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Proline-Derived Aminotriazole Ligands: Preparation and Use in the Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation

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Abstract: The preparation of 2-triazolyl- and 2-triazolylmethylpyrrolidines from L-proline and L-*trans*-4-hydroxyproline is described, along with their evaluation as chiral ligands in ruthenium-catalyzed asymmetric transfer hydrogenation. Modular evolution of the ligands by introduction of remote substituents is also presented, showing a surprisingly important effect on the performance of the ligands.

Keywords: asymmetric catalysis; click chemistry; hydrogen transfer; proline; ruthenium; triazoles

Introduction

Since the birth of *click chemistry*[1] and, more particularly, the discovery of Cu(I)-based catalytic systems for the cycloaddition between azides and alkynes,[2] the triazole group has drawn increasing attention, finding application in many different research fields.[3]

In biological chemistry, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been applied for modification of biopolymers by conjugation with small molecules.[4] Also, the development of the Huisgen cycloaddition under physiological conditions opened a door for *in vivo* click chemistry, applicable in imaging of cellular processes.[5] In medicinal chemistry it has been used as an effective means for creating molecular diversity in an easy and modular manner.[6]

This reaction has reached its great importance in materials chemistry, as a means for modification of surfaces by linking different kinds of molecules, preparation of dendrimers or copolymers, and immobilization of catalysts and other functional units onto polymers.[7] In our group we have been actively engaged in this field, extensively exploring CuAAC for the immobilization of organic catalysts[8,9] and ligands[10] onto polystyrene resins.

Finally, also in the field of catalysis, CuAAC has been used as a reliable means for introducing structural variability in tuneable ligands such as monophosphines (ClickPhos)[11] or ferrocenyl diphosphines (ClickFerrophos),[12] as well as in organic catalysts.[13]

In all these approaches, the triazole group has been exploited just as a structural fragment or as a linker, although it may exert some influence in the final properties of the materials mainly by polar or steric effects, but not for an intrinsic reactivity of the triazole itself. However, the ability of the triazole group to act as a donor in coordination chemistry is not only apparent from observation of its structure (bearing two non-bonding electron pairs, orthogonal to the aromatic π-system) but has also been confirmed by experimental studies. As an example, in the course of the research developed in our group on the immobilization of ligands for the catalytic enantioselective addition of organozinc compounds to aldehydes,[10a] an important decrease in the enantioselectivity was registered when triazole-linked catalysts were used (compared to the ether-linked analogue), which was explained by a competition of the triazole and the amino alcohol moieties for complexing the zinc reagent.

Moreover, other systems containing triazole units acting as donors in metal complexes have been reported in the last years,[14] including even some applications in catalysis (Figure 1). Namely, the tris(triazole) ligands **1** and **2**, described by the Sharpless group[15] and by us[16] turned out to be very effective catalysts for the CuAAC reaction. Also, (triazolylmethyl)phosphines (Clickphine, **3**)[17] have been applied

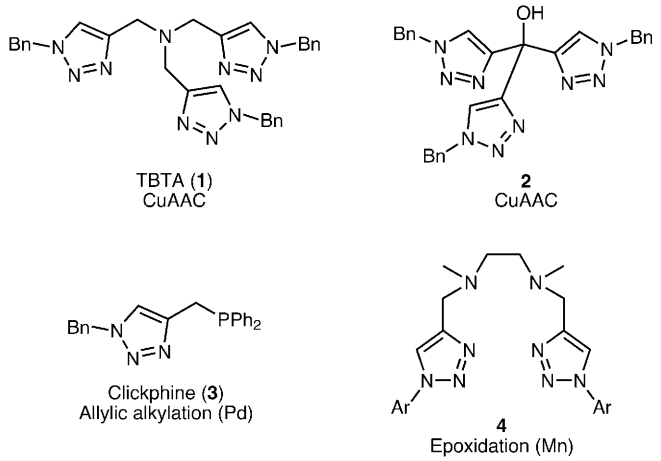


Figure 1. Triazole-based ligands used in catalysis.

as ligands for Pd-catalyzed allylic alkylation reactions and tetradentate bis(triazolylamines) (**4**) for Mn-catalyzed epoxidation reactions.[18] In some cases, direct coordination of either the N-2 or N-3 nitrogen atoms of the triazole group to the metal was demonstrated by different means including X-ray crystallographic analysis, as in the case of tristriazole-copper[16] and phosphinito-triazole-rhodium[19] complexes. Enantioselective applications, however, remain completely unexplored.

In the light of all these data, we envisioned to assess the applicability of triazoles as donors in metal-based asymmetric catalysis. With this purpose, we designed ligands **5** and **6** (Scheme 1), constituted by the conjuction of a well-known, easily accessible chiral backbone and a triazole group, in two complementary approaches. Herein we report our studies on the preparation and the initial application in catalysis of such ligands.

As a benchmark reaction for initially testing the chiral aminotriazole ligands, we chose the ruthenium-catalyzed transfer hydrogenation of ketones. This reaction has been extensively studied in the last two decades, since the groundbreaking work by Noyori on the use of ruthenium-arene complexes with monotosylated diamines[20] (Figure 2). Along this route, many different types of ligands have been described for this process,[21] presenting as a general feature the presence of a primary or secondary amine (a free NH group being essential for good catalytic activity),[22] accompanied by other auxiliary group (such as tosylamide, alcohol, thiol, etc.). Most frequently, but not exclusively, the auxiliary group acts as an anionic ligand, thus giving place to neutral ruthenium complexes.

With this in mind, aminotriazole ligands **5** and **6** (Scheme 1) were expected to form chelate complexes with ruthenium coordinated to the triazole moiety through different nitrogen atoms (Figure 3), both likely to be active as catalysts for the transfer hydrogenation of ketones.

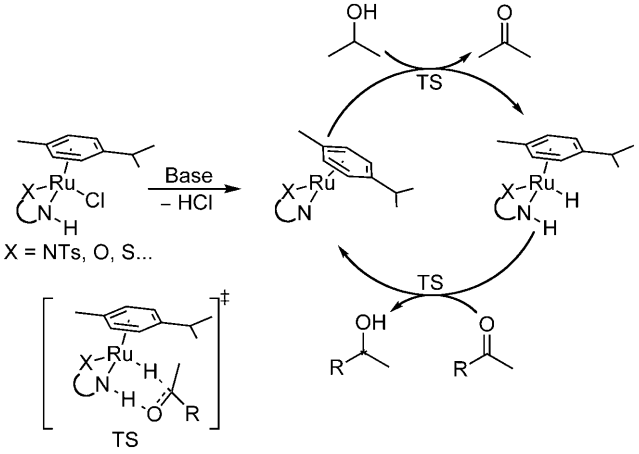


Figure 2. General structure and catalytic cycle of Noyori-type catalysts for transfer hydrogenation.

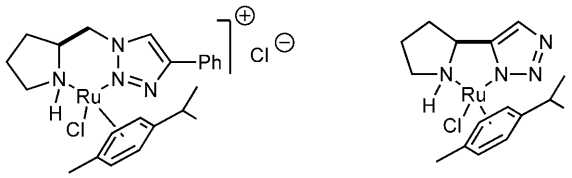
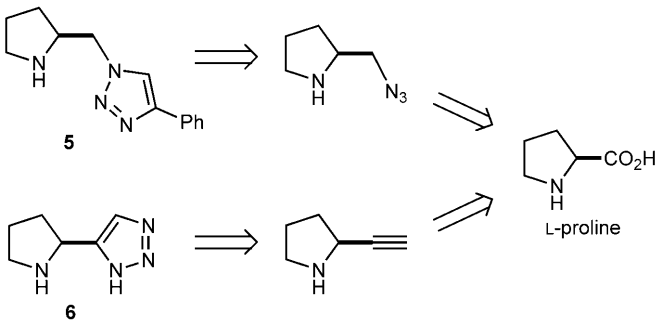


Figure 3. Putative ruthenium(II) complexes with chiral aminotriazole ligands **5** and **6**.

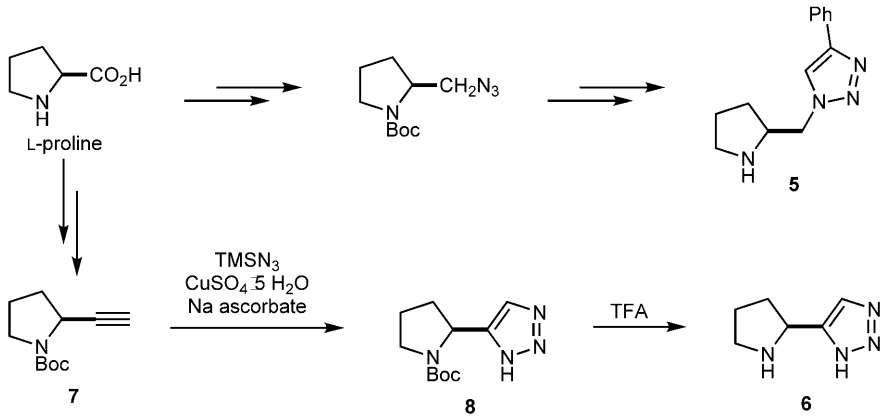


Scheme 1. Proline-derived chiral triazole-based ligands.

Results and Discussion

Synthesis of the Ligands

The preparation of ligands with the targeted structures from commercially available L-proline was planned as having its key step in a CuAAC reaction, either with a proline-derived chiral azide and an alkyne or with a proline-derived chiral alkyne and an azide (Scheme 1).



Scheme 2. Preparation of proline-derived chiral aminotriazole ligands **5** and **6**.

Compound **5** had already been described as an organic catalyst for the Michael reaction between ketones and nitrostyrene derivatives.[13a] It was readily prepared for the work presented herein by a modification of the previously reported procedures, starting from enantiopure L-proline (Scheme 2).[24]

On the other hand, ligand **6** was prepared by CuAAC of the known chiral alkyne **7** and azidotrimethylsilane followed by deprotection (Scheme 2),[24] alkyne **7** having been itself obtained also from enantiopure L-proline.[23]

Preliminary Tests in Catalysis

With enantiopure 2-(4-phenyltriazolyl)methylpyrrolidine (**5**) and 2-(5-triazolyl)pyrrolidine (**6**) in hand, we set out to test their performance as ligands in the Ru-catalyzed transfer hydrogenation of acetophenone (**9a**) leading to (*S*)-1-phenylethanol (**10a**). Reactions were carried out with both ligands, using potassium hydroxide as the base and isopropyl alcohol as the reducing agent (Scheme 3).

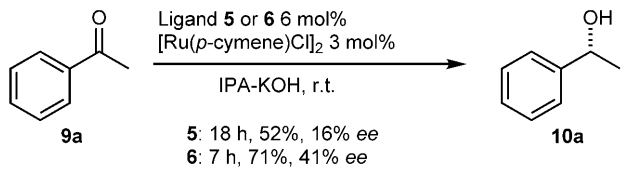
Although both ligands represented active catalysts for the reaction, the results made apparent the superiority of ligand **6**, bearing a free triazole NH group. Although the use of neutral ligands in this reaction (giving place to cationic ruthenium catalysts) has been described, it is worth noting that the vast majority of the successful ligands in this kind of systems act as anionic ones (giving place to neutral catalysts). Based on these results, we decided to take the structure **6** as the reference one for further development of our ligand family.

Second Generation

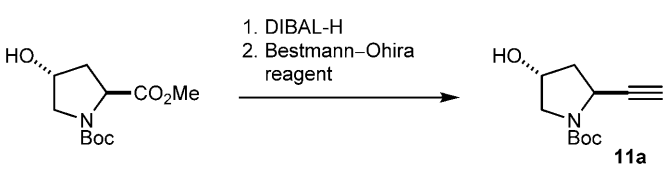
To obtain ligands with improved catalytic behaviour, we planned to introduce structural variability in the pyrrolidine ring by testing different substitutions. Bearing in mind the availability of *trans*-4-hydroxyproline, we envisioned to use it as the starting point for the development of new ligands. This strategy was expected also to help us in assessing whether remote substituents, far away from the catalytic metal centre, could exert an influence on the catalytic performance either by polar effects,[25] by steric effects (by blocking one of the faces of the pyrrolidine ring), or through the simultaneous operation of both factors.

A simplified procedure[26] entailing reduction of the *N*-Boc-*trans*-4-hydroxyproline methyl ester to aldehyde followed, in one pot, by treatment with the Bestmann–Ohira reagent[27] allowed straightforward access to the enantiopure hydroxyalkyne **11a** (Scheme 4).

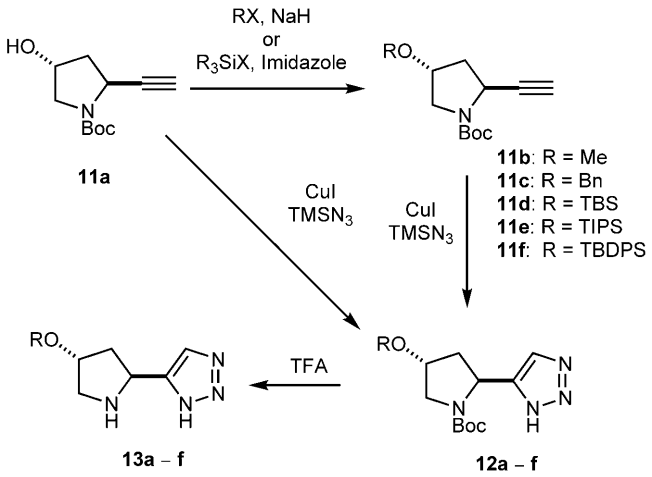
With this alkyne in hand, introduction of different substituents on the hydroxy group, by well known protecting group chemistry allowed preparation of various ether and silyl ether derivatives **11b–f**. Cu-catalyzed cycloaddition with trimethylsilyl azide, followed by deprotection, led uneventfully to the target ligands **13a–f** (Scheme 5).[23]



Scheme 3. ATH of acetophenone with ligands **5** and **6**.



Scheme 4. One-pot preparation of hydroxyalkyne **11a**.



Scheme 5. Preparation of the family of ligands **13a–f**.

Catalytic Tests

ATH experiments run with these ligands under the same conditions as previously used for **5** and **6** showed the results displayed in Table 1.

Gratifyingly enough, even the presence of a free hydroxy group at C-4 on the pyrrolidine ring (ligand **13a**) caused a 23% increase in the *ee* compared to the unsubstituted pyrrolidine (ligand **6**), although this was accompanied by an important decrease in catalytic activity. With the other ligands, bearing different protecting groups on the oxygen atom (**13b–f**), better conversions and *ee*s were recorded in all the cases.

For alkyl ethers, ligand **13b**, bearing the less bulky methoxy substituent afforded better results, both in terms of catalytic activity and enantioselectivity. Somewhat intriguingly, in the case of silyloxy substituents the trend was exactly the opposite, the best results being those obtained with ligand **13f**, bearing the bulkiest TBDPS group. This contrasting behaviour may follow polar effects, and be related to the different polarities of C–O and Si–O bonds.

Table 1. Tests in ATH of acetophenone with amino triazole ligands **13a–f**.[a]

Ligand	Time [h]	Conv. [%][b]	$TOF_{1/2}$ [h^{-1}][c]	% *ee*[b]
6	7	71	2.46	41
13a	18	9	0.08[d]	64
13b	18	93	3.17	84
13c	18	71	2.00	77
13d	18	87	3.48	70
13e	5	60	4.06	74
13f	4	93	7.96	81

[a] All reactions performed at room temperature, with 0.1 M concentration of acetophenone and 1:1:10:17 Ru:ligand:base:substrate ratio.
[b] Determined by gas chromatography.
[c] TOF calculated at 50% conversion.
[d] TOF calculated at 9% conversion.

Taking as a reference ligand **13f**, we decided to run some experiments aimed at determining optimal reaction conditions. As shown by the results on Table 2, neither the use of different arene ligands or potassium *tert*-butoxide as the base resulted in any improvement (entries 1–4). Contrarily, in fact, with benzene or hexamethylbenzene as arene ligands, a strong decrease in the enantioselectivity of the process, as well as in the catalytic activity, was observed (entries 2 and 3).

Additionally, the influence of the metal to ligand ratio was also studied by performing a series of experiments where this ratio was systematically modified (entries 4–8). With respect to catalytic activity, the results showed that it reaches a maximum around a 1:1 ratio, being significantly lower with a two-fold excess of any of the components. *This strongly suggests the active species to be a complex of 1:1 stoichiometry, with the triazolylpiridine acting as a bidentate ligand*. With respect to enantioselectivity, slightly better results were recorded in the presence of excess ligand, and the conditions of entry 7 were considered to be optimal.

Finally, we explored the performance of the catalyst derived from ligand **13f** in the transfer hydrogenation of a family of diversely substituted ketones under the optimized reaction conditions. The results of this study are summarized in Table 3.

Acetophenone derivatives **9b–g** with different substitution patterns on the phenyl ring were first evaluated, with varying results both in terms of catalytic activity and enantioselectivity. In all the cases except for *p*-methoxyacetophenone (**9d**, entry 4), good conversions were recorded after four hours. On the other hand, moderate to good *ee*s were registered, except in the case of *o*-methoxyacetophenone (**9b**, entry 2).

With acetonaphthones **9h**, **i** as substrates (entries 8 and 9), bearing a larger planar substituent, high conversions and *ee*s were observed in both cases. With rigid cyclic ketones such as 1-tetralone **9j** and 1-chromanone **9k** (entries 10 and 11), excellent *ee*s were achieved although at expense of a moderate decrease in the catalytic activity.

Finally, use of propiophenone **9l** as the substrate (entry 12) resulted in moderate decreases both in conversion and *ee*, compared to those obtained with acetophenone.

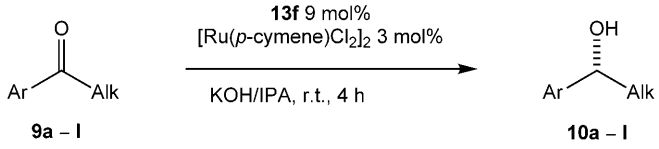
As an approach for obtaining a better understanding of the role played by the ether or silyl ether substituents in the C-4 position, the enantiodifferentiating step of the reduction of chromanone (**9k**) leading to **10k** was studied by theoretical means, using a DFT approach with the B3LYP functional as implemented

Table 2. Effect of base, arene ligand and metal to ligand ratio in the ATH of acetophenone with ligand **13f**.[a]

Entry	Arene	Base	M:L	Conv. [%][b]	$TOF_{1/2}$ [h^{-1}][c]	% *ee*[b]
1	*p*-cymene	*t*-BuOK	1:1	86	8.20	81
2	C_6Me_6	*t*-BuOK	1:1	40	1.69[d]	57
3	C_6H_6	*t*-BuOK	1:1	51	2.11	43
4	*p*-cymene	KOH	1:1	93	7.96	81
5	*p*-cymene	KOH	2:1	84	5.52	70
6	*p*-cymene	KOH	3:2	91	8.94	79
7	*p*-cymene	KOH	2:3	91	8.03	82
8	*p*-cymene	KOH	1:2	81	5.52	84

[a] All the reactions run for 4 h under the conditions described in Table 1, changing only the variables indicated in the table.
[b] Determined by gas chromatography.
[c] TOF calculated at 50% conversion
[d] TOF calculated at 40% conversion.

Table 3. Substrate scope of the ATH reaction with ligand **13f**.[a]



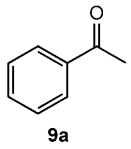
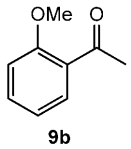
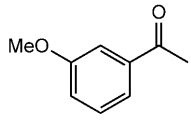
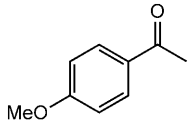
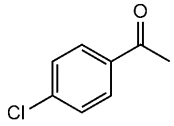
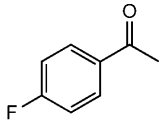
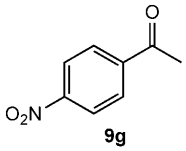
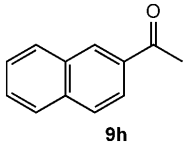
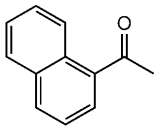
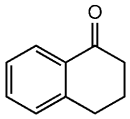
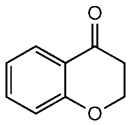
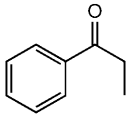
Entry	Substrate	Conv. [%][b]	% *ee*[b]
1	 **9a**	91	82
2	 **9b**	96	34
3	 **9c**	85	75
4	 **9d**	24	71
5	 **9e**	93	66
	 **9f**	60	70

Table 3. (Continued)

Entry	Substrate	Conv. [%][b]	% *ee*[b]
7	 **9g**	97	69
8	 **9h**	79	87
9	 **9i**	80	90
10	 **9j**	42	94
11	 **9k**	67	>99
12	 **9l**	78	70

[a] All reactions run for 4 h under the conditions described in Table 2, entry 7.
[b] Determined by gas chromatography.

in Gaussian 09.[28] The SDD basis set, including SDD cartesian pseudopotentials for the ruthenium atom, was employed.

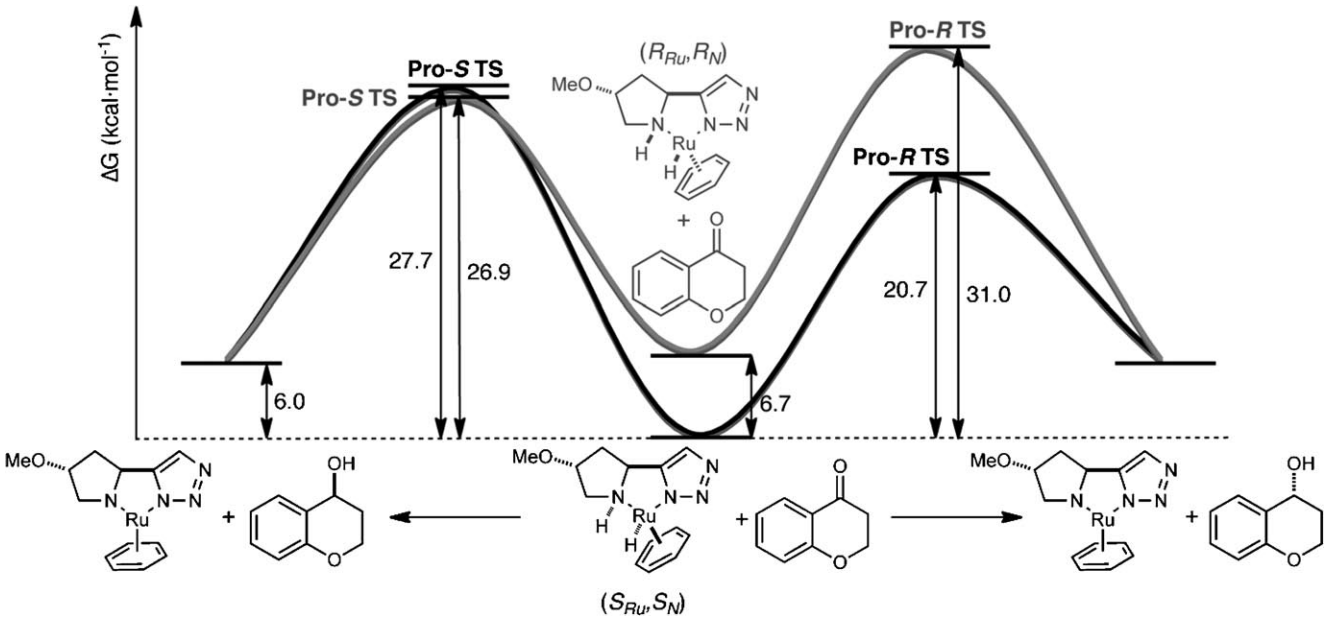


Figure 4. DFT calculated reaction profile for the ruthenium-catalyzed ATH of chromanone (**9k**) with ligand **13b**.

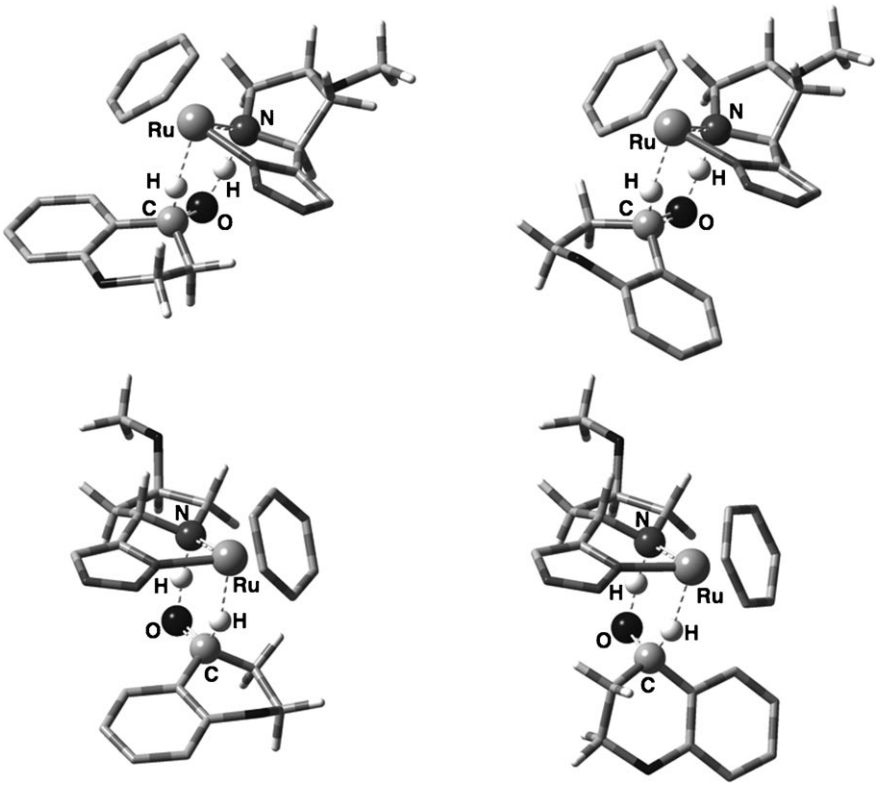


Figure 5. DFT calculated transition states for the ruthenium-catalyzed ATH of chromanone (**9k**) with ligand **13b**; *top left:* (S_{Ru},S_N)-pro-*R*; *top right:* (S_{Ru},S_N)-pro-*S*; *bottom left:* (R_{Ru},R_N)-pro-*S*; *bottom right:* (R_{Ru},R_N)-pro-*R*.

The two possible configurations at the ruthenium and nitrogen atoms, and the two possible approaches of the ketone undergoing reduction (pro-*R* and pro-*S*) were explored. The results have been summarized in Figure 4 and Figure 5.

Of the two possible ruthenium hydride catalysts, the one with the *S* configuration at the Ru and N centres, was clearly favoured (6.7 kcal mol^{-1}) over the one with the *R* configuration. This preference was also reproduced in the corresponding transition states,

the lowest energy one for the (S_{Ru},S_N) system being 6.2 kcal mol^{-1} more favourable than the lowest energy one for the (R_{Ru},R_N) system.

Between the two possible approaches of the ketone, in the (S_{Ru},S_N) catalyst, the pro-*R* one was favoured by 7.0 kcal mol^{-1}, and this is consistent with the complete enantioselectivity experimentally observed when the reduction of **9k** is performed with the analogous ligand **13f** (Table 3, entry 11).

It is interesting to recall that even with the unsubstituted ligand **6**, the sign of enantioselectivity (preferential production of the *R* enantiomer) is preserved. It thus appears that the more compact (S_{Ru},S_N)-pro-*S* type transition states are intrinsically less stable than the (S_{Ru},S_N)-pro-*R* type ones. Interestingly, the critical region of the transition state where the enantiodifferentiating bond-making process takes place is closer to the R-oxy substituent at C-4 in the pro-*S* (Figure 5, *top right*) than in the pro-*R* transition state. Thus, the effect exerted by the remote C-4 substituent in ligands **13** would be that of further destabilizing the (S_{Ru},S_N)-pro-*S* type transition states.

Conclusions

In conclusion, we have demonstrated the applicability of triazolyl units as donors in metal chelates for asymmetric catalysis through the development of a new family of enantiopure 2-(5-triazolyl)pyrrolidines and their use in the Ru-catalyzed asymmetric transfer hydrogenation of ketones. Taking into account that triazoles can be installed in a very controlled manner on almost every organic molecule containing a singly bonded functional group through the CuAAC reaction,[2] the present finding will probably give rise to new ligand designs for many types of catalytic processes. Further work in this direction is in progress in our laboratories and will be reported in due course.

Experimental Section

(*S*)-*tert*-Butyl 2-(1*H*-1,2,3-Triazol-5-yl)pyrrolidine-1-carboxylate (8)

Alkyne **7** (332 mg, 1.70 mmol) was placed together with $CuSO_4{\cdot}5H_2O$ (12 mg, 34 μmol) and sodium ascorbate (34 mg, 0.17 mmol) in a flask. A 1:1 *tert*-butyl alcohol-water mixture (5 mL) was added, followed by trimethylsilyl azide (247 μL, 1.79 mmol), and the resulting mixture was stirred overnight at room temperature. Then, water was added and the organics were extracted with diethyl ether. The resulting solution was dried with anhydrous sodium sulphate and concentrated under reduced pressure to give a pale yellow oil. The crude material was purified by flash chromatography through deactivated silica, eluting with hexane-ethyl acetate mixtures. After removal of the solvents, the title product was obtained as a colourless oil; yield: 225 mg (55%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.48$ (s, 9H), 1.92 to 2.34 (br, 4H), 3.40 to 3.62 (br, 2H), 5.07 (br, 1H), 7.55 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 25.6$, 28.8, 31.7, 48.3, 55.1, 77.9, 129.3, 150.3, 156.2; IR (ATR): $\nu = 3348$ (NH), 2975, 1701 (C=O), 1523, 1367, 1166 cm^{-1}; HR-MS (ES+): $m/z = 239.1499$, calcd. for $C_{11}H_{19}N_4O_2^+$ (M+H): 239.1508; $[\alpha]_D^{25}$: −19.8 (*c* 1.05, MeOH).

(*S*)-5-(Pyrrolidin-2-yl)-*1H*-1,2,3-triazole (Trifluoroacetic Acid Salt) (6·TFA)

Triazole **8** (200 mg, 0.83 mmol) was dissolved in DCM (4.0 mL) and TFA (4.0 mL) was added. The resulting mixture was stirred for 30 min at room temperature, monitoring the progress of the reaction by TLC. After this time, the volatile compounds were removed under reduced pressure and the product was dried for 4 h under high vacuum. The solid obtained was triturated with diethyl ether to obtain, after filtering and drying again, the title product as a tan solid; yield: 210 mg (99%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 2.15$ to 2.41 (m, 4H), 3.36 (ddd, $J = 12.1$, 6.5, 4.6 Hz, 1H), 3.61 (dd, $J = 12.1$, 5.6 Hz, 1H), 5.11 (dd, $J = 10.9$, 6.2 Hz, 1H), 7.79 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD, 373 K): $\delta = 26.5$ (CH_2), 32.1 (CH_2), 49.2 (CH_2), 56.6 (CH), 129.5 (CH), 142.3 (C); ^{19}F NMR (CD_3OD, 376 MHz): $\delta = -76.2$ (s); IR (ATR): $\nu = 2948$, 1662 (C=O TFA), 1191, 836 cm^{-1}; HR-MS (ES+): $m/z = 139.0986$, calcd. for $C_6H_{11}N_4^+$ (M+H): 139.0984; $[\alpha]_D^{25}$:−23.0 (*c* 1.05, MeOH); mp 85–88 °C.

(2*S*,4*R*)-*tert*-Butyl 2-Ethynyl-4-methoxypyrrolidine-1-carboxylate (11b)

Over a suspension of sodium hydride (32.9 mg, 1.30 mmol) in dry DMF (3.0 mL) under an inert atmosphere, at −20 °C, a solution containing **11a** (250 mg, 1.18 mmol) in DMF (3.0 mL) was added. The mixture was stirred at the same temperature for 1 h. After this time, methyl iodide (89 μL, 1.4 mmol) was added and the mixture was allowed to reach room temperature while stirring for further 5 h. Finally, the reaction was quenched with aqueous ammonium chloride solution, the product was extracted with diethyl ether and the organic layer was washed several times with ammonium chloride and water, it was dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was then purified by flash chromatography through deactivated silica, eluting with hexane-ethyl acetate mixtures. After removal of the solvents, the title product was obtained as a pale-yellow oil; yield: 201 mg (75%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.44$ (s, 9H), 2.09 (ddd, $J = 13.1$, 6.1, 5.3 Hz, 1H), 2.25 (ddd, $J = 13.0$, 7.9, 4.4 Hz, 1H), 2.95 (d, $J = 2.2$ Hz, 1H), 3.40 (d, $J = 4.2$ Hz, 2H), 4.01 (quintuplet, $J = 4.5$ Hz, 1H), 4.42 (ddd, $J = 8.0$, 5.9, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta =$ 27.8 (CH_3), 38.3 (CH_2), 46.0 (CH), 50.1 (CH_2), 55.5 (CH), 71.9 (CH), 77.4 (CH_3), 78.8 (C), 84.0 (C), 153.1 (C); IR (ATR): $\nu = 3264$ (CH), 2977 (CH MeO), 1692 (C=O), 1393, 1367, 1156, 1096 cm^{-1}; HR-MS (ES+): $m/z = 226.1435$, calcd. for $C_{12}H_{20}NO_3^+$ (M+H): 226.1443; $[\alpha]_D^{25}$:−25.7 (*c* 1.13, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(Benzyloxy)-2-ethynylpyrrolidine-1-carboxylate (11c)

The same method described for **11b** was applied, employing sodium hydride (34.2 mg, 1.35 mmol), **11a** (260 mg, 1.23 mmol) and benzyl bromide (180 μL, 1.48 mmol) in DMF (6 mL). After purification, the title product was obtained as a pale yellow oil; yield: 274 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.48$ (s, 9H), 2.20 (dt, $J = 12.9$, 5.5 Hz, 1H), 2.24 to 2.39 (br, 2H), 3.43 to 3.68 (br, 2H), 4.23 (br, 1H), 4.47 to 4.65 (br, 3H), 7.27 to 7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.4$ (CH_3), 38.8 and 39.8 (CH_2, br, rotamers), 46.6 (CH, br), 50.4 and 51.1 (CH_2, br, rotamers), 71.3 (CH_2), 75.9 (CH, br), 80.2 (C), 84.5 (C), 127.6 (CH), 127.8 (CH), 128.5 (CH), 137.8 (C), 154.1 (C); IR (ATR): $\nu = 3276$ (CH), 2978, 1696 (C=O), 1395, 1156 cm^{-1}; HR-MS (ES+): $m/z = 302.1749$, calcd. for $C_{18}H_{23}NO_3^+$ (M+H): 302.1756; $[\alpha]_D^{25}$: −63.0 (*c* 1.18, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(*tert*-Butyldimethylsilyloxy)-2-ethynylpyrrolidine-1-carboxylate (11d)

Over a solution of **11a** (251 mg, 1.19 mmol) and imidazole (98.9 mg, 1.43 mmol) in DMF (4.0 mL), at 0 °C, another solution containing *tert*-butylchlorodimethylsilane (221 mg, 1.43 mmol) in DMF (2.0 mL) was added dropwise. The mixture was allowed to warm up to room temperature and stirred overnight. After this time, the reaction was quenched with aqueous ammonium chloride solution and the product was extracted with diethyl ether. The organic layer was washed several times with ammonium chloride in order to remove the DMF and, then, dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product thus obtained was purified by flash chromatography through deactivated silica eluting with hexane-ethyl acetate mixtures to obtain, after removal of the solvents, the title product as a pale-yellow oil; yield: 216 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (two signals, 6H), 0.87 (s, 9H), 1.48 (s, 9H), 2.13 (br, 2H), 2.26 (br, 1H), 3.28 (br, 1H), 3.52 (br, 1H), 4.46 (m, 1H), 4.57 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.9$ (CH_3), 17.9 (C), 25.7 (CH_3), 28.4 (CH_3), 41.9 and 42.6 (CH_2, br, rotamers), 46.4 (CH, br), 53.5 and 54.0 (CH_2, br, rotamers), 69.6 and 70.3 (CH, br, rotamers), 80.0 (C), 84.3 (C); *IR* (ATR): $\nu = 3291$ (CH), 2978, 1677 (C=O), 1394, 1251 (δ_s Si-CH_3) cm^{-1}; HR-MS (ES+): $m/z = 326.2146$, calcd. for $C_{17}H_{32}NO_3Si^+$ (M+H): 326.2151; $[\alpha]_D^{25}$: +8.3 (*c* 1.07, MeOH).

(2*S*,4*R*)-*tert*-Butyl 2-Ethynyl-4-(triisopropylsilyloxy)-pyrrolidine-1-carboxylate (11e)

The same method described for **11d** was applied, employing **11a** (124 mg, 0.586 mmol), imidazole (50.1 mg, 0.703 mmol) and triisopropylsilyl trifluoromethanesulphonate (195 μL, 0.703 mmol) in DMF (3.0 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 117 mg (54%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.02$ (d, $J = 6.4$ Hz, 18H), 1.07 (s, 9H), 1.19 (m, 3H), 2.05 (ddd, $J = 13.0$, 6.1, 4.7 Hz, 1H), 2.25 (ddd, $J = 13.0$, 7.7, 4.4 Hz, 1H), 2.87 (d, $J = 2.1$ Hz, 1H), 3.29 (dd, $J = 11.1$, 4.6 Hz, 1H), 3.41 (ddd, $J = 11.1$, 3.4, 1.6 Hz, 1H), 4.55 (m, 1H), 4.61 (t, $J = 4.5$ Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 12.3$ (CH), 18.1 (CH_3), 26.2 (CH_3), 37.6 (CH_2), 46.2 (CH), 54.0 (CH_2), 69.2 (CH), 71.8 (CH), 78.7 (C), 83.7 (C), 153.2 (C); IR (ATR): $\nu = 3301$ (CH), 2793, 1702 (C=O), 1392, 1109 cm^{-1}; HR-MS (ES+): $m/z = 368.2633$, calcd. for $C_{20}H_{38}NO_3Si^+$ (M+H): 368.2621; $[\alpha]_D^{25}$: +23 (*c* 1.11, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(*tert*-Butyldiphenylsilyloxy)-2-ethynylpyrrolidine-1-carboxylate (11f)

The same method described for **11d** was applied, employing **11a** (285 mg, 1.35 mmol), imidazole (115 mg, 1.62 mmol) and TBDPSCl (430 μL, 1.62 mmol) in DMF (7 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 606 mg (quantitative). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.06$ (s, 9H), 1.45 (s, 9H), 2.02 (ddd, $J = 12.8$, 6.3, 4.9 Hz, 1H), 2.25 (dddd, $J = 12.8$, 7.7, 4.5, 1.5 Hz, 1H), 2.85 (d, $J = 2.1$ Hz, 1H), 3.31 (dd, $J = 11.3$, 4.7 Hz, 1H), 3.40 (ddd, $J = 11.3$, 3.2, 1.5 Hz, 1H), 4.52 to 4.57 (m, 2H), 7.41 to 7.47 (m, 6H), 7.62 to 7.65 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 18.2$ (C), 26.3 (CH_3), 27.7 (CH_3), 41.6 (CH_2), 46.0 (CH), 53.2 (CH_2), 70.7 (CH), 71.8 (CH), 78.7 (C), 83.7 (C), 127.3 (CH), 129.4 (CH), 134.7 (CH), 136.3 (C), 153.2 (C); IR (ATR): $\nu = 3281$ (CH), 2930, 2857, 1699 (C=O), 1392, 1159, 1111, 703 (δ_{oop} Ar CH) cm^{-1}; HR-MS (ES+): $m/z = 450.2458$, calcd. for $C_{27}H_{36}NO_3Si^+$ (M+H): 450.2464; $[\alpha]_D^{25}$: +17 (*c* 0.996, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-Hydroxy-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12a)

Under inert atmosphere, **11a** (50.0 mg, 0.237 mmol) and copper(I) iodide (2.3 mg, 12 μmol) were dissolved in a degassed 9:1 DMF-MeOH mixture (2.4 mL). DIPEA (62 μL, 0.36 mmol) was added, with the reaction mixture turning immediately red, followed by azidotrimethylsilane (49 μL, 0.36 mmol), and the mixture was warmed up to 100 °C (reflux) and stirred at this temperature for 12 h. After this time, the reaction mixture was allowed to cool down to room temperature, diluted with ethyl acetate and washed several times with aqueous ammonium chloride solution. The organic layer was dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The crude material was then purified by flash chromatography through deactivated silica eluting with hexane-ethyl acetate mixtures. After removal of the solvents the title product was obtained as a pale-yellow oil; yield: 44.6 mg (74%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.31$ (s, 9H), 2.10 to 2.22 (m, 2H), 3.37 (ddd, $J = 11.1$, 3.4, 1.1 Hz, 1H), 3.52 (dd, $J = 11.2$, 5.1 Hz, 1H), 4.37 (quin, $J = 4.5$ Hz, 1H), 4.70 (br, 1H), 5.02 (t, $J = 7.0$ Hz, 1H), 7.55 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 27.7$ (CH_3), 41.3 (CH_2, br), 51.2 (CH, br), 54.1 (CH_2), 67.8 (CH), 78.1 (C), 126.4 (CH), 147.1 (C), 153.5 (C); IR (ATR): $\nu = 3144$, 2977, 1671 (ν C=O), 1397, 1160 cm^{-1}; HR-MS (ES+): $m/z = 255.1450$, calcd. for $C_{11}H_{19}N_4O_3^+$ (M+H): 255.1457; $[\alpha]_D^{25}$: +5.5 (*c* 1.10, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-Methoxy-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12b)

The same method described for **12a** was applied, employing **11b** (144 mg, 0.638 mmol), copper(I) iodide (6.2 mg, 32

μmol), DIPEA (168 μL, 0.958 mmol) and azidotrimethylsilane (133 μL, 0.958 mmol) in a 9:1 DMF-methanol mixture (1.3 mL). After purification, the title product was obtained as a pale-yellow oil; yield:123 mg (72%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.31$ (s, 9H), 2.17 to 2.22 (m, 1H), 2.32 (ddd, $J = 13.1$, 7.8, 4.4 Hz, 1H), 3.28 (s, 3H), 3.53 (d, 4.1 Hz, 2H), 4.07 (quintuplet, $J = 4.4$ Hz, 1H), 4.99 (t, 6.98 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 27.7$ (CH_3), 38.0 (CH_2), 50.3 (CH_2), 50.7 (CH), 55.5 (CH_3), 77.6 (CH), 78.4 (C), 127.9 (CH), 142.3 (C), 153.4 (C); IR (ATR): $\nu = 3139$ (NH), 2978, 1685 (C=O), 1393, 1153 cm^{-1}; HR-MS (ES+): $m/z = 269.1621$, calcd. for $C_{21}H_{21}N_4O_3^+$ (M+H): 269.1614; $[\alpha]_D^{25}$: +13° (*c* 1.05, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-Benzyloxy-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12c)

The same method described for **12a** was applied, employing **11c** (254 mg, 0.842 mmol), copper(I) iodide (8.2 mg, 42 μmol), DIPEA (221 μL, 1.26 mmol) and azidotrimethylsilane (175 μL, 1.26 mmol) in a 9:1 DMF-methanol mixture (2.2 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 230 mg (79%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.32$ (s, 9H), 2.25 (bm, 1H), 2.39 (ddd, $J = 13.0$, 7.9, 4.4 Hz, 1H), 3.55 (dd, $J = 11.6$, 4.9 Hz, 1H), 3.60 (ddd, $J = 11.5$, 3.2, 0.5 Hz, 1H), 4.30 (quintuplet, $J = 4.4$ Hz, 1H), 4.52 (d, $J = 12.1$ Hz, 1H), 4.55 (d, $J = 12.1$ Hz, 1H), 5.04 (dd, $J = 7.7$, 6.3 Hz, 1H), 7.26 to 7.39 (m, 5H), 7.58 (b, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = 27.7$ (CH_3), 38.4 (CH_2), 51.1 (CH_2), 51.4 (CH), 70.0 (CH_2), 76.1 (CH), 78.4 (C), 126.9 (CH), 127.0 (CH), 127.8 (CH), 138.2 (C), 153.4 (C); IR (ATR): $\nu = 3140$ (NH), 2977, 1671 (C=O), 1393, 1156 cm^{-1}; HR-MS (ES+): $m/z = 345.1922$, calcd for $C_{18}H_{25}N_4O_3^+$ (M+H): 345.1927; $[\alpha]_D^{25}$: −11.2 (*c* 1.02, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(Trimethylsilyloxy)-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12d)

The same method described for **12a** was applied, employing **11d** (196 mg, 0.602 mmol), copper(I) iodide (5.8 mg, 30 μmol), DIPEA (158 μL, 0.904 mmol) and azidotrimethylsilane (125 μL, 0.904 mmol) in a 9:1 DMF-methanol mixture (1.6 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 77.0 mg (34%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 0.09$ and 0.10 (s, 6H together), 0.90 (s, 9H), 1.32 (s, 9H), 2.20 (dd, $J = 6.6$, 4.8 Hz, 2H), 3.40 (dd, $J = 11.2$, 3.3 Hz, 1H), 3.53 (dd, $J = 11.0$, 4.8 Hz, 1H), 4.55 (quintuplet, $J = 4.4$ Hz, 1H), 5.03 (t, $J = 7.2$ Hz, 1H), 7.58 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 373 K): $\delta = -4.7$ (CH_3), 17.8 (C), 25.6 (CH_3), 27.9 (CH_3), 40.1 (CH_2), 54.1 (CH), 54.9 (CH_2), 73.2 (CH), 78.6 (C), 129.5 (CH), 146.3 (C), 153.7 (C); IR (ATR): $\nu = 3346$ (NH), 2929, 1671 (C=O), 1367, 1153, 835 cm^{-1}; HR-MS (ES+): $m/z = 369.2324$, calcd. for $C_{17}H_{33}N_4O_3Si^+$ (M+H): 369.2322; $[\alpha]_D^{25}$: +9.8 (*c* 0.983, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(Triisopropylsilyloxy)-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12e)

The same method described for **12a** was applied, employing **11e** (117 mg, 0.319 mmol), copper(I) iodide (3.1 mg, 16 μmol), DIPEA (84 μL, 0.48 mmol) and azidotrimethylsilane (66 μL, 0.48 mmol) in a 9:1 DMF-methanol mixture (1 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 126 mg (96%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.01$ (d, $J = 6.4$ Hz, 18H), 1.06 (s, 9H), 1.29 (m, 3H), 2.23 (m, 1H), 2.30 (m, 1H), 3.46 (dd, $J = 11.3$, 4.6 Hz, 1H), 3.55 (dd, $J = 11.3$, 2.8 Hz, 1H), 4.57 (m, $J = 4.0$ Hz, 1H), 5.17 (t, $J = 6.9$ Hz, 1H), 7.48 (s, 1H); ^{13}C NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 12.5$ (CH), 18.2 (CH_3), 27.7 (CH_3), 41.3 (CH_2), 51.2 (CH), 54.0 (CH_2), 70.9 (CH), 78.4 (C), 129.7 (CH), 145.4 (C), 153.7 (C); IR (ATR): $\nu = 3208$ (NH), 2795, 1701 (C=O), 1394, 1096 cm^{-1}; HR-MS (ES+): $m/z = 411.2799$, calcd. for $C_{20}H_{39}N_4O_3Si^+$ (M+H): 411.2791; $[\alpha]_D^{25}$: +17.3 (*c* 1.09, MeOH).

(2*S*,4*R*)-*tert*-Butyl 4-(*tert*-Butyldiphenylsilyloxy)-2-(1*H*-1,2,3-triazol-5-yl)pyrrolidine-1-carboxylate (12f)

The same method described for **12a** was applied, employing **11f** (400 mg, 0.890 mmol), copper(I) iodide (8.6 mg, 45 μmol), DIPEA (234 μL, 1.33 mmol) and azidotrimethylsilane (185 μL, 1.33 mmol) in a 9:1 DMF-methanol mixture (2 mL). After purification, the title product was obtained as a pale-yellow oil; yield: 277 mg (63%). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 1.06$ (s, 9H), 1.33 (s, 9H), 2.13 (m, 1H), 2.31 (m, 1H), 3.40 (dd, $J = 11.4$, 4.5 Hz, 1H), 3.51 (dd, $J = 11.3$, 3.0 Hz, 1H), 4.60 (quintuplet, $J = 4.0$ Hz, 1H), 5.10 (t, $J = 7.2$ Hz, 1H), 7.41 to 7.47, m, 6H), 7.53 (s, 1H), 7.63 (dd, $J = 8.1$, 1.5 Hz, 4H); ^{13}C NMR (500 MHz, DMSO-d_6, 373 K): $\delta = 18.3$ (C), 26.4 (CH_3), 27.7 (CH_3), 41.3 (CH_2), 51.2 (CH), 54.0 (CH_2), 70.9 (CH), 78.4 (C), 127.4 (CH), 129.4 (CH, two peaks), 133.2 (C, rotamers), 134.7 (CH, two peaks), 153.6 (C); IR (ATR): $\nu = 3136$ (NH), 2960, 1693 (C=O), 1391, 1106, 701 (δ_{oop} Ar CH) cm^{-1}; HR-MS (ES+): $m/z = 493.2639$, calcd. for $C_{27}H_{37}N_4O_3Si^+$ (M+H): 493.2635; $[\alpha]_D^{25}$: +9.1 (*c* 1.03, MeOH).

(3*R*,5*S*)-5-(1*H*-1,2,3-Triazol-5-yl)pyrrolidin-3-ol Trifluoroacetic Acid Salt (13a·TFA)

Boc-protected aminotriazole **12a** (120 mg, 0.472 mmol) was dissolved in DCM (2.5 mL) and TFA (2.5 mL) was added. The mixture was stirred at room temperature for 30 min and then the volatile materials were removed under vacuum. The solid residue was triturated with diethyl ether and filtered several times and finally it was dried under reduced pressure, to obtain the title product as a tan solid; yield: 121 mg (96%). ^{1}H NMR (400 MHz, CD_3CN): $\delta = 2.42$ (m, 2H), 3.34 (d, $J = 12.6$ Hz, 1H), 3.60 (dd, $J = 12.6$, 4.6 Hz, 1H), 4.64 (m, 1H), 5.16 (dd, $J = 10.1$, 7.7 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 40.0$ (CH_2), 52.6 (CH), 55.1 (CH_2), 69.7 (CH), 126.9 (CH), 147.8 (C); IR (ATR): $\nu = 2961$, 1671 (C=O TFA), 1198, 1135 cm^{-1}; HR-MS (ES+): $m/z = 155.0936$, calcd. for $C_6H_{11}N_4O^+$ (M+H): 155.0933; $[\alpha]_D^{25}$: +26.3 (*c* 0.956, MeOH); mp 110–113 °C.

5-[(2*S*,4*R*)-4-Methoxypyrrolidin-2-yl]-1*H*-1,2,3-triazole Trifluoroacetic Acid Salt (13b·TFA)

The same procedure described for **13a** was applied, employing **12b** (93 mg, 0.35 mmol) in DCM (2 mL) and TFA (2 mL). The title product was obtained as a tan solid; yield: 71.0 mg (72%); ^{1}H NMR (400 MHz, CD_3CN): $\delta = 2.38$ (ddd, $J = 13.9$, 11.6, 4.7 Hz, 1H), 2.56 (ddt, $J = 14.0$, 6.3, 1.4 Hz,

1H), 3.32 (s, 3H), 3.44 (dt, $J=12.8$, 1.4 Hz, 1H), 3.63 (dd, $J=12.8$, 4.8 Hz, 1H), 4.25 (t, $J=4.6$ Hz, 1H), 5.02 (dd, $J=11.5$, 6.4 Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=36.7$ (CH_2), 51.3 (CH_2), 54.2 (CH), 56.9 (CH_3), 79.5 (CH), 117.9 (C, q, $J_{C,F}=294$ Hz), 129.3 (CH), 141.8 (C), 161.9 (C, q, $J_{C,F}=34$ Hz); ^{19}F NMR (376 MHz, CD_3CN): $\delta=-76.1$ (s); IR (ATR): $\nu=3137$, 2948, 2784, 1662 (C=O TFA), 1187, 1061, 836, 721 cm^{-1}; HR-MS (ES+): $m/z=169.1088$, calcd. for $C_7H_{13}N_4O^+$ (M+H): 169.1089; $[\alpha]_D^{25}$: +31.9 (c 1.14, MeOH); mp 98–99 °C.

5-[(2*S*,4*R*)-4-Benzyloxypyrrolidin-2-yl)-1*H*-1,2,3-triazole (13c)

The same procedure described for **13a** was applied, employing **12c** (150 mg, 0.436 mmol) in DCM (2.5 mL) and TFA (2.5 mL). In this case the crude product, after removal of the volatile materials, was dissolved again in DCM and treated with aqueous sodium bicarbonate solution. The mixture was stirred for 30 min and then the layers were separated and the organic one was washed with brine and water, dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure, to obtain the title product as a pale-yellow oil; yield: 26 mg (24%). ^{1}H NMR (400 MHz, CD_3CN): $\delta=2.09$ (ddd, $J=13.2$, 9.0, 5.8 Hz, 1H), 2.40 (dd, $J=13.4$, 6.7 Hz, 1H), 3.18 (d, $J=12.3$ Hz, 1H), 3.27 (dd, $J=12.3$, 4.2 Hz, 1H), 4.25 (b, 1H), 4.47 (d, $J=12.0$ Hz, 1H), 4.51 (d, $J=12.0$ Hz, 1H), 4.65 (t, $J=7.9$ Hz, 1H), 6.56 (b, 2H), 7.27 to 7.34 (m, 5H), 7.50 (s, 1H); ^{13}C NMR (100 MHz, CD_3CN): $\delta=39.1$ (CH_2), 52.3 (CH_2), 52.9 (CH), 71.1 (CH_2), 79.5 (CH), 127.8 (CH), 127.9 (CH), 128.6 (CH), 128.9 (CH), 138.1 (C), 146.9 (C); IR (ATR): $\nu=2854$, 1437, 1175, 1026 cm^{-1}; HR-MS (ES+): $m/z=245.1399$, calcd. for $C_{13}H_{17}N_4O^+$ (M+H): 245.1402; $[\alpha]_D^{25}$: +13 (c 0.98, MeOH).

5-[(2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)pyrrolidin-2-yl)-1*H*-1,2,3-triazole (13d)

The same procedure described for **13c** was applied, employing **12d** (55 mg, 0.15 mmol) in DCM (0.7 mL) and TFA (0.7 mL). The title product were obtained as a pale-yellow oil; yield: 39 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.07$ and 0.08 (s, 6H), 0.88 (s, 9H), 2.09 to 2.22 (m, 2H), 2.98 (d, $J=11.4$ Hz, 1H), 3.30 (d, $J=11.3$ Hz, 1H), 4.53 (br, 1H), 4.71 (t, $J=8.3$ Hz, 1H), 7.49 (s, 1H), 8.27 (b, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.8$ (CH_3, two signals), 18.0 (C), 25.8 (CH_3), 42.4 (CH_2), 52.6 (CH), 55.3 (CH_2), 72.8 (CH), 128.3 (CH), 146.6 (C); IR (ATR): $\nu=2928$, 2855, 1462, 1254, 1078, 832, 744 cm^{-1}; HRMS (ES+): $m/z=269.1802$, calcd. for $C_{12}H_{25}N_4OSi^+$ (M+H): 269.1798; $[\alpha]_D^{25}$: +60.0 (c 1.12, MeOH).

5-[(2*S*,4*R*)-4-(Triisopropylsilyloxy)pyrrolidin-2-yl]-1*H*-1,2,3-triazole (13e)

The same procedure described for **13c** was applied, employing **12e** (100 mg, 0.244 mmol) in DCM (1.2 mL) and TFA (1.2 mL). The title product was obtained as a pale-yellow oil; yield: 42.8 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.05$ to 1.08 (m, 21H), 2.11 to 2.18 (m, 1H), 2.25 (dd, $J=13.0$, 6.7 Hz, 1H), 3.04 (d, $J=11.3$ Hz, 1H), 3.15 (dd, $J=11.3$, 6.4 Hz, 1H), 4.49 (m, 1H), 4.79 (dd, $J=8.6$, 6.5 Hz, 1H), 7.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=12.0$ (CH), 17.9 (CH_3), 42.8 (CH_2), 52.7 (CH), 55.7 (CH_2), 73.0 (CH), 128.4 (CH), 146.8 (C); IR (ATR): $\nu=2940$, 2864, 1461, 1084, 821, 678 cm^{-1}; HR-MS (ES+): $m/z=311.2261$, calcd. for $C_{15}H_{31}N_4OSi^+$ (M+H): 311.2267; $[\alpha]_D^{25}$: +44.2 (c 1.03, MeOH).

5-[(2*S*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)pyrrolidin-2-yl]-1*H*-1,2,3-triazole (13f)

The same procedure described for **13c** was applied, employing **12f** (230 mg, 0.467 mmol) in DCM (2.5 mL) and TFA (2.5 mL). The title product was obtained as a white solid; yield: 164 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.06$ (s, 9H), 1.93 (ddd, $J=12.7$, 9.5, 5.7 Hz, 1H), 2.24 (dd, $J=13.1$, 6.7 Hz, 1H), 3.02 (d, $J=11.7$ Hz, 1H), 3.11 (dd, $J=11.8$, 4.5 Hz, 1H), 4.52 (br, 1H), 4.73 (dd, $J=8.9$, 7.1 Hz, 1H), 7.35 to 7.42 (m, 7H), 7.55 (br, 2H), 7.64 (t, $J=7.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.0$ (C), 26.9 (CH_3), 42.5 (CH_2), 52.7 (CH), 55.4 (CH_2), 74.1 (CH), 127.7 (CH), 128.6 (CH), 129.7 (CH), 133.8 (C), 135.6 (CH, two signals), 147.6 (C); IR (ATR): $\nu=2855$, 1427, 1107, 699 cm^{-1}; HR-MS (ES+): $m/z=393.2108$, calcd. for $C_{22}H_{29}N_4OSi^+$ (M+H): 393.2111; $[\alpha]_D^{25}$: +17.34 (c 1.14, MeOH); mp 139–141 °C.

General Procedure for Asymmetric Transfer Hydrogenation of Prochiral Ketones

In a typical experiment, under an inert atmosphere, a solution containing ligand **13f** (3.53 mg, 9.00 μmol) in dry and degassed isopropyl alcohol (1 mL) was added onto dichloro-(*p*-cymene)ruthenium(II) dimer (1.84 mg, 3.00 μmol), and the resulting mixture was stirred at room temperature for 40 min. After this time, a solution containing potassium hydroxide (1.85 mg, 33.0 μmol) in isopropyl alcohol (0.5 mL) was added, and the mixture was stirred for further 20 min. Finally, another solution containing acetophenone (12.0 mg, 100 μmol) in isopropyl alcohol (0.5 mL) was added, this moment being considered as the starting time of the reaction. Samples were extracted at different times, passed through a short column of silica and diluted with DCM to a concentration of approximately 1 mg mL^{-1}, and then analyzed directly by GC (see Supporting Information for conditions). In 4 h, a conversion of 91% was obtained, with 82% enantiomeric excess.

Alternatively, the same procedure excluding the extraction of samples and with a final work-up consisting in addition of saturated NH_4Cl aqueous solution, extraction with DCM and drying with anhydrous sodium sulphate afforded, after purification by flash chromatography through silica, the reduced product in pure form; yield: 11.0 mg (90%).

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