Asymmetric transfer hydrogenation of ketones catalyzed by rhodium complexes containing amino acid triazole ligands†

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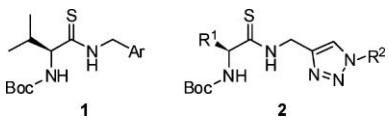
Received 8th July 2010, Accepted 6th August 2010
DOI: 10.1039/c0ob00400f

Active and selective catalysts for the asymmetric reduction of ketones, under transfer hydrogenation conditions, were obtained by combining $[RhCl_2Cp^*]_2$, with a series of L-amino acid thioamide ligands functionalized with 1,2,3-triazoles. The obtained secondary alcohol products were formed with up to 93% ee.

Asymmetric reductions of pro-chiral unsaturated compounds, such as alkenes, ketimines and ketones, are important organic transformations.[1] The obtained enantiomerically enriched alkanes, amines, and alcohols are often employed as building blocks incorporated into compounds possessing biological activity (*e.g.* pharmaceuticals or agrochemicals). In most applications, catalytic hydrogenations with transition metal catalysts in combination with molecular hydrogen are being used. In contrast, asymmetric transfer hydrogenation (ATH) represents a mild, practical and safe alternative to catalytic hydrogenation.[2] The ATH process is characterized by the presence of a hydrogen donor, often the solvent, and a transition metal catalyst with the ability to abstract a hydride and a proton from the donor and deliver these atoms to the substrate (the acceptor). Hydrogen donors such as 2-propanol or formic acid are frequently employed in ATH reactions. The substrates most suitable for transfer hydrogenations are compounds possessing polarized unsaturation. The ATH reaction is therefore mainly performed on ketones and ketimines, although reductions of activated olefins can be accomplished. The classic example of a hydrogen transfer process is the Meerwein–Ponndorf–Verley reduction (MPV), in which aluminium isopropoxide is used to mediate the transfer of a hydride from the isopropoxide to the coordinated ketone substrate.[3] Today, most transfer hydrogenations are performed using transition metal complexes, predominantly based on ruthenium, rhodium or iridium.[2] In the mid 1990's, Noyori and co-workers found that ruthenium η^6-arene complexes in combination with vicinal amino alcohol or diamine ligands, respectively, served as efficient catalysts for the reduction of ketones and ketimines under ATH-conditions.[4] This milestone discovery opened the field for further investigations, and currently there are a number of different ligand classes existing, that have been derived and employed in selective transfer hydrogenations.[5]

An important feature when developing a new ligand for any catalytic asymmetric application is the existence of modular ligand building blocks. α-Amino acids are excellent examples of building blocks which easily can be transformed into a variety of compounds, possessing interesting coordination properties and thus being suitable as ligands in asymmetric catalyzed reactions. We,[6] and others,[7] have constructed active and selective ATH-catalysts based on the use of α-amino acids. In one of our previously described protocols for the rhodium-catalyzed ATH reaction, we employed amino acid thioamide ligands (**1**).[8] We found that the activity and selectivity of the catalysts could be fine tuned by structural variations of the ligands.[8c] Hence, variations of the size of the aryl group (Ar) in **1** resulted in different steric hindrance imposed by the ligand on the substrate during the hydrogen transfer process. Herein, we report on a novel amino acid-based ligand system (**2**), where the incorporation of 1,2,3-triazoles allows for further fine tuning of the catalyst activity and selectivity.



1 **2**

An elegant method for the regioselective preparation of 1,4-disubstituted 1,2,3-triazoles is the copper-catalyzed 1,3-dipolar cycloaddition of organic azides and terminal alkynes.[9] The synthetic ease with which triazoles can be integrated into more complex structures has led to numerous applications in quite diverse areas.[10] However, in catalysis there are only a few examples of transition metal complexes where triazole-based ligands are applied.[11] In our previous studies of the ATH of acetophenone in 2-propanol, using a rhodium-complex with ligand **1** (Ar = 2-pyridyl) we obtained good catalytic activity and enantioselectivity of the formed secondary alcohol.[8c] This observation indicates that the presence of a potentially coordinating heteroatom in the aryl group of the ligand did not diminish the catalytic activity of the complex. To further our understanding on how other heterocycles positioned at the C-terminal of the amino acid thioamide ligand scaffold would affect the catalytic behaviour, we prepared a series of compounds containing the 1,2,3-triazole unit. The preparative route for the ligands with the common structure **2** is outlined in Scheme 1. Activation of *N*-Boc-protected amino acids (**3**) by isobutylchloroformate followed by treatment of the obtained mixed anhydride with propargylamine led to the formation of *N*-propargyl-substituted amino acid amides (**4**). Amino acid amides containing 1,4-disubstituted 1,2,3-triazoles (**5**) were readily obtained reacting **4** with various aryl and benzylic azides using the Sharpless protocol.[9a] Treatment of the obtained amino acid amides with Lawesson's reagent resulted in the formation of the desired ligand structures **2**.

With the novel amino acid derivatives **2a–i** in hand, we set out to investigate the catalytic activity of these compounds when used as ligands in the rhodium-catalyzed ATH of acetophenone. The

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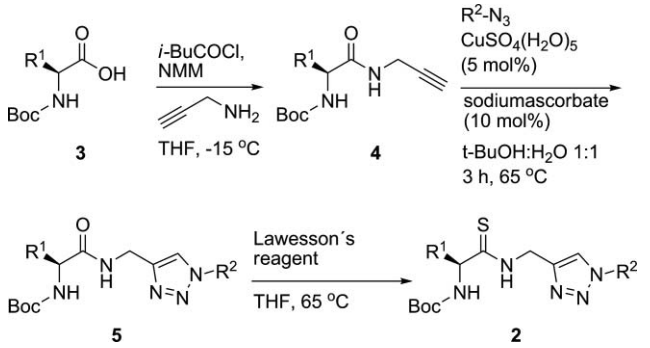
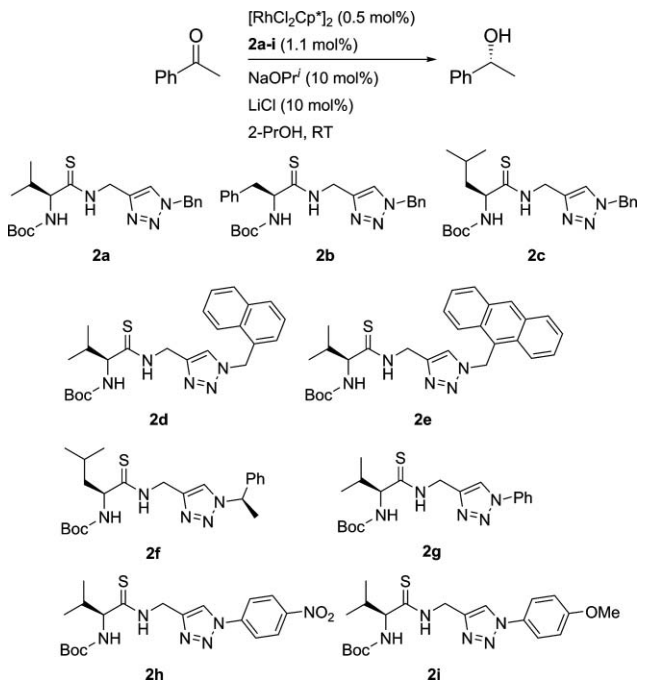
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data. See DOI: 10.1039/c0ob00400f



Scheme 1 Synthetic method for the preparation of amino acid thioamides functionalized with 1,2,3-triazoles For explanations of substituents R^1 and R^2, see Scheme 2.



Scheme 2 Conditions for the rhodium-catalyzed ATH of acetophenone.

reaction conditions for the catalytic reduction, along with the structures of the investigated ligands, are shown in Scheme 2.

The active reduction catalyst was formed *in situ* from the rhodium–arene precatalyst $\{[RhCl_2Cp^*]_2\}$ in combination with the appropriate ligand (**2a–i**) in the presence of sodium isopropoxide and lithium chloride. The catalytic ATH reaction was performed in 2-propanol with an acetophenone concentration of 0.2 M. We have previously discovered that the addition of lithium chloride has a beneficial effect on the catalytic activity and selectivity of the ATH process.[6f] The reason for higher activity and selectivity is attributed to a tighter transition state in the hydride transfer step from the rhodium-catalyst to the substrate, where a lithium ion plays a crucial role in coordinating both substrate and catalyst. Hence, under the conditions described, acetophenone was reduced and the results are presented in Table 1. In the ligand screening process, all reactions were sampled after 10 min and after 2 h. As presented in Table 1, the ATH reactions proceeded smoothly with most of the catalysts, reaching conversions ranging from 62–79% after 10 min with 1 mol% catalyst loading.

Table 1 Rhodium-catalyzed asymmetric transfer hydrogenation of acetophenone[a]

Entry	Ligand	Reaction time/min	Conv.(%)[b]	ee (%)[c]	TOF_{10}/h^{-1}[d]
1	**2a**	10	76	90 (*R*)	456
2	**2a**	120	88	89 (*R*)	
3	**2b**	10	62	89 (*R*)	372
4	**2b**	120	81	87 (*R*)	
5	**2c**	10	79	71 (*R*)	474
6	**2c**	120	90	66 (*R*)	
7	**2d**	10	67	89 (*R*)	402
8	**2d**	120	87	86 (*R*)	
9	**2e**	10	68	88 (*R*)	408
10	**2e**	120	79	88 (*R*)	
11	**2f**	10	68	72 (*R*)	408
12	**2f**	120	84	67 (*R*)	
13	**2g**	10	76	93 (*R*)	456
14	**2g**	120	91	90 (*R*)	
15	**2h**	10	73	93 (*R*)	438
16	**2h**	120	88	89 (*R*)	
17	**2i**	10	68	92 (*R*)	408
18	**2i**	120	90	88 (*R*)	

[a] Reaction conditions: see Scheme 2. General procedure for the asymmetric transfer hydrogenation of acetophenone using ligands **2a–i** (Table 1); $\{[RhCl_2Cp^*]_2\}$ (3.1 mg, 0.005 mmol), ligand (0.011 mmol) and LiCl (4.2 mg, 0.1 mmol) were dried under vacuum in a dry Schlenk tube for 15 min. Distilled 2-propanol (4.5 mL), acetophenone (116 μL, 1 mmol) and a solution of 0.1 M i-PrONa (1.0 mL, 0.1 mmol) were added under nitrogen in sequential order. The reaction mixture was stirred at ambient temperature. Aliquots were taken according to reaction times indicated in Table 1, and were passed through a pad of silica using EtOAc as eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB). [b] Conversion determined by GLC. [c] Enantiomeric excess determined by GLC (CP Chirasil DEXCB). [d] Turnover frequencies were calculated based on the conversion obtained after 10 min.

The obtained conversions correspond to turn over frequencies (TOF_{10}) of >400 h^{-1}. In comparison to other amino acid-based catalyst systems used in the ATH of acetophenone, these triazole-functionalized catalysts show significantly higher activity. The enantioselectivity of the formed 1-phenylethanol ranged between 71–93%, with the best ees obtained using the catalysts derived from the valine ligands **2a** and **2g–i** (entries 1, 13, 15 and 17).[12] The use of the phenylalanine ligand **2b** resulted in 89% ee (entry 3), whereas the catalytic reduction using the leucine-based ligand **2c** only gave the product in 71% ee. Comparing the results after two hours show that higher conversions were obtained in all cases, however, no reaction went to completion.

The enantioselectivity of the product decreased in most reactions, indicating that the equilibrium between starting materials (acetophenone and 2-propanol) and products (1-phenylethanol and acetone) was reached. Ligands **2g–i**, derived from aryl azides possessing different electronic properties, were included in the study to get information on possible coordination from the triazole to the rhodium ion.[13] Theoretically, the triazole in **2i** would coordinate stronger due to the electron releasing 4-methoxy substituent on the aryl ring. However, as seen in Table 1, comparing the results obtained with ligands **2g–i**, only small differences were observed, and no conclusion regarding triazole coordination can be drawn. Attempts were made to isolate the catalyst formed between the rhodium–arene precursor and these novel amino acid-based ligands; however, so far we have been unsuccessful in obtaining material suitable for characterization.

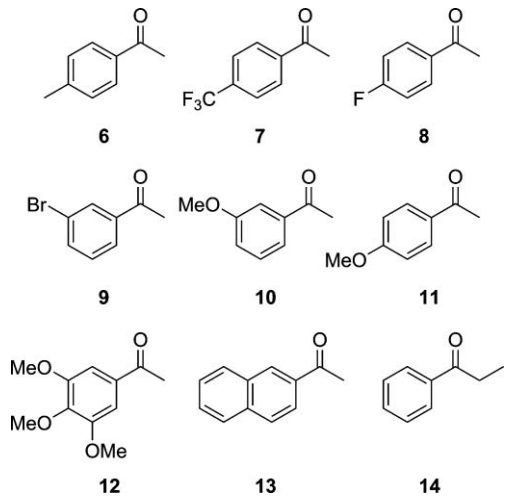


Fig. 1 Aryl alkyl ketones screened in the ATH catalyzed by Rh-**2a**.

Table 2 Rhodium-catalyzed asymmetric transfer hydrogenation of aryl alkyl ketones[a]

Entry	Substrate	Reaction time/min	Conversion (%)[b]	ee (%)[c]
1	**6**	120	73	79 (*R*)
2[d]	**7**	10	97	87 (*R*)
3[d]	**7**	120	>99	86 (*R*)
4	**8**	10	81	81 (*R*)
5	**8**	120	91	79 (*R*)
6	**9**	10	97	87 (*R*)
7	**9**	120	99	86 (*R*)
8	**10**	10	77	92 (*R*)
9	**10**	120	91	89 (*R*)
10	**11**	120	51	73 (*R*)
11	**12**	120	89	84 (*R*)
12[e]	**13**	120	90	89 (*R*)
13	**14**	120	85	90 (*R*)

[a] General procedure for the asymmetric transfer hydrogenation of ketones **6–14** using ligand **2a** (Table 2); {[$RhCl_2Cp^*]_2$} (3.1 mg, 0.005 mmol), **2a** (4.4 mg, 0.011 mmol) and LiCl (4.2 mg, 0.1 mmol) were dried under vacuum in a dry Schlenk tube for 15 min. Distilled 2-propanol (4.5 mL), ketone (1 mmol) and a solution of 0.1 M i-PrONa (1.0 mL, 0.1 mmol) were added under nitrogen in sequential order. The reaction mixture was stirred at ambient temperature. Aliquots were taken according to the reaction times indicated in Table 1, and were passed through a pad of silica using EtOAc as eluent. The resulting solutions were analyzed by GLC (CP Chirasil DEXCB). [b] Conversion determined by GLC. [c] Enantiomeric excess determined by GLC (CP Chirasil DEXCB). [d] 0.1 mol% catalyst loading. [e] 0.5 mol% catalyst loading.

Since the results obtained using the different amino acid thioamide triazoles were so similar, we decided to go further and evaluate the scope of the ATH on different ketones with the catalyst based on ligand **2a**. The results from the reduction of ketones **6–14** (Fig. 1) are summarized in Table 2. As expected, substrates possessing electron withdrawing substituents generally gave better results in comparison with their counterparts. With the exception of 4′-methoxyacetophenone (**11**), all reactions reached conversions higher than 70% after 2 h reaction time. Particularly high catalytic activity was observed in the reduction of the electron poor 4′-trifluoromethylacetophenone (**7**), where we were able to decrease the catalytic loading to 0.1 mol% and yet achieve high conversion after only 10 min (Table 2, entry 2). The turnover frequency (TOF_{10}) in this particular reaction reaches an impressing 5820 h^{-1}.[14] The enantioselectivity of the products was unfortunately only moderate to good, and clearly inferior in comparison to reactions catalyzed by rhodium–arene complexes combined with other amino acid thioamide ligands.

Conclusions

In conclusion, we have demonstrated that highly active catalysts for the asymmetric reduction of aryl alkyl ketones can be formed from amino acid thioamide triazole ligands. The ligands were readily prepared in good yields, using a straightforward procedure where the copper-catalyzed [3+2] cycloaddition between *N*-propargyl amino acid amides and aryl or benzylic azides was the key step. The catalytic activity of the *in situ* formed rhodium complexes was in general very good, and in the case of the reduction of 4′-trifluoromethylacetophenone we were able to reduce the catalytic loading to only 0.1 mol%. The typical amount of catalyst used in ATH processes is 0.5–1 mol%, and going below this amount usually results in unproductive conversions. The high activity demonstrated by catalysts based on the triazole-functionalized amino acid derivatives presented here makes them promising for further studies.

Acknowledgements

This work was financially supported by the Swedish Research Council, the Carl Trygger Foundation, the Wenner-Gren Foundations, the K & A Wallenberg Foundation, and the Magn. Bergvall Foundation.

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