

Application of Ruthenium Complexes of Triazole-Containing Tridentate Ligands to Asymmetric Transfer Hydrogenation of Ketones

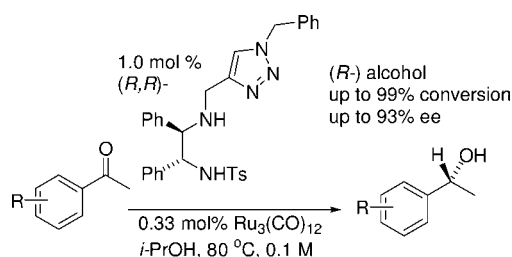
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ABSTRACT



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 $\text{Ru}_3(\text{CO})_{12}$ 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,^{2–4} 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

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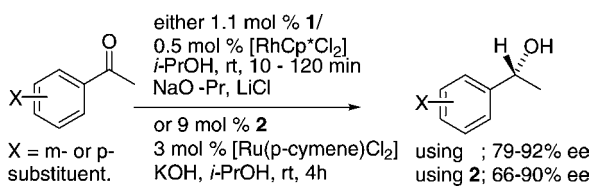
(4) (a) Timmis, F.; Adolffson, H. *Org. Biomol. Chem.* **2010**, *8*, 4536–4539. (b) Cambreiro, X. C.; Pericas, M. A. *Adv. Synth. Catal.* **2011**, *353*, 113–124. (c) Evans, D. A.; Nelson, S. G.; Gagne, M. R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800–9801. (d) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817–3818. (e) Yutong, J.; Qiongzong, J.; Guoxin, Z.; Xumu, Z. *Tetrahedron Lett.* **1997**, *38*, 6565–6568. (f) Bøgevig, A.; Pastor, I. M.; Adolffson, H. *Chem.—Eur. J.* **2004**, *10*, 294–302. (g) Zaitsev, A. B.; Adolffson, H. *Org. Lett.* **2006**, *8*, 5129–5132. (h) Diaz-Valenzuela, M. B.; Phillips, S. D.; France, M. B.; Gunn, M. E.; Clarke, M. L. *Chem.—Eur. J.* **2009**, *15*, 1227–1232. (i) Baratta, W.; Benedetti, F.; Del Zotto, A.; Fanfoni, L.; Felluga, F.; Magnolia, S.; Putignano, E.; Rigo, P. *Organometallics* **2010**, *29*, 3563–3570.

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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 ee values 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 than 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 (Figure 1).

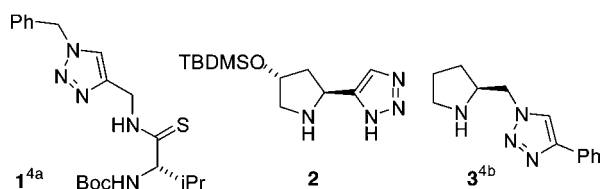


Figure 1. Triazole-containing ligands used in ketone ATH.

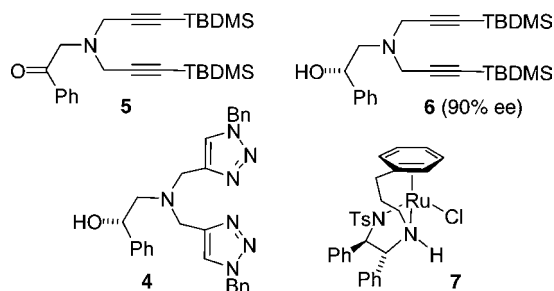
In initial studies, we examined a series of ligands which contain one or two triazole groups, some of which could potentially act as either tri-⁴ or tetradentate⁶ ligands. Ligand **4** was prepared via asymmetric reduction of α -amino ketone **5** to alcohol **6** in 90% ee using the tethered catalyst **7**.^{7,8} Following the precedent set by

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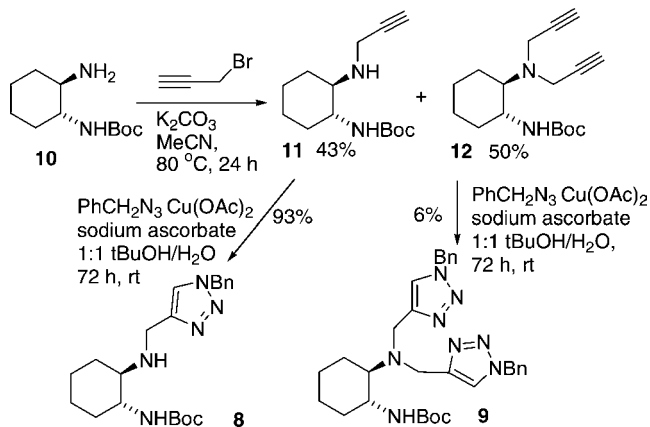
(8) The reduction of the analogous substrate to **5** but with Ph in place of TBS groups gave an alcohol of 97% ee.

related ligands,⁴ Cu(I)-catalyzed 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. Nonprotected derivative **15** was also prepared.

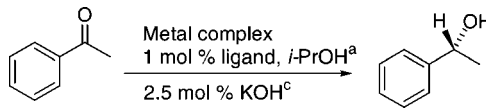
Scheme 2. Synthesis of Ligands **8** and **9**



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 Ru₃(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

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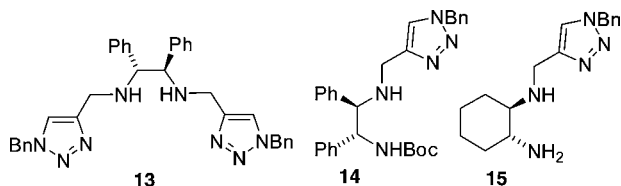
(10) (a) Takasu, K.; Azuma, T.; Takemoto, Y. *Tetrahedron Lett.* **2010**, *51*, 2737–2740. (b) Takasu, K.; Azuma, T.; Erkhtavan, I.; Takemoto, Y. *Molecules* **2010**, *15*, 8327–8348.

Table 1. ATH of Acetophenone Using Ligands **4**, **8**, **9** and **13**^a


entry	ligand	metal/(mol %)	temp (°C)	t (h)	conv (%)	ee %	R/S
1	8	RuCl ₃ ·3H ₂ O (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. ^bx, y = 1,5; 2,9; 3,12. ^cNo KOH.

did not give an improved result with this combination of reagents.



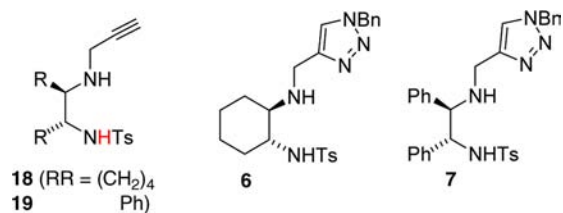
Changing the metal to ligand ratio resulted in improved conversions; a ratio of 1:1 proved to be optimal, and the initial selection of a 3:1 metal to ligand ratio was based on a related system where a cluster complex was proposed to be the active catalyst.¹¹

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.

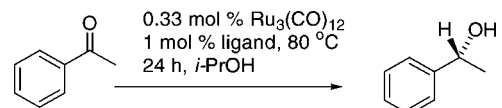
With these promising results in hand, further tests were carried out under the revised conditions (Table 2) with **14** and the deprotected **15**. In addition, the N-tosylated ligands **16** and **17** were prepared using a CuAAC cycloaddition of the propargylic intermediates **18** and **19**, respectively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



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% ee 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 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 behavior of challenging *ortho*-substituted substrates in ATH reactions, as discussed earlier.²

Table 2. ATH of Acetophenone Using Ligands **8** and **14–17**^a


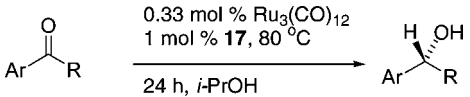
entry	ligand	conv (%)	ee %	R/S
1	8	98	78	R
2	14	97	76	R
3	15	12	3	R
4	16	94	80	R
5	17	97	92	R

^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.

To gather information about the mechanism of the reaction, ligands **20–23** were prepared. Compound **21** is a known compound,² and **20** was prepared by an analogous reductive amination procedure. Ligand **22** was prepared via reductive methylation¹⁰ of **19** using methanal

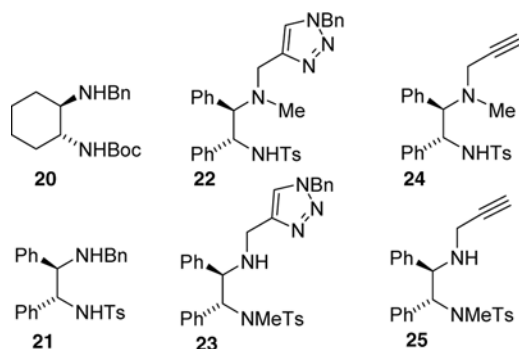
(11) Zhang, H.; Yang, C.-B.; Li, Y.-Y.; Donga, Z.-R.; Gao, J.-X.; Nakamura, H.; Murata, K.; Ikariya, T. *Chem. Commun.* **2003**, 142–143.

Table 3. Reduction of a Range of Ketones Using **17**^a


entry	Ar	R	t (h)	conv (%)	ee %	R/S
1	4-CF ₃ C ₆ H ₄	Me	16	99	91	R
2	4-MeOC ₆ H ₄	Me	65	91	89	R
3	3-MeOC ₆ H ₄	Me	16	97	93	R
4	2-MeOC ₆ H ₄	Me	16	98	85	R
5	2-FC ₆ H ₄	Me	16	99	83	R
6	2-ClC ₆ H ₄	Me	16	96	84	R
7	2-BrC ₆ H ₄	Me	65	99	77	R
8	2-MeC ₆ H 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

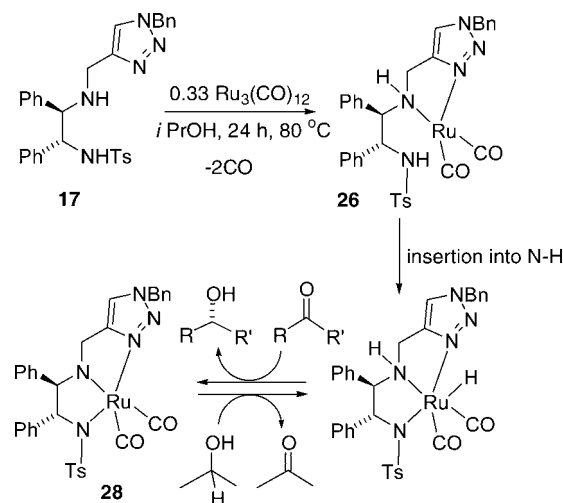
^a[Ketone] = 0.1 M.

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 K₂CO₃, 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 center 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.

The ligands may form an active catalyst through an initial reaction with fragmentation of Ru₃(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

Scheme 3. Proposed Mechanism of Catalysis by **17**/Ru₃(CO)₁₂

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 Ru₃(CO)₁₂ at 80 °C in toluene for 5 h resulted in formation of a complex which contained two signals at ca. –16 and –17 ppm in the 300 MHz ¹H NMR spectrum (CDCl₃), that is, indicative of the formation of a Ru–H species. These signals may be due to formation of hydride species in the proposed mechanism.

In conclusion, tridentate diaminotriazoles in conjunction with Ru₃(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% ee.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral GC data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.