50, P_{H2} = 30 bar, solvent: MeOH, c_0 (**S1**) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b]

Table 2. Solvent and temperature screening in the AH of acetophenone (**S1**) with $RuCl_3(H_2O)_x$/Trost ligand (*S*,*S*)-**L**.[a]

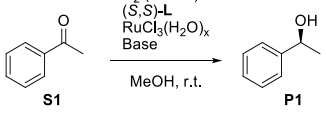


Entry	Solvent	*T* (°C)	Conv. (%)[b]	*ee* (%),[b] abs. conf.[c]
1	MeOH	60	99	46, *S*
2	MeOH	35	98	67, *S*
3	**MeOH**	**22**	**97**	**69, *S***
4	MeOH	0	63	65, *S*
5	*i*PrOH	60	>99	0
6	DMF	60	>99	35, *S*
7	Benzene	60	74	17, *R*
8	MeCN	60	72	13, *S*
9	Toluene	60	>99	22, *S*
10	THF	60	>99	28, *S*
11	EtOH	60	98	5, *S*
12	1:1 MeOH/H_2O	60	>99	0
13	4:1 MeOH/H_2O	60	81	0
14	1:1 *i*PrOH/H_2O	60	13	6, *R*
15	4:1 *i*PrOH/H_2O	60	>99	0

[a] Reaction conditions: **S1**/$RuCl_3(H_2O)_x$/(*S*,*S*)-**L**/KO*t*Bu 100/5/5/50, P_{H2} = 30 bar, c_0 (**S1**) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b]

Although full conversion could be achieved with several different solvents (Table 2, entries 1, 5-6 and 9-11), the best ee value was obtained in MeOH (entry 1). Decreasing the temperature led to higher *ee* values without substantially affecting the yield (Table 2, entries 2-3), although no improvements could be obtained below room temperature (entry 4). Notably, the presence of water was found to dramatically affect the enantioselectivity: when MeOH/H_2O mixtures were used, the *ee* dropped to zero (Table 2, entries 12-13). Furthermore, running the reaction in *i*PrOH yielded racemic **P1** due to the background base-promoted transfer hydrogenation (Table 2, entries 5 and 14-15). On the basis of these results, we decided to carry out further optimization in MeOH at room temperature (Table 3).

Table 3. Investigation on the role of the base in the AH of acetophenone (**S1**) with $RuCl_3(H_2O)_x$/Trost ligand (*S*,*S*)-**L**.[a]



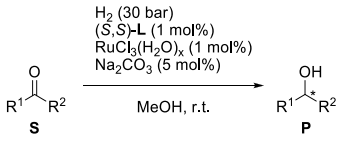
Entry	Base	Base/cat.	Cat. loading (mol%)	Conv. (%)[b]	*ee* (%)[b,c]
1	None	-	5	0	0
2	KO*t*Bu	10	5	93	70
3	KO*t*Bu	5	5	97	76
4	KO*t*Bu	1	5	0	0
5	KOH	5	5	>99	71
6	K_2CO_3	5	5	98	53
7	Cs_2CO_3	5	5	98	69
8	LiO*t*Bu	5	5	98	63
9	$LiOH{\cdot}H_2O$	5	5	>99	64
10	NaOMe	5	5	99	70
11	NaO*i*Pr	5	5	31	86
12	NaO*t*Bu	5	5	98	66
13	NaOH	5	5	99	89
14	Na_3PO_4	5	5	99	87
15	Na_2CO_3	5	5	99	89
16	Na_2CO_3	5	2.5	>99	93
17	**Na_2CO_3**	**5**	**1**	**>99 (96%)**[g]	**96**
18	Na_2CO_3	5	0.5	97	94
19[d]	Na_2CO_3	5	0.5	>99	95
20	Na_2CO_3	5	0.1	0	-
21[d]	Na_2CO_3	5	0.1	0	-
22[e]	Na_2CO_3	5	1	42	94
23[f]	Na_2CO_3	5	1	63	95

[a] Reaction conditions: P_{H2} = 30 bar, c_0 (**S1**) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b] [d] P_{H2} = 80 bar. [e] Reaction carried out in the presence of 3 Å molecular sieves. [f] Reaction carried out in the presence of $Hg^{(0)}$ (10 mmol/100 equiv). [g] Isolated yield (reaction carried out on a 6 mmol scale).

The role of base was investigated, and it was found that without KO*t*Bu the reaction does not proceed (Table 3, entry 1).[10a,15] Varying the base/catalyst ratio (Table 3, entries 2-4), 5:1 turned out to be the optimum (entry 3). From a base screening (Table 3, entries 5-15), it emerged that the base employed has a strong influence on the enantioselectivity. Remarkably, simple inorganic bases such as alkaline hydroxides and carbonates were found to efficiently promote the reaction (Table 3, entries 5-7, 9, 13-15). Among them, those bearing sodium as counter ion led to higher

ee values than the others. Decreasing the catalyst loading to 1 mol% in the presence of Na_2CO_3 led to a remarkable increase of the enantioselectivity (up to 96% *ee*) without affecting the conversion (Table 3, entries 16-17 vs. 15). No further improvement in terms of *ee* could be obtained below 1 mol% catalyst loading (Table 3, entries 18-21). However, full conversion could be still obtained at 0.5 mol% catalyst loading, corresponding to a TON of 200. A similar effect was also observed using NaOH and Na_3PO_4 as base (see the Supporting Information). Increasing hydrogen pressure had modest or no influence on the enantioselectivity (Table 3, entry 19), while decreasing it to 10 bar led to a drop of conversion and *ee* (see the Supporting Information). Since the presence of H_2O is harmful to the enantioselectivity (see Table 2), a reaction was run in the presence of 3 Å molecular sieves (to scavenge any H_2O traces), but the only observed effect was a drop of conversion (Table 3, entry 22). Finally, running the hydrogenation in the presence of an excess of Hg(0) led only to a slight decrease of conversion, which leads to the conclusion that the active catalyst is probably homogeneous.[3c,16]

Table 4. Substrate screening in the AH of ketones catalyzed by $RuCl_3(H_2O)_x$/(*S*,*S*)-**L**.[a]



Entry	Substrate	Conv. (%)[b]	*ee* (%),[c] abs. conf.[d]
1	**S1**	>99 (96%)[e]	96, *S*
2	**S2**	>99 (97%)[e]	95, *S*
3	**S3**	98	95, *S*
4	**S4**	>99	93, *S*
5	**S5**	>99	95, *S*
6	**S6**	32	28, *S*
7	**S7**	>99	92, *S*
8	**S8**	>99 (95%)[e]	84, *S*
9	**S9**	31	77, *S*
10	**S10**	>99	94, *S*
11	**S11**	>99	92, *S*
12	**S12**	40	11, *R*
13	**S13**	64	96, *S*
14	**S14**	>99	0

[a] Reaction conditions: P_{H2} = 30 bar, c_0 (substrate) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis in the presence of an internal standard (hexadecane). GC traces showed only the presence of the reaction products (secondary alcohols) and, when the reaction is not complete, of the starting ketones (see the Supporting Information). Given the high chemoselectivity, percent conversions and percent isolated yields are practically coincident. [c] Determined by GC or HPLC on a chiral stationary phase (see the Supporting Information). [d] Absolute configuration assigned by comparison of the optical rotation sign with literature data (see the Supporting Information). [e] Isolated yield (reaction carried out on a 6 mmol scale).

Using the optimized reaction conditions, the substrate scope of the $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system was investigated (Table 4). In general, 3- and 4-substituted acetophenones were hydrogenated with good yields and high *ee* (92-95%) irrespective of the electron withdrawing or electron donating properties of the substituent (Table 4, entries 2-5 and 7). The only exception was 1-(3-aminophenyl)ethanone **S9** (Table 4, entry 9) which – possibly due to catalyst poisoning by coordination of the amino group to ruthenium – gave a low conversion and a diminished *ee* (77%). Remarkably, the 3,5-disubstituted acetophenone **S8**, precursor of the anti-emetic drug Aprepitant,[17] was hydrogenated with excellent yield and good *ee* (Table 4, entry 8). On the contrary, low conversion and *ee* were obtained with 1-(2-chlorophenyl)ethanone **S6**, most certainly due to the steric bulk created by its *ortho* substituent (Table 4, entry 6 vs. entries 4-5). Other aryl- and heteroaryl-methyl ketones such as **S10** and **S11** were hydrogenated with full conversion and high *ee* (Table 4, entries 10-11), whereas the fully aliphatic methyl ketone **S12** gave low conversion and *ee* (entry 12). Propiophenone **S13** was reduced with the same *ee* as acetophenone (96%) albeit with lower conversion (Table 4, entry 12 vs. 1), thus confirming that the catalyst is rather sensitive to steric factors. Finally, the cyclic ketone **S14** was transformed into the corresponding alcohol with full conversion but no enantioselectivity at all (Table 4, entry 14).

To get some information about the $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system, we determined the kinetics of the hydrogenation of acetophenone (**S1**) under the optimized catalytic conditions. The conversions were calculated from the hydrogen uptake.

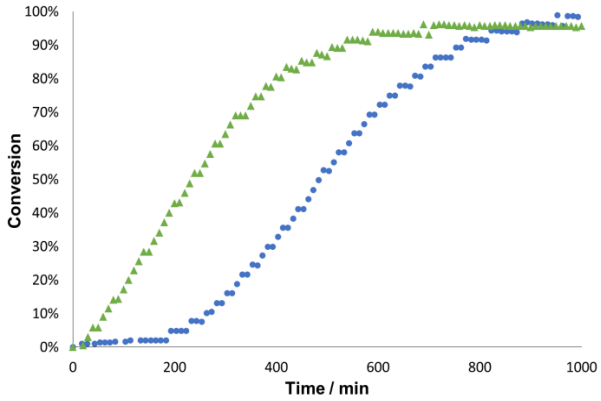


Figure 2. Kinetics of acetophenone AH catalyzed by [Ru]/(*S*,*S*)-**L** under the optimized reaction conditions (•) and after overnight pre-treatment (see the Supporting Information) of $RuCl_3(H_2O)_x$ with refluxing *i*PrOH (▲). Hydrogenation conditions: **S1**/[Ru]/(*S*,*S*)-**L**/Na_2CO_3 100/1/1/5; solvent: MeOH; c_0 (**S1**) = 0.95 M; P_{H2} = 30 bar; *T* = 19 °C; $c_{cat.}$ = 9.5 mM. Measured kinetic parameters (trace ▲): $k = 3.03 \cdot 10^{-4}$ mol min^{-1} L^{-1}; $t_{1/2}$ = 229 min.

In the plot of conversion vs. time shown in Figure 2 (trace •) it can be noted that the reaction has a long induction time (about 3 h). Notably, this induction period remained the same independent of the complexation time of (*S*,*S*)-**L** with $RuCl_3(H_2O)_x$ under Ar atmosphere preceding the introduction of H_2 in the reaction vessel. However, the induction time disappeared when $RuCl_3(H_2O)_x$ was pre-treated with refluxing *i*PrOH (i.e., a reducing agent), before carrying out the hydrogenation under the optimized conditions (Figure 2, trace ▲). This finding suggests that formation of the hydrogenation catalyst occurs after reduction of $RuCl_3(H_2O)_x$ to a lower-valent species, probably Ru(II). The conversion plot appears to obey to a zero-order kinetic law in the 0-75% conversion range. Unfortunately, our attempts to isolate and/or characterize the active complex were unsuccessful due to its high sensitivity.

In summary, we have described a new ruthenium-catalyzed AH of ketones based on the use of the Trost ligand (*S*,*S*)-**L**, which had so far never found application in metal-catalyzed reductions. The new $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system can be readily prepared in situ and provides access to a range of chiral alcohols with good conversions and high enantioselectivity (up to 96% *ee*). Kinetic studies demonstrate that formation of the catalytically active species takes place slowly in the presence of H_2. Compared to numerous other known methodologies for ketone AH,[10] the one described in this paper has the advantage of employing a commercially available chiral ligand (**L**) and a Ru source [$RuCl_3(H_2O)_x$] which is the cheapest available on the market. Therefore, our new methodology represents a step forward to address the catalyst cost issues that often discourage the industrial use of asymmetric catalysis.

Experimental Section

General Procedure for Hydrogenation.
In a Schlenk vessel under argon atmosphere, a stock solution of catalyst was prepared dissolving $RuCl_3(H_2O)_x$ (2.7 mg, 0.01 mmol), ligand (*S*,*S*)-**L** (6.9 mg, 0.01 mmol) and Na_2CO_3 (5.3 mg 0.05 mmol) in 5 mL of dry methanol. The solution was stirred for 45 min at room temperature, and then 0.5 mL-aliquots (each corresponding to 0.001 mmol / 0.01 equiv of [Ru]) were dispensed into vials containing the freshly distilled substrate(s) (0.1 mmol, 1 equiv) placed into an argon-filled vessel. The vials were transferred into an autoclave, which was purged three times with H_2 and then pressurized to 30 bar and magnetically stirred at room temperature for 22 h. After venting H_2, hexadecane (0.1 mmol) was added in each vial and GC analysis was performed. The *ee* values determined by chiral GC or HPLC (see the Supporting Information for detail).

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Keywords: ruthenium • hydrogenation • asymmetric catalysis • ketones • Trost ligand

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