Application of ruthenium complexes of triazole-containing tridentate ligands to asymmetric transfer hydrogenation of ketones

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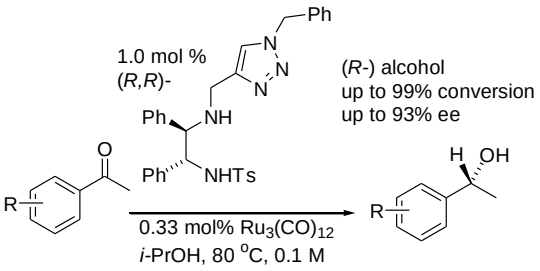
ABSTRACT

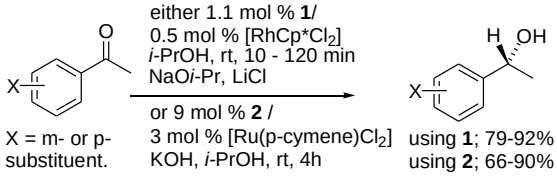


The synthesis of a series of tridentate ligands based on a homochiral 1,2-diamine structure attached to a triazole group, and their subsequent applications to the asymmetric transfer hydrogenation of ketones, are described. In the best cases, alcohols of up to 93% ee were obtained. Although base is not required, the use of $Ru_3(CO)_{12}$ as metal source is essential, indicating a unique mechanism for the formation of the active catalyst.

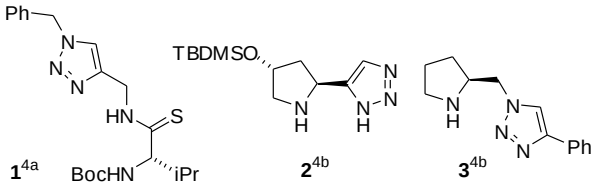
The development of improved catalysts for the asymmetric reduction of ketones represents a continuing challenge to synthetic chemists.[1] During the course of an ongoing project directed at the development of new catalysts for asymmetric transfer hydrogenation (ATH) of ketones and imines[2,3,4] we elected to study the use of ligands containing triazole donor groups.[5] Several examples of tridentate ligands have been reported for ATH reactions,[4] some of which contain a triazole donor group, such as **1**[4a] and **2**[4b] (Scheme 1). Closely related ligand **3** was not as effective. A complex of ligand **2** also reduced tetralone in 94% ee and 4-chromanone in >99% ee, although the reduction of *ortho*-methoxyacetophenone gave a product of just 34% ee.[4b]

The enantioselective reduction by ATH of *ortho*-substituted products of ketone reduction is generally considered to be more challenging than that of related *meta*- and *para*-substituted substrates.[2] Most established systems commonly reduce such substrates in lower ees than the analogous *meta*- or *para*-substituted substrates.

Scheme 1 Asymmetric transfer hydrogenation of ketones using ligands containing a triazole group.[4a,b]



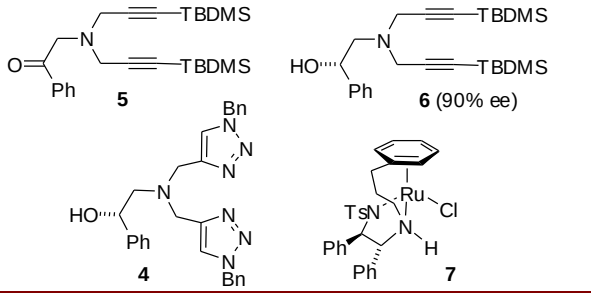
We therefore chose to investigate a ligand structure and metal combination sharply different to those previously reported, in the expectation that these might provide an opportunity to develop catalysts for the asymmetric reduction of a wider range of substrates.



1[4a] 2[4b] 3[4b]

Figure 1 Triazole-containing ligands used in ketone ATH.

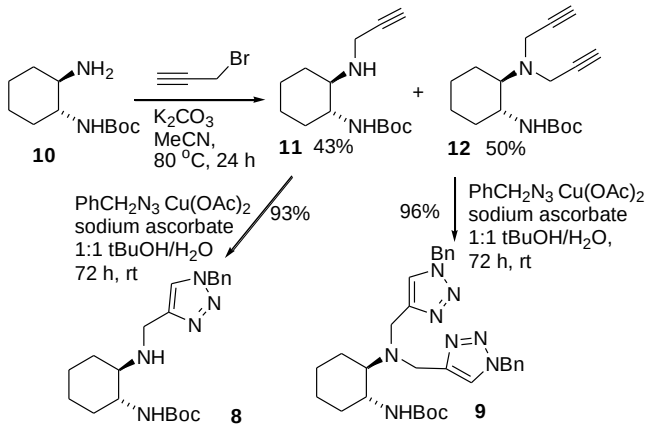
In initial studies we examined a series of ligands which contain one or two triazole groups, some of which could potentially act as either tri-[4] or tetradentate[6] ligands. Ligand **4** was prepared via asymmetric reduction of α-amino ketone **5** to alcohol **6** in 90% ee using the tethered catalyst **7**.[7,8] Following the precedent set by related ligands,[4] Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) was found to be an effective method for the creation of the required heterocyclic groups.[9]

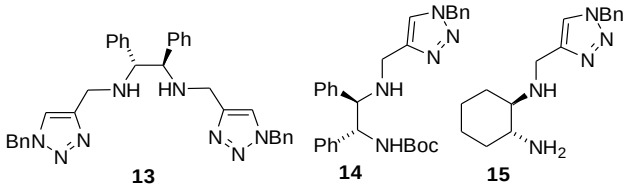


Ligands **8** and **9** were prepared using the two alkylation products (**11**[10] and **12**) of Boc-protected cyclohexyl-1,2-diamine **10** isolated from the first step of the sequence (Scheme 2). Reaction of 1,2-diphenyl-1,2-diaminoethane with propargyl bromide could be partially controlled to give the N,N' dialkylated (38%) or the N-monoalkylated (52%) products. Subsequent [3+2]-cycloaddition of these intermediates with benzylazide furnished ligands **13** and **14** respectively. Non-protected derivative **15** was also prepared._

Initial tests focused on the use of a range of metals with ligand **8**, which was closest in structure to those previously reported. Of these, only $Ru_3(CO)_{12}$ gave a product of any significant ee. However this represented a promising result, using a metal source not commonly employed in ATH reactions (Table 1). The use of the other ligands did not give an improved result with this combination of reagents._

Scheme 2 Synthesis of ligands **8** and **9**.





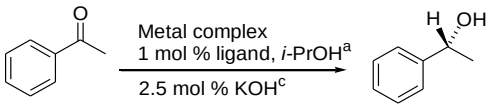
Changing the metal to ligand ratio resulted in improved conversions, a ratio of 1:1 proved to be optimal; the initial selection of a 3:1 metal to ligand ratio was based on a related system where a cluster complex was proposed to be the active catalyst.[11] _

Lowering the temperature to 60 °C resulted in lower conversion, and eventually to the loss of all catalytic activity. Most interestingly, control experiments showed that a base was not required for reduction to take place. No reaction occurred when a 5:2 formic acid/triethylamine (FA/TEA) mixture was used as the solvent and hydrogen donor.

With these promising results in hand, further tests were carried out under the revised conditions (Table 2) with **14** and the deprotected **15**. In addition, the N-tosylated ligands **16** and **17** were prepared using a CuAAC cycloaddition of the propargylic intermediates **18** and **19** respectively (Table 2).

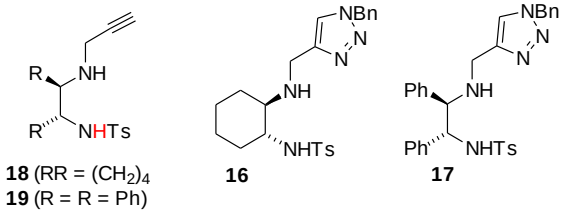
Ligand **14** was similar in reactivity to **8**. Removal of the Boc group from **8**, however, resulted in almost total loss of activity. The best results were provided by the diamine-based ligands **16** and **17**; a product was formed in 92% ee and almost quantitative conversion using **17**.

Table 1 ATH of acetophenone using ligands **4**, **8, 9** and **13**.[a]



en-try	lig-and	metal/ (mol%)	temp /°C	*t*/ h	conv /%	ee/ %	*R/S*
1	**8**	$RuCl_3.3H_2O$ (1)	80	24	0	-	-
2	**8**	$[Ru(benzene)Cl_2]$ (0.5)	80	24	53	0	-
3	**8**	$[RhCp^*)Cl_2]$ (0.5)	80	24	74	0	-
4	**8**	$[RhCp^*)Cl_2]$ (0.5)	28	24	80	67	*R*
5	**8**	$Fe_X(CO)_y$[b] (1)	80	24	0	-	-
6	**8**	$Ru_3(CO)_{12}$ (1)	80	6	48	80	*R*
7	**8**	$Ru_3(CO)_{12}$ (0.66)	80	6	48	81	*R*
8	**8**	$Ru_3(CO)_{12}$ (0.33)	80	6	88	78	*R*
9	**4**	$Ru_3(CO)_{12}$ (1)	80	24	18	18	*R*
10	**9**	$Ru_3(CO)_{12}$ (0.33)	80	48	70	44	*S*
11	**10**	$Ru_3(CO)_{12}$ (0.33)	80	24	16	2	*R*
12	**13**	$Ru_3(CO)_{12}$ (0.33)	80	24	99	69	*S*
13	**8**	$Ru_3(CO)_{12}$ 0.33)	60	24	63	76	*R*
14	**8**	$Ru_3(CO)_{12}$ (0.33)[c]	80	24	98	79	*R*

a. [acetophenone] = 0.1 M, b. x,y = 1,5; 2,9; 3,12. c. no KOH.



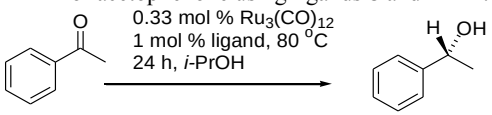
18 (RR = $(CH_2)_4$
19 (R = R = Ph)

16

17

Having identified **17** as an optimal ligand, the reduction of a further series of substrates was completed (Table 3).An electron-withdrawing trifluoromethyl group in the *para* position of the substrate had little effect on the reaction, with essentially quantitative conversion and 91 % e.e. after 16 h. An electron-donating *para*-methoxy group required a longer reaction time of 65 h to reach 91 % conversion. A methoxy group in the *ortho* or *meta* positions did not impact on the reactivity; in both cases the reaction was complete after 16 h. It is noteworthy that a series of *ortho*-substituted acetophenones could be reduced in good enantioselectivity without significant reduction of the ee, which stands in contrast to the usual behaviour of challenging *ortho*-substituted substrates in ATH reactions, as discussed earlier.[2]

Table 2 ATH of acetophenone using ligands **8** and **14-17**.[a]

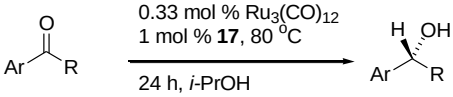


entry	ligand	conv/ %	ee/%	*R/S*
1	**8**	98	78	*R*
2	**14**	97	76	*R*
3	**15**	12	3	*R*
4	**16**	94	80	*R*
5	**17**	97	92	*R*

a [acetophenone] = 0.1 M.

A bulky bromine substituent in the *ortho* position, however, resulted in a longer reaction time and reduced enantioselectivity. Substitution in the α- position is not tolerated, with propiophenone being reduced in just 4% conversion and α-chloroacetophenone resisting any reduction, even after long reaction times. This may indicate a very well-defined binding pocket in the active catalyst. Cyclohexyl methyl ketone was reduced in 93 % conversion but required 88 h and the enantioselectivity was low. An attempted reduction of alkyne-containing PhCCCOMe failed to give any reduction product.

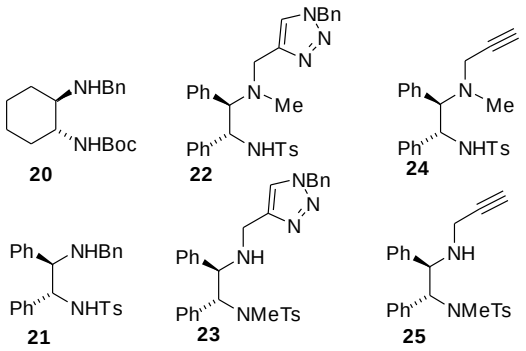
Table 3. Reduction of a range of ketones using **17**.



en-try	Ar	R	*t*/h	conv/ %	ee/%	*R/S*
1	4-$CF_3C_6H_4$	Me	16	99	91	*R*
2	4-$MeOC_6H_4$	Me	65	91	89	*R*
3	3-$MeOC_6H_4$	Me	16	97	93	*R*
4	2-$MeOC_6H_4$	Me	16	98	85	*R*
5	2-FC_6H_4	Me	16	99	83	*R*
6	2-ClC_6H_4	Me	16	96	84	*R*
7	2-BrC_6H_4	Me	65	99	77	*R*
8	2-MeC_6H_4	Me	44	89	87	*R*
9	Tetralone	-	88	27	79	*R*
10	4-Chromanone	-	20	96	91	*R*
11	2-pyridyl	Me	44	52	67	*R*
12	Cyclohexyl	Me	88	93	13	*R*

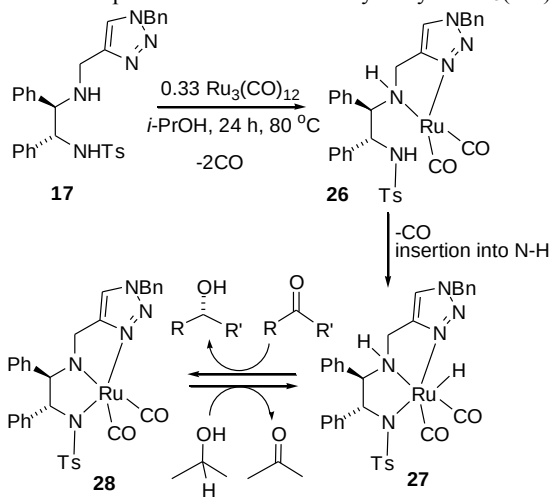
a. [ketone] = 0.1 M.

To gather information about the mechanism of the reaction, ligands **20-23** were prepared. Compound **21** is a known compound,[2j] and **20** was prepared by an analogous reductive amination procedure. Ligand **22** was prepared via reductive methylation[10] of **19** using methanal and sodium cyanoborohydride to give **24**, followed by a CuAAC reaction with benzylazide to form the required ligand **22**. Methylation of **19** using MeI and K_2CO_3, in contrast, furnished **25**, which was subsequently converted to **23**.



The reduction of acetophenone with benzyl-substituted diamines (*R*,*R*)-**20** and (*R*,*R*)-**21** gave only trace conversions of acetophenone to 1-phenylethanol, indicating that the triazole may be bound to the metal centre in the active catalyst. A similar observation was made when **22** and **23** were applied to the ATH of acetophenone; <5 % reduction was observed in either case, which indicates that the presence of both NH groups is essential for formation of a competent catalyst.

Scheme 3 Proposed mechanism of catalysis by **17**/$Ru_3(CO)_{12}$.



The ligands may form an active catalyst through an initial reaction with fragmentation of $Ru_3(CO)_{12}$ to form a bidentate complex via loss of CO to give **26**, followed by insertion of ruthenium into the N-H(Ts) bond to form ruthenium hydride **27** (Scheme 3) which transfers two hydrogen atoms to substrate to give **28**. Reaction of **28** with *i*-PrOH may then regenerate **27** to complete a catalytic cycle. The mechanism of transfer of hydrogen from **27** to a ketone may be analogous to the known 'bifunctional' catalysis mechanism exhibited by related Ru(II)/TsDPEN ATH catalysts.[12]

Heating **17** and $Ru_3(CO)_{12}$ at 80°C in toluene for 5h resulted in formation of a complex which contained two signals at ca -16 and -17 ppm in the 300 MHz ^{1}H NMR spectrum ($CDCl_3$), i.e. indicative of the formation of an Ru-H species. These signals may be due to formation of hydride species in the proposed mechanism.

In conclusion, tridentate diaminotriazoles in conjunction with $Ru_3(CO)_{12}$ in 2-propanol formed effective catalysts for ATH reactions of ketones. The reductions proceed without the need for base and enantioselectivities of up to 93 % were obtained. Notably, a range of *ortho* substituted acetophenones could be reduced in up to 99 % conversion and 85 % e.e.

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Supporting Information Available; Experimental procedures, NMR spectra and chiral GC data.

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