Triazole-based P,N ligands : discovery of an enantioselective copper-catalyzed propargylic amination reaction

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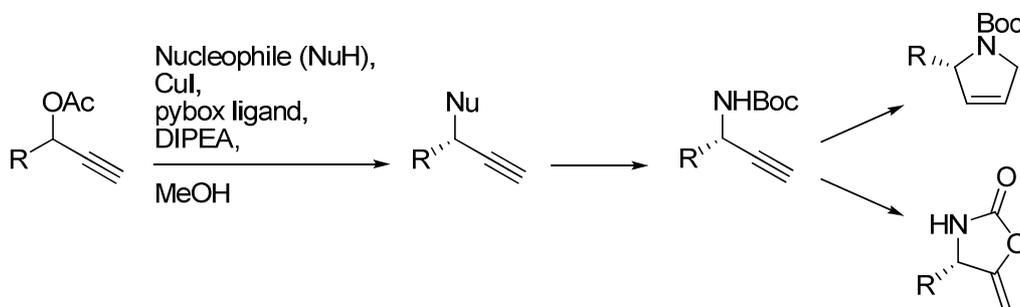
CHAPTER 4

Enantioselective Copper-Catalyzed Propargylic Substitution: Expanding the Scope and Applications[*]

ABSTRACT: Different amine nucleophiles were applied in the enantioselective copper-catalyzed propargylic amination reaction, affording the desired products in good yields (66-97%). The enantioselectivity obtained was highest for aniline, and its derivatives (up to 87% *ee*). Interestingly, some carbon nucleophiles could also be used, and with indoles excellent *ee* values were obtained (up to 98% *ee*). The versatility of the acquired propargylic amines was demonstrated by their elaboration into formal total syntheses of two biologically active compounds: (+)-anisomycin and (−)-cytoxazone.

4.1 INTRODUCTION

Propargylic amines are versatile building blocks for organic synthesis. Next to their synthetic utility, some derivatives possess interesting biological properties.[1] During the last decade a considerable number of enantioselective routes towards propargylic amines were reported. The most important synthetic access is still offered by the addition of terminal alkynes to imines. Since Li and Wei published an enantioselective copper(I)-catalyzed addition of alkynes to imines,[2] several catalytic systems promoting such asymmetric additions are reported.[3] Besides the asymmetric addition reaction also a route based on enzymatic resolution exists providing optically active propargylic amines.[4] Remarkably, substitution on the propargylic position in an enantioselective fashion is very rare. Nishibayashi *et al.* showed that a chiral ruthenium complex could induce asymmetry in the C-C bond formation during the propargylation of aromatic compounds or acetone with propargylic alcohols (up to 95% ee, see Chapter 1, § 1.4).[5] However, propargylic substitution reactions with heteroatom-centered nucleophiles, such as alcohols, amines, thiols, and diphenylphosphine oxide, did not proceed enantioselectively with this diruthenium complex.[6b] Recently, the first example of an enantioselective version of the copper-catalyzed propargylic amination was discovered both by our group and the group of Nishibayashi (see also Chapter 3).[6] This new method, which is an enantioselective version of the originally reported propargylic substitution reaction by Murahashi *et al.*,[7] provides propargylic amines in very high yields and optical purities.
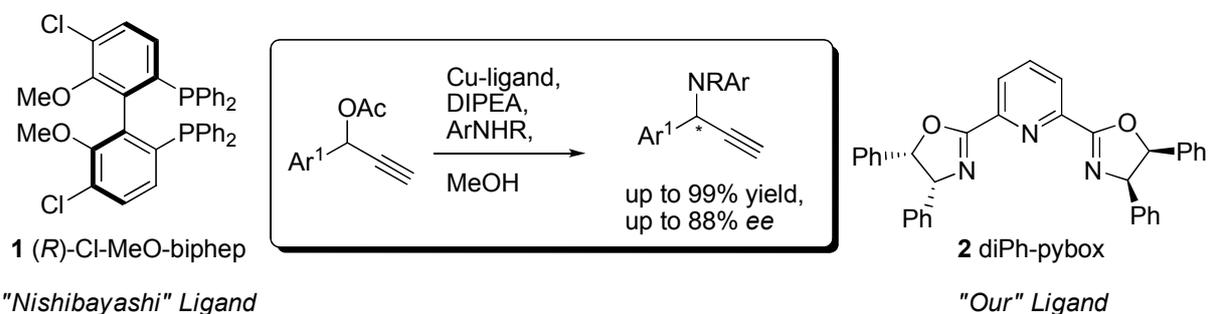
Scheme 4.1 Enantioselective propargylic amination

The major difference between Nishibayashi's and our method is the structure of the chiral ligand. Where Nishibayashi uses a diphoshine ligand (((R)-Cl-OMe-biphep, **1**), we used optically active 2,6-bis(oxazolinyl)pyridine (pybox, **2**). In sharp contrast to our system, showing high yields and ee's with primary amines, such as *o*-anisidine (Scheme 4.1, R = H), Nishibayashi's method gave best results if secondary amines, *e.g. N*-methylaniline, were used (Scheme 4.1, R = Me). The use of aniline gave an enantiomeric excess of only 53%.[6b] This observation prompted us to have a closer look at the applicability of other nitrogen-centered, but also carbon-centered nucleophiles.

4.2   NITROGEN NUCLEOPHILES

   After studying several propargylic acetates in our enantioselective propargylic amination reaction (see previous chapter), this paragraph deals with the investigation of the scope of the nitrogen nucleophile (Table 4.1). Knowing that *p*-methoxyphenyl (PMP) is a commonly used protective group for amines, *p*-anisidine was included in our series using the optimal reaction conditions (see Chapter 3) and diPh-pybox **2** as the ligand (entry 2). The observed enantioselectivity was, unfortunately, slightly lower as compared to *o*-anisidine. Also 2,4-dimethoxyaniline (entry 3) gave lower *ee* values than *o*-anisidine, so that the latter was thus chosen as the masked primary amine in our protocol. Similar results as for *o*-anisidine were obtained using both aniline and 4-(trifluoromethyl)aniline (entries 4 and 5). Nitroanilines did not react properly and only gave a small amount of product among many side products. In analogy to the Nishibayashi method, we applied *N*-methylaniline as the nucleophile and as compared with the primary anilines, a significantly lower *ee* value was observed (entry 6). In this respect, both methods are complementary.

Recently, Carreira *et al.* reported the use of 4-piperidone hydrate hydrochloride as an interesting masked primary amine in the copper-catalyzed three-component reaction of aldehydes, alkynes, and amines.[8] Once the 4-piperidone is attached at the propargylic moiety, double dealkylation by an excess of a primary amine affords the unprotected propargylic amine. Carreira managed to immobilize the piperidone byproduct using a solid-supported amine. However, when 4-piperidone hydrate hydrochloride was applied in our reaction, the product was obtained in good yield but in almost racemic form (entry 7). *N*-Benzylhydroxylamine, which also serves as a masked primary amine, gave the anticipated product in good yield. All attempts to separate the enantiomers by chiral HPLC failed and no *ee* value could be determined (entry 8). With *O*-benzylhydroxylamine, the product was afforded in good yield (74%), but with low *ee* (36% *ee*, entry 9). On the other hand, with *N*-benzyl-*N*-*p*-methoxybenzylamine, the desired product was obtained in high yield and with a moderate selectivity (entry 10). This suggests that more hindered secondary amines may provide products in even higher enantiopurity.

   The removal of the *o*-anisidyl group was achieved in reasonable to high yields for most substrates as is described in paragraph 4.4 (see also: Chapter 6, § 6.2.1). It was nevertheless interesting to know whether other types of nitrogen nucleophiles would also lead to the desired products. In single-attempt experiments (not shown) a set of different nitrogen nucleophiles was tested under the optimal reaction conditions. *t*-Butyl carbamate and di-*t*-butyl iminodicarbonate were applied in the substitution reaction, but without success. In both cases the starting material decomposed into unidentified compounds. The nucleophilicity of the nitrogen atom is probably too low in these cases. Apparently the desired reaction is unable to compete with an unknown decomposition pathway, which we also observed if only base was added in the absence of nucleophile. The same observation was made with several other nitrogen nucleophiles, such as phthalimide, 4-nitrophenylsulfonamide, tritylsulfenylamide, and *P*,*P*-diphenylphosphinic amide.

Table 4.1 Propargylic amination with various nitrogen nucleophiles.[a]

| entry	NuH	time (h)	T (°C)	product	yield[b] (%)	*ee* (%)[c]
1	(2-OMe-phenyl)NH$_2$	24	−20	**4a**	97	85
2	(4-MeO-phenyl)NH$_2$	19	−20	**4b**	93	78
3	(2,4-diOMe-phenyl)NH$_2$	1.5	rt	**4c**	90	64
4	PhNH$_2$	42	−20	**4d**	94	87
5	(4-F$_3$C-phenyl)NH$_2$	43	−20	**4e**	87	86
6	Me-NH-Ph	1	rt	**4f**	90	60
7	4,4-dihydroxypiperidine•HCl	3	rt	**4g**	66	3
8	HO-NH-CH$_2$Ph	2	0	**4h**	77	n.d.
9	H$_2$N-O-CH$_2$Ph	1.5	0	**4i**	74	36
10	(4-MeO-benzyl)N(H)Bn	24	−20 to 0	**4j**	94	68

[a] Reaction conditions: propargylic acetate **3g** (0.20 mmol), NuH (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **2i** (0.024 mmol) were stirred in methanol (2 mL). [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. n.d. = could not be determined by chiral HPLC

4.3 CARBON NUCLEOPHILES

The copper-catalyzed propargylic substitution reaction, as is illustrated in the previous paragraph (Paragraph 4.2), is rather sensitive regarding the nitrogen nucleophile. The question arose whether also carbon nucleophiles could be applied. If possible, this would lead to a novel and promising carbon-carbon bond formation process, which is always the utmost challenge for organic chemists.

Carbon nucleophiles have, to the best of our knowledge, never been used in asymmetric copper-catalyzed propargylations. The only examples of asymmetric substitution at the propargylic moiety with carbon nucleophiles, reported by Nishibayshi *et al.*, rely on a chiral thiolate-bridged diruthenium complex.[5] Having in mind its success in Nishibayashi's ruthenium catalyzed substitution,[5c] the special π-nucleophilicity and biological relevance of indole prompted us to subject it to our reaction conditions. The first attempt of this novel copper-catalyzed asymmetric Friedel-Crafts propargylation of indole gave very promising results. Treatment of 1-phenylprop-2-ynyl acetate **3a** with indole using diPh-pybox **2** gave propargylated indole **5a** in high yield and with excellent selectivity (94% *ee*) (Table 4.2, entry 1). Very delighted with this result, we submitted *N*-methylindole to the same conditions providing product **5b** in high yield and with even higher selectivity (98% *ee*). *N*-Triisopropylsilylindole, which gave the best results in the ruthenium catalyzed propargylation, gave no product at all, which may be ascribed to steric hindrance.

Starting from propargylic acetates with aliphatic side chains, the substitution reaction became slower so higher temperatures were required, as was already illustrated in the previous chapter (Chapter 3, § 3.6 and 3.7). For these substrates the highest selectivities in the copper-catalyzed propargylic amination reaction were obtained when Me-pybox **6** was used as the ligand. However, using indole as the nucleophile, with both ligands, **2** or **6**, no desired product was formed (Table 4.2, entry 4).
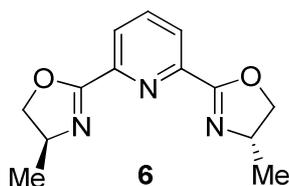
After the establishment of the enantioselective copper-catalyzed propargylic substitution with indoles, we envisaged that other carbon π-nucleophiles may also be applicable (Table 4.2, entries 5-7). Unfortunately, 2-methoxyfuran gave disappointing results and only a small amount of product was isolated (entry 5). Using the sterically less encumbered nucleophile *tert*-butyl(1-methoxyvinyloxy)dimethylsilane gave the same result (entry 6).

Interestingly, with 2,2,5-trimethyl-1,3-dioxane-4,6-dione the propargylic acetate was fully converted (entry 7). Besides the anticipated product **5g**, also **7** and **8** were observed in the ^{1}H NMR spectrum of a crude sample, indicating that an intriguing cascade of reactions had

Table 4.2 Copper-catalyzed enantioselective propargylation of indoles.[a]

entry	NuH	R^1	time (h)	T (°C)	product	yield[b] (%)	ee[c] (%)
1	(indole, NH)	Ph	24	–20	**5a**	71	94
2	(N-Me indole)	Ph	24	–20	**5b**	91	98
3	(N-Si(iPr)₃ indole)	Ph	24	–20	**5c**	n.r.	
4[d]	(indole, NH)	Bn	144	rt - 50	**5d**	n.r.	
5	(furan-OMe)	Ph	24	rt	**5e**	~10	n.d.
6	(OTBDMS, OMe enol ether)	Ph	24	rt	**5f**	~10	n.d.
7[e]	(dimethyl methyl malonate dioxinone)	Ph	24	–20	**5g**	64	6

[a] Reaction conditions: propargylic acetate **3** (0.20 mmol), NuH (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **2** (0.024 mmol) were stirred in methanol (2 mL). [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [d] In this reaction also ligand **6** was used instead of **2** and the pivalate ester of **3** instead of acetate. [e] In this reaction only 0.22 mmol of the nucleophile was used, and after completion the reaction mixture was first quenched with satd. NH₄Cl (aq) and extracted, before chromatographic purification. n.r. = no product isolated, n.d. = not determined

occurred. Probably, after formation of **5g**, small amounts of methoxide, present in the basic reaction medium, have attacked one of the ester functionalities (Scheme 4.3). This liberated, after losing acetone, a carboxylate anion, which on its turn attacked the copper-activated alkyne moiety. After proteolysis, product **7** was obtained, which was identified by ^{1}H NMR analysis. Another methanolysis step forms the dimethyl ester enolate, which isomerizes to ketone **8**. After prolonged reaction time at higher temperature (70 °C), NMR analysis indicated total conversion to this product, which was isolated in moderate yield (40%). If the temperature was kept low, product **5g** could be isolated in good yield (64%), although as a racemate.
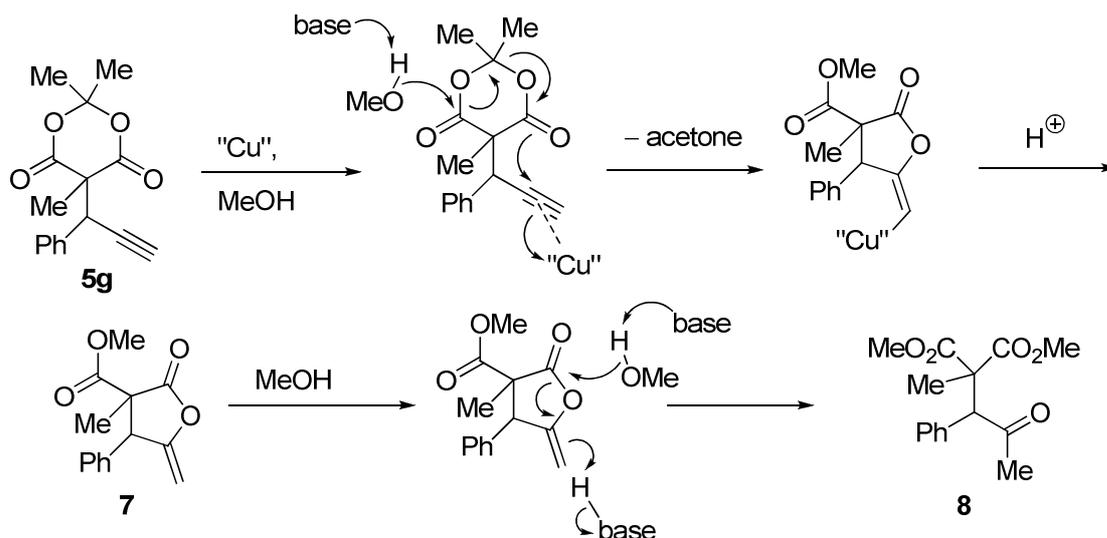
Scheme 4.3 Unexpected reaction cascade

4.4 APPLICATIONS

The establishment of the enantioselective copper-catalyzed propargylic amination protocol motivated us to find new applications for the resulting optically active propargylic amines. The alkyne moiety is amenable to further functionalization and conversion into natural products and biologically interesting molecules. This virtue in combination with the easy variation of the side chains (R) make the new protocol a simple and versatile synthetic procedure. In this and the next sections we show some of the target molecules that can be made in this way.

Optically active propargylic amines have been used before as starting materials, and this type of compounds is usually prepared starting from α-amino acids.[9,12,26a] However, multiple steps are required and the procedures are prone to racemization.[10]
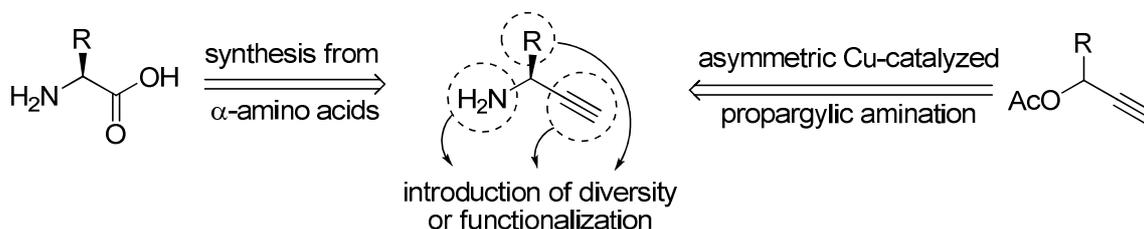
With our protocol a large array of substituents (R) is available. Because the absolute configuration of the product is determined by the configuration of the chiral pybox ligand, and both enantiomers of the ligands are available, complete stereocontrol of the product is possible. In the next section, we illustrate that the enantioselective propargylic amination gives access to alkyne-containing α-amino acid analogues that can be used in peptidomimetic chemistry.

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4.4.1 CYCLIC PEPTIDES

In our research group the synthesis of small cyclic peptides is an important topic of interest. Cyclization to such a peptide is often a difficult process. The Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction between an alkyne and an azide to give a 1,4-connected 1,2,3-triazole moiety, now acting as an amide bond isostere, has proven to be a powerful tool in overcoming these problems.[11] In the synthetic scheme for forming these triazole-containing cyclic pseudopeptides, alkyne-containing pseudo amino acids play an important role. During the synthesis of these building blocks starting from natural amino acids, racemization may occur. The enantioselective propargylic amination method provides a new and short route to such compounds.
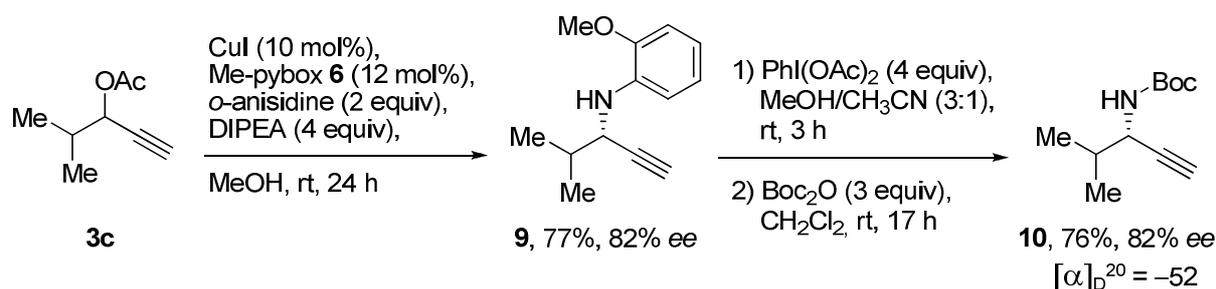
Scheme 4.4 Synthesis of the alkyne-containing amino acid analogue of valine

When substrate **3c** was converted into propargylic amine **9** (see also Chapter 3, § 3.7), a valine analogue was obtained (Scheme 4.4). Oxidative removal of the anisidyl moiety with iodobenzene diacetate and subsequent *N*-protection with a *t*-butoxycarbonyl group gave propargylic amine **10** in good yield. The absolute configuration was determined by comparison of the optical rotation with a literature value ($[\alpha]_D^{20}$ = −59.9, 96% *ee*).[12] The *S*-Me-pybox ligand **6** gave *S*-valine analogue **10**, which is similar to the natural amino acid configuration. The compound was incorporated in the triazole-containing cyclic pseudopeptide *cyclo*-[Pro–Val–ψ(triazole)–Gly–Tyr(OBn)] in our group.[13] This illustrates an important application of the optically active propargylic amine prepared by our new methodology.

*cyclo*-[Pro–Val–ψ(triazole)–Gly–Tyr(OBn)]
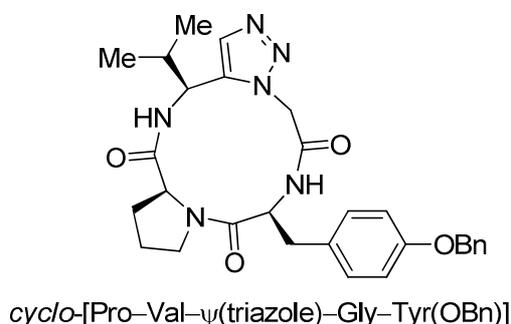
4.4.2 FORMAL TOTAL SYNTHESIS OF (+)-ANISOMYCIN

Propargylic amines can function as versatile building blocks for the synthesis of many biologically active compounds. Elaboration of the optically enriched products obtained by the copper-catalyzed enantioselective propargylic amination into Boc-protected amines opens a

pathway for further transformation. The pyrrolidine ring is an important structural motif in many alkaloids such as hygrine, nicotine, and cocaine. Their biological activity make these alkaloids attractive synthetic targets. In this section a formal total synthesis of anisomycin will be detailed.

The antibiotic anisomycin was isolated from culture filtrates of two *Streptomyces* species (*S. griseolus* and *S. roseochromogenes*) in the early fifties.[14] In the sixties the structure was elucidated by the combined work of several groups.[15] The natural product, (–)-anisomycin **12a**, was found to specifically block peptide bond formation in eukaryotic ribosomes, and this made it a valuable tool in molecular biology.[16] In addition to its fungicidal activity,[14,16] anisomycin and some of its derivatives display high *in vitro* antitumor activity.[17]

11   (–)-anisomycin **12a**   (+)-**12b**
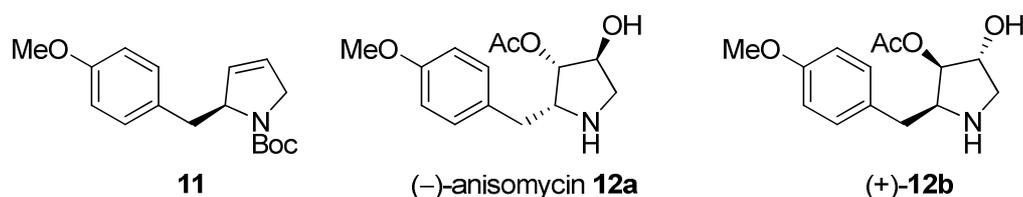
This diverse biological activity of anisomycin stimulated many scientists to develop new routes for its synthesis in both racemic, and enantiopure form.[18] Retrosynthetically, anisomycin may be prepared from 3,4-dehydropyrrolidine **11**, as described by Jegham and Das.[18d,k] Arriving at **11**, starting from a propargylic amine, would afford a formal synthesis of *ent*-anisomycin **12b** now based on the enantioselective copper-catalyzed propargylic amination.

During the last five years the use of gold-complexes in catalytic chemical transformations has undergone an extensive growth.[19] Gold catalysis provides a new synthetic pathway to construct complex chemical architectures in a mild manner that would otherwise be difficult to achieve. We envisaged that the 3,4-dehydropyrrolidine ring may be acquired by a gold-catalyzed ring closure of an aminoallene derived from an *N*-Boc protected propargylic amine (Scheme 4.5). Access to this aminoallene may be provided by the Crabbé reaction. Crabbé and coworkers found that terminal alkynes react with *para*-formaldehyde and diisopropylamine to form allenes under the influence of copper(I).[20]
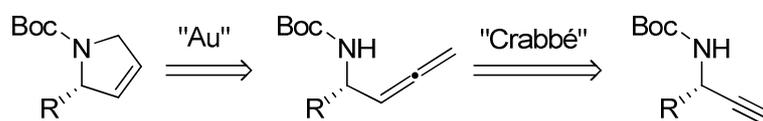
Scheme 4.5 Retrosynthetic scheme for the synthesis of 3,4-dehydropyrrolidines

The enantioselective copper-catalyzed propargylic amination reaction provided benzyl substituted propargylic amines **14** and **15** in reasonable yield and high *ee* (Scheme 4.6). Even after prolonged reaction time no full conversion of starting material was observed, which may be ascribed to catalyst deactivation. Next to the desired products we could recover the starting materials. Oxidative removal of the anisidyl moiety of **14** by iodobenzene diacetate followed

by treatment with di-*tert*-butyl dicarbonate gave Boc-protected propargylic amine **16** in good overall yield. Surprisingly, the same procedure applied to **15** gave **17** in only 29% yield. This is probably due to partial oxidation of the electron-rich *p*-methoxybenzyl moiety, lowering the yield of the desired product.
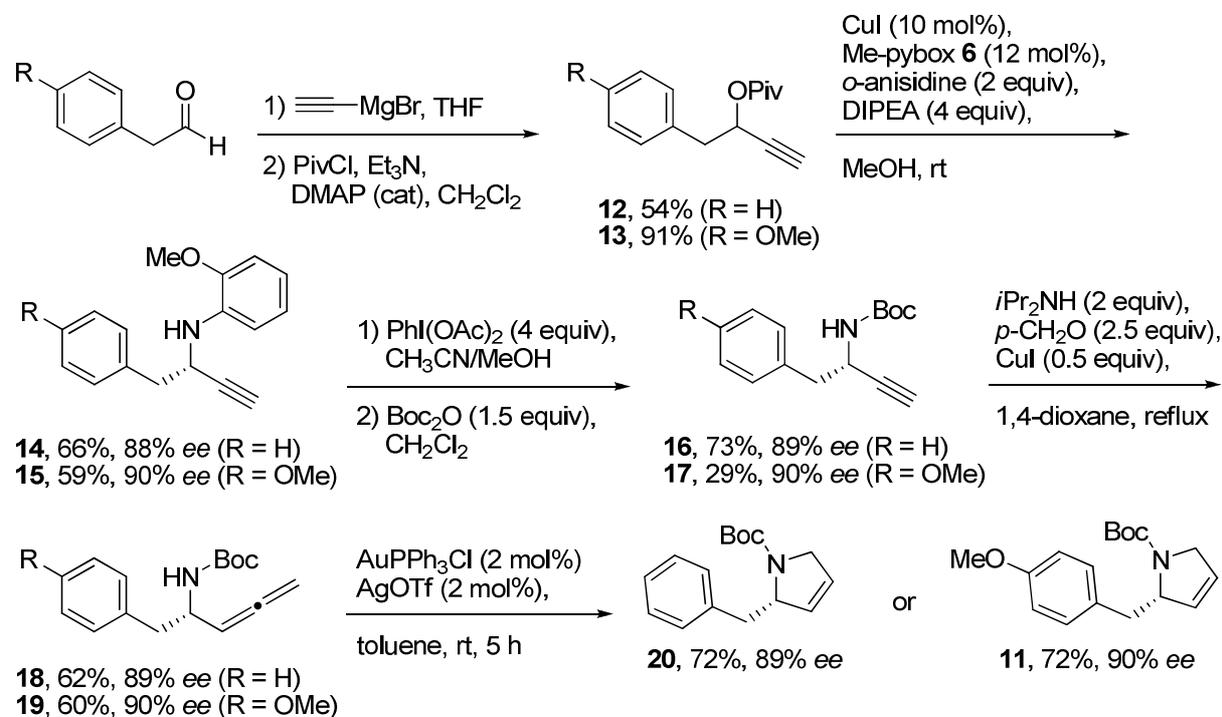

Scheme 4.6 Synthesis of *N*-Boc-protected 3,4-dehydropyrrolidines

Subsequent subjection to the Crabbé reaction provided allenic amines **18** and **19** in reasonable yield. The optical rotation of allene **18** ($[\alpha]^{24}_D$ +16, c 1.3, CHCl$_3$) was in good agreement with the literature value[28] ($[\alpha]^{26}_D$ +20.0, *c* 0.274, CHCl$_3$) of the enantiopure compound. In a first cyclization attempt with **18**, catalyzed by an *in situ* prepared cationic gold complex, **20** was obtained in high yield (86%). In another attempt the starting material was totally recovered, indicating the reaction was difficult to reproduce. It seems that at small scale the reaction is sensitive to traces of water and/or air oxygen, probably due to the very hygroscopic AgOTf. Altogether, both *N*-Boc-protected 3,4-dehydropyrrolidines **20** and **11** were obtained in satisfactory yield (72%), although higher conversions should be feasible.

With the synthesis of **11** we accomplished the formal synthesis of (+)-anisomycin **12b**. Predominantly due to the problematic anisidyl cleavage, the overall yield of **11** from commercially available *p*-methoxyphenylacetaldehyde of 7% was disappointing. However, the route consists of only seven steps and the substituent at the 2-position is easily varied, as is illustrated by the synthesis of **20**, allowing facile synthesis of anisomycin analogues.

4.5 TOTAL SYNTHESIS OF (−)-CYTOXAZONE

Since the isolation and structural elucidation of (−)-cytoxazone (**21**) by Osada and coworkers in 1998,[21] several groups have published a total synthesis of this novel cytokine modulator.[22] The compound was isolated from cultures of *Streptomyces* species and interferes with cytokine IL4, IL10, and IgG production via selective inhibition of the signaling pathway in Th2 cells.
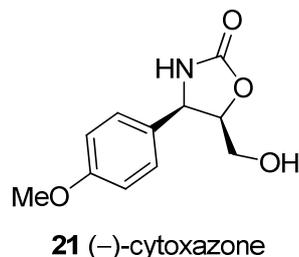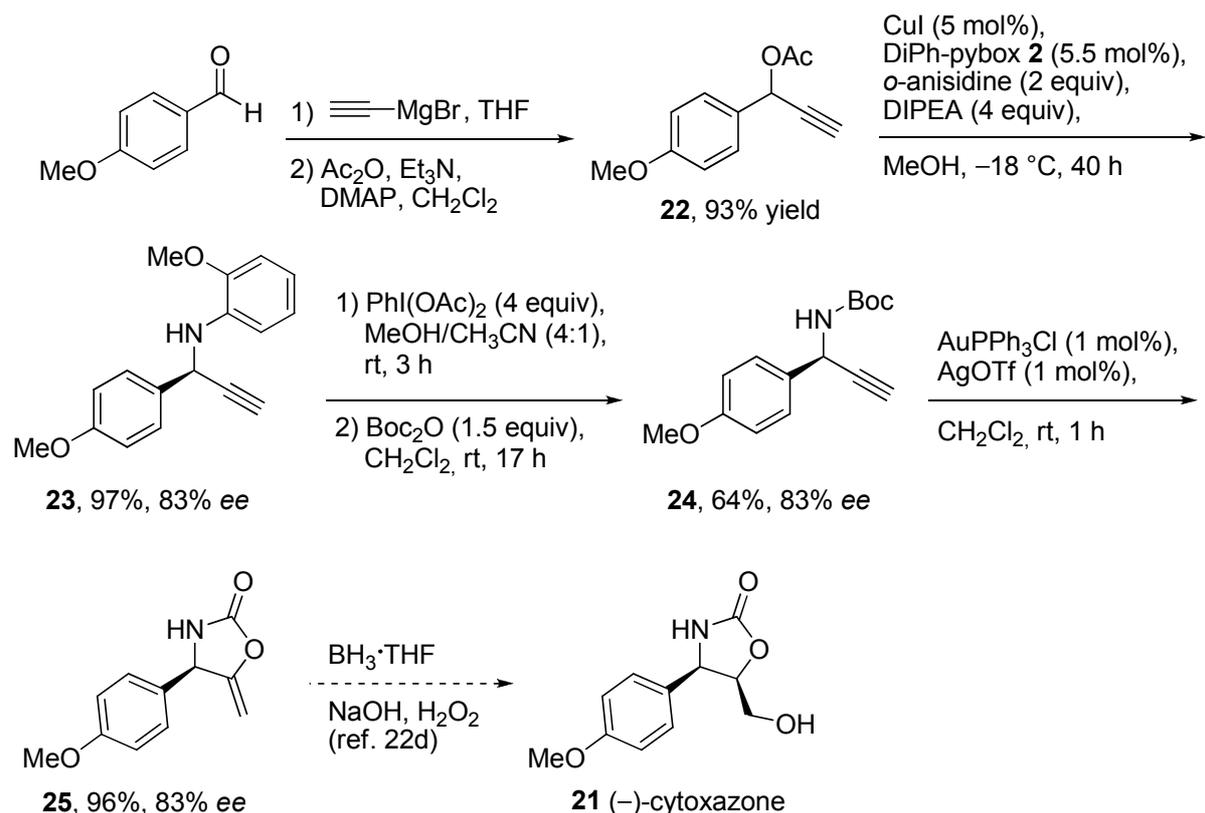
21 (−)-cytoxazone

We envisioned a short synthetic route to oxazolidinones, such as (−)-cytoxazone **21**, by gold-catalyzed cyclization, as described by Shin *et al.*,[22d] of *N*-Boc protected propargylic amines, prepared by enantioselective copper-catalyzed propargylic amination (Scheme 4.7). Hydroboration would afford (−)-cytoxazone **21**, or other interesting oxazolidinones, such as **27**.
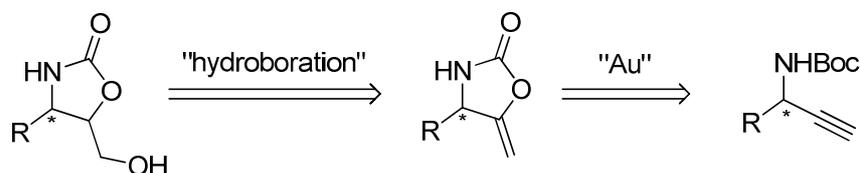
Scheme 4.7 Retrosynthetic scheme for the synthesis of oxazolidinones

As shown in Scheme 4.8, our new amination methodology was applied for a short synthesis of (−)-cytoxazone. Commercially available *p*-anisaldehyde was converted in propargylic acetate **22** upon reaction with ethynylmagnesium bromide and subsequent acetylation. The enantioselective copper-catalyzed propargylic amination gave propargylic amine **23** in high yield and enantioselectivity. After removal of the anisidyl moiety by iodobenzene diacetate, the primary amine was treated with di-*tert*-butyl dicarbonate affording Boc-protected propargylic amine **24** in good overall yield. At this point the cyclization, catalyzed by a cationic gold(I) complex prepared *in situ* from Au(PPh$_3$)Cl and AgOTf in toluene as reported by Shin *et al.*,[22d] provided us oxazolidinone **25** in excellent yield. Although successful according to Shin *et al.*, in our hands the hydroboration of the double bond of **25** did not afford (−)-cytoxazone **21** in good yield, only traces of the desired compound were observed during NMR and LC-MS analysis of the crude product. Thus, although the total synthesis of (−)-cytoxazone **21** regrettably ended before the intended last step of the sequence, we accomplished a short synthesis of enantioenriched oxazolidinones, such as **25**, in high overall yield (6 steps to **25** in 55% yield).

Scheme 4.8 Formal total synthesis of (−)-cytoxazone

Oxazolidinones are also important as key building blocks for the synthesis of HIV protease inhibitors, such as saquinavir.[23] Because variation of the substituent at the 4-position is facile due to our copper-catalyzed propargylic amination methodology, oxazolidinone analogues are easily prepared. This was illustrated by the synthesis of the benzyl-substituted oxazolidinone **26**, which was obtained in excellent yield by gold-catalyzed cyclization of the previously described **16** (see § 4.4.2, Scheme 4.6) without loss of optical purity as determined by chiral HPLC (Scheme 4.9).
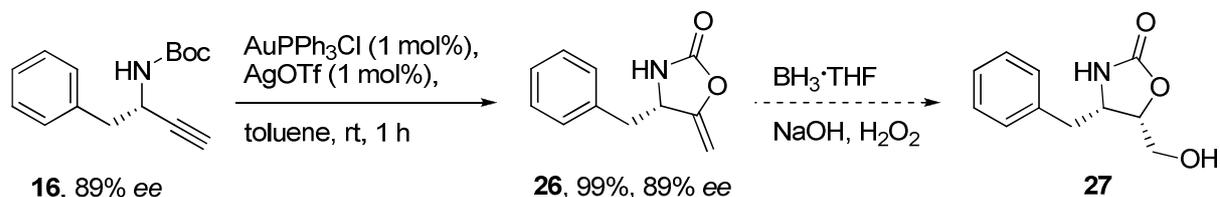
Scheme 4.9 Synthesis of benzyl-substituted oxazolidinone **26**

Also for this example the hydroboration step failed, and the synthesis of anticipated alcohol **27**, which is reported as one of the key building blocks for saquinavir,[23] remained unaccomplished.

4.6 CONCLUSIONS

In the enantioselective copper-catalyzed propargylic amination reaction a series of primary and secondary amines were tested as nucleophiles. Aniline and its derivatives gave the best results, affording the corresponding propargylic amines in high yield (up to 97%) and high optical purity (up to 87% *ee*). With other nitrogen nucleophiles the results were less promising, although reasonable enantioselectivity (68% *ee*) was obtained with the sterically hindered secondary amine *N*-benzyl-*N*-*p*-methoxybenzylamine. Carbon nucleophiles were also evaluated in the propargylic substitution reaction. Especially indole and *N*-methylindole stand out in this series, giving high yields (up to 91%) and enantioselectivities (up to 98% *ee*). Some of the propargylic amines, synthesized by our new protocol, were converted into α-amino acid derivatives, and further elaborated into formal total syntheses of two biologically active compounds: (+)-anisomycin and (−)-cytoxazone.

4.7 ACKNOWLEDGEMENTS

4.8 EXPERIMENTAL SECTION

General Remarks – The general information is described in Chapter 2 and 3.

General procedure for the propargylic substitution with pybox ligand 2. Copper iodide (3.8 mg, 0.020 mmol) and 2,6-bis((4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (**2**) (12.5 mg, 0.024 mmol) were suspended in methanol (1.4 mL). The mixture was stirred for 20 minutes before addition of a solution of the propargylic acetate (0.20 mmol) in methanol (0.3 mL). At the indicated temperature, a solution of nucleophile (0.40 mmol) and DIPEA (139 μL, 0.80 mmol) in methanol (0.3 mL) was added. The suspension was stirred until TLC analysis indicated total conversion of the propargylic acetate. When finished the reaction mixture was concentrated *in vacuo*. Silica gel chromatography gave the pure product.
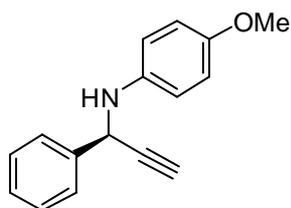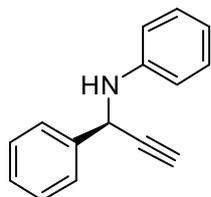

(*S*)-4-Methoxy-*N*-(1-phenylprop-2-ynyl)aniline (**4b**). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the mixture of p-anisidine (49 mg, 0.4 mmol) and DIPEA. After stirring for 19 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH₂Cl₂/PE 2:1) afforded product **4b** as a colourless oil (44 mg, 93% yield, 78% *ee*): [α]²⁰_D +67 (c 1.0, CHCl₃). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 14.8 min (minor isomer), 17.0 min (major isomer). ¹H NMR (400 MHz); δ (ppm) = 7.65-7.61 (m, 2H), 7.44-7.34 (m, 3H), 6.83 (d, *J* = 9.0 Hz,

2H), 6.74 (d, *J* = 9.0 Hz, 2H), 5.24 (br d, *J* = 2.1 Hz, 1H, CH), 3.82 (br s, 1H, NH), 3.77 (s, 3H, OMe), 2.50 (d, *J* = 2.2 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 153.1, 140.5, 139.3, 128.9, 128.3, 127.4, 115.9, 114.8, 83.4, 73.3, 55.8, 51.0; FTIR (film, cm^{-1}); 3263 (w), 3284 (m), 1511 (s), 1242 (s), 1035 (m), 821 (m); HRMS (FAB+) m/z: calcd. (MH$^+$) 238.1232, found 238.1235.
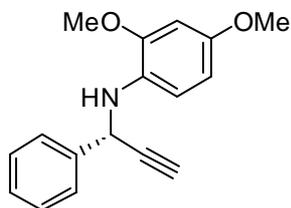
(*R*)-2,4-Dimethoxy-*N*-(1-phenylprop-2-ynyl)aniline (4c). The general procedure was followed. Compound **5a** (35 mg, 0.20 mmol) was added to the catalyst suspension (enantiomer of the diPh-pybox **2** was used) before adding the mixture of 2,4-dimethoxyaniline (57 μL, 0.4 mmol) and DIPEA in MeOH. After stirring for 1.5 hours the mixture was concentrated under reduced pressure and silica gel chromatography (CH$_2$Cl$_2$/PE 4:1) afforded product **4c** (48 mg, 90% yield, 64% *ee*). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 14.1 min (major isomer), 16.7 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.66-7.63 (m, 2H), 7.43-7.33 (m, 3H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 6.43 (dd, *J* = 2.6 Hz, *J* = 8.6 Hz, 1H), 5.26 (br s, 1H, CH), 4.38 (br s, 1H, NH), 3.82 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.48 (d, *J* = 2.3 Hz, 1H, C≡CH).
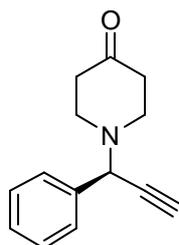
(*S*)-*N*-(1-Phenylprop-2-ynyl)aniline (4d). The general procedure was followed. Compound **5a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the mixture of aniline (36 μL, 0.4 mmol) and DIPEA. After stirring for 42 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH$_2$Cl$_2$/PE 2:1) afforded product **4d** as a white solid (39 mg, 94% yield, 87% *ee*): mp 82-83 °C; [α]$^{20}_D$ +103 (c 1.0, CHCl$_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 15.4 min (major isomer), 20.9 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.68-7.65 (m, 2H), 7.47-7.37 (m, 3H), 7.29-7.24 (m, 2H), 6.87-6.77 (m, 3H), 5.35 (br s, 1H, CH), 4.10 (br s, 1H, NH), 2.53 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 146.4, 139.1, 129.3, 128.9, 128.4, 127.4, 118.9, 114.1, 83.1, 73.3, 49.9; FTIR (film, cm^{-1}); 3371 (m), 3278 (s), 1600 (s), 1500 (s), 1452 (m), 1427 (m), 1305 (m), 1265 (m), 1236 (m), 1100 (m), 1070 (m); HRMS (FAB+) m/z: calcd. (MH$^+$) 208.1126, found 208.1126.
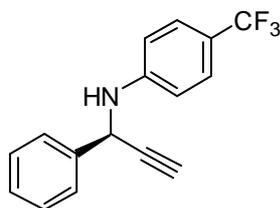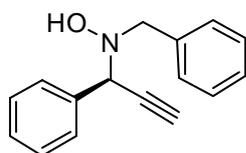
(*S*)-*N*-(1-Phenylprop-2-ynyl)-4-(trifluoromethyl)aniline (4e). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the mixture of aminobenzotrifluoride (50 μL, 0.4 mmol) and DIPEA in MeOH. After stirring for 43 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH$_2$Cl$_2$/PE 1:1) afforded product **4e** as a yellow oil (48 mg, 87% yield, 86% *ee*): [α]$^{20}_D$ +76 (c 1.0, CHCl$_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 13.8 min (major isomer), 15.1 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.61 (d, *J* = 8.8 Hz, 2H), 7.47-7.35 (m, 5H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.34 (dd, *J* = 7.0 Hz, *J* = 2.1 Hz, 1H, CH), 4.39 (br d, *J* = 6.8 Hz, 1H, NH), 2.52 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 148.8, 138.3, 129.1, 128.7, 127.3, 126.7, 124.9 (q, *J* = 271 Hz, CF$_3$), 120.4 (q, *J* = 33 Hz, C-CF$_3$), 113.3, 82.2, 73.8, 49.5; FTIR (film, cm^{-1}); 3300 (m), 1617 (m), 1529 (m), 1328 (s), 1189 (m), 1163 (m), 1115 (s), 1063 (m), 826 (m); HRMS (FAB+) m/z: calcd. (MH$^+$) 276.1000, found 276.0996.
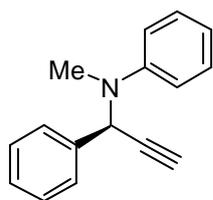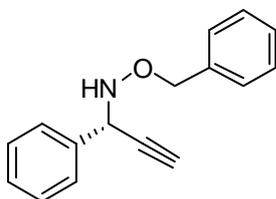
(S)-N-Methyl-N-(1-phenylprop-2-ynyl)aniline (4f). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension before adding the mixture of *N*-methylaniline (43 μL, 0.4 mmol) and DIPEA in MeOH. After stirring for 1 hour the mixture was evaporated to dryness and silica gel chromatography (CH$_2$Cl$_2$/PE 3:2) afforded product **4f** as a yellow oil (40 mg, 90% yield, 60% *ee*). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 5.7 min (minor isomer), 6.9 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.64-7.61 (m, 2H), 7.43-7.31 (m, 5H), 7.05-7.01 (m, 2H), 6.92-6.87 (m, 1H), 5.85 (d, *J* = 1.6 Hz, 1H, CH), 2.75 (s, CH$_3$), 2.56 (d, *J* = 2.4 Hz, 1H, C≡CH). NMR-data corresponds with literature.[24]
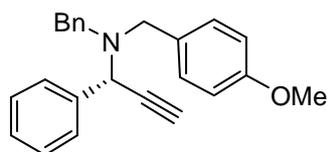
(S)-1-(1-Phenylprop-2-ynyl)piperidin-4-one (4g). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the mixture of 4-piperidone hydrate HCl (61 mg, 0.4 mmol) and DIPEA in MeOH. After stirring for 24 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH$_2$Cl$_2$ to 2% MeOH in CH$_2$Cl$_2$) afforded product **4g** (28 mg, 66% yield, 3% *ee*). HPLC conditions: Chiralcel OD (4.6 × 250 mm), 9:1 heptane:HOi-Pr, 0.8 mL/min, λ = 254 nm, 7.0 min (minor isomer), 7.6 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.64-7.61 (m, 2H), 7.40-7.30 (m, 3H), 4.81 (d, *J* = 2.1 Hz, 1H), 2.83 (t, *J* = 6.2 Hz, 4H), 2.58 (d, *J* = 2.3 Hz, 1H, C≡CH), 2.52-2.38 (m, 4H); ^{13}C NMR (101 MHz); δ (ppm) = 209.1, 137.6, 128.5, 128.2, 128.1, 78.7, 76.4, 60.6, 49.2, 41.6.
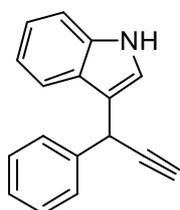
(S)-N-Benzyl-N-(1-phenylprop-2-ynyl)hydroxylamine (4h). The general procedure was followed. Compound **3a** (50 mg, 0.29 mmol) was added to the catalyst suspension and cooled to 0 °C before adding the mixture of *N*-benzylhydroxylamine (93 mg, 0.58 mmol) and DIPEA in MeOH. After stirring for 2 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH$_2$Cl$_2$ to 3% EtOAc in CH$_2$Cl$_2$) afforded product **4h** (53 mg, 77% yield): [α]^{20}$_D$ +16 (c 1.35, CHCl$_3$). No separation of the enantiomers on Chiralcel OD/OD-H and AD column. ^{1}H NMR (400 MHz, DMSO); δ (ppm) = 7.81 (br s, 1H, OH), 7.53 (d, *J* = 7.2 Hz, 2H), 7.37-7.20 (m, 8H), 4.82 (s, 1H), 3.84 (s, 2H), 3.49 (d, *J* = 2.8 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz, DMSO); δ (ppm) = 138.5, 138.1, 128.9, 128.5, 128.0 (4C), 127.5, 126.8, 80.7, 78.0, 62.4 (br, CH), 60.2 (br, CH$_2$).

(R)-O-Benzyl-N-(1-phenylprop-2-ynyl)hydroxylamine (4i). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension (enantiomer of the diPh-pybox **2** was used) and cooled to 0 °C before adding the mixture of *O*-benzylhydroxylamine HCl salt (64 mg, 0.40 mmol) and DIPEA (174 μL, 1.0 mmol) in MeOH. After stirring for 1.5 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH$_2$Cl$_2$/PE 4:1) afforded product **4i** (35 mg, 74% yield, 36% *ee*): [α]^{20}$_D$ −6 (c 0.5, CHCl$_3$). HPLC conditions: Chiralcel OD (4.6 × 250 mm), 99:1 heptane:HOi-Pr, 0.8 mL/min, λ = 254 nm, 10.2 min (minor isomer), 10.7 min (major isomer), no baseline separation. ^{1}H NMR (400 MHz); δ (ppm) = 7.54-7.51 (m, 2H), 7.41-7.28 (m, 8H), 5.65 (d, *J* = 6.8 Hz, 1H), 4.87 (dd, *J* = 2.2 Hz, *J* = 6.8 Hz, 1H), 4.74 (A of AB, *J$_{ab}$* = 11.6 Hz, 1H), 4.66 (B of AB, *J$_{ab}$* = 11.6 Hz, 1H), 2.54 (d, *J* = 2.3 Hz, 1H, C≡CH).
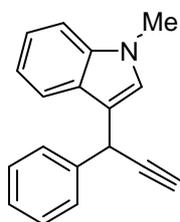
(*R*)-*N*-Benzyl-*N*-(4-methoxybenzyl)-1-phenylprop-2-yn-1-amine (4j). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension (enantiomer of the diPh-pybox **2** was used) and cooled to –20 °C before adding the mixture of *N*-benzyl-*N*-*p*-methoxybenzylamine (91 mg, 0.4 mmol) and DIPEA in MeOH. After stirring for 24 hours (slowly warmed to 0 °C) the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (PE/EtOAc 4:1) afforded product **4j** as a colourless oil (64 mg, 94% yield, 68% *ee*): $[\alpha]^{20}_D$ –15 (c 0.15, CHCl$_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 5.1 min (major isomer), 5.9 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.68 (d, *J* = 7.8 Hz, 2H), 7.42-7.23 (m, 10H), 6.87 (m, 2H), 4.75 (s, 1H) 3.81 (s, 3H, OMe), 3.76-3.67 (m, AB system, 2H), 3.46-3.38 (m, AB system, 2H), 2.67 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 158.8, 139.7, 138.8, 131.5, 130.1, 129.0, 128.4, 128.3, 128.2, 127.6, 127.1, 113.8, 78.9, 76.2, 55.4 (CH + OCH$_3$), 54.3, 53.9.
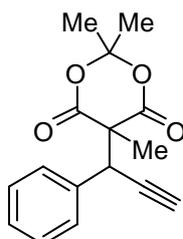
3-(1-Phenylprop-2-ynyl)-1*H*-indole (5a). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the mixture of indole (47 mg, 0.4 mmol) and DIPEA in MeOH. After stirring for 24 hours (slowly warmed to 0 °C) the mixture was evaporated to dryness and silica gel chromatography (PE/EtOAc 10:1) afforded product **5a** as a yellow oil (33 mg, 71% yield, 94% *ee*). HPLC conditions: Chiralcel OD (4.6 × 250 mm), 9:1 heptane:HOi-Pr, 0.8 mL/min, λ = 254 nm, 15.3 min (minor isomer), 22.1 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 8.00 (br s, 1H, NH), 7.57-7.51 (m, 3H), 7.43-7.20 (m, 5H), 7.14-7.08 (m, 2H), 5.30 (d, *J* = 2.4 Hz, 1H, α-CH), 2.48 (d, *J* = 2.4 Hz, 1H, C≡CH). NMR-data corresponds with literature.[5c]

1-Methyl-3-(1-phenylprop-2-ynyl)-1*H*-indole (5b). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the mixture of *N*-methylindole (52 mg, 0.4 mmol) and DIPEA in MeOH. After stirring for 18 hours (slowly warmed to –5 °C) the mixture was evaporated to dryness and silica gel chromatography (PE/EtOAc 10:1) afforded product **5b** as a yellow oil (45 mg, 91% yield, 98% *ee*) containing some *N*-methylindole (5 mg): $[\alpha]^{20}_D$ –11 (c 0.8, CHCl$_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 95:5 heptane:HOi-Pr, 1.0 mL/min, λ = 254 nm, 7.2 min (minor isomer), 8.7 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.54-7.48 (m, 3H), 7.34-7.19 (m, 5H), 7.08-7.04 (m, 1H), 6.96 (s, 1H), 5.27 (d, *J* = 2.5 Hz, 1H, α-CH), 3.75 (s, NCH$_3$), 2.44 (d, *J* = 2.6 Hz, 1H, C≡CH). NMR-data corresponds with literature.[5c,25]

2,2,5-Trimethyl-5-(1-phenylprop-2-ynyl)-1,3-dioxane-4,6-dione (5g). The general procedure was followed. Compound **3a** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the mixture of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (64 mg, 0.4 mmol) and DIPEA in MeOH. After stirring for 20 hours (slowly warmed to 0 °C), the mixture was quenched with saturated NH$_4$Cl (aq, 10 mL) and extracted twice with CH$_2$Cl$_2$ (8 mL). The organic layers were washed with brine (6 mL) and dried over anhydrous MgSO$_4$. Evaporation and silica gel chromatography (CH$_2$Cl$_2$/PE 4:1) afforded product **5g** (35 mg, 64% yield, 6% *ee*). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 96:4 heptane:HOi-Pr, 0.8 mL/min, λ =

220 nm, 9.8 min (minor isomer), 10.6 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.39-7.28 (m, 5H), 4.49 (d, *J* = 2.7 Hz, 1H, α-CH), 2.51 (d, *J* = 2.7 Hz, 1H, C≡CH), 1.86 (s, 3H, Me), 1.59 (s, 3H, Me), 0.96 (s, 3H, Me); ^{13}C NMR (101 MHz); δ (ppm) = 169.3, 167.3, 135.5, 129.4, 128.9, 128.7, 105.5 (c_q), 80.5, 74.7, 54.5 (c_q), 46.1, 29.9, 28.0, 24.0.
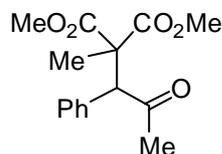
Dimethyl 2-methyl-2-(2-oxo-1-phenylpropyl)malonate (8). The same procedure was followed as for **5g**. The reaction was stirred for 15 minutes at room temperature and subsequently heated till 70 °C for 5 hours. After one night stirring at room temperature the reaction mixture was evaporated to dryness and after silica gel chromatography (CH$_2$Cl$_2$) product **8** (22 mg, 40% yield) was obtained. ^{1}H NMR (400 MHz); δ (ppm) = 7.31-7.29 (m, 3H), 7.17-7.13 (m, 2H), 4.76 (s, 1H), 3.74 (s, 3H, CO$_2$Me), 3.66 (s, 3H, CO$_2$Me), 2.10 (s, 3H, C(O)Me), 1.56 (s, 3H, Me).
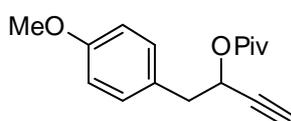
1-(4-Methoxyphenyl)but-3-yn-2-yl pivalate (12). To a solution of ethynylmagnesium bromide (0.5 M in THF, 28 mL, 14 mmol) in THF was added at 0 °C a solution of 2-(4-methoxyphenyl)acetaldehyde (2.00 g, 13.3 mmol) in THF (15 mL) using a dropping funnel. After stirring for 2 hours, the reaction mixture was poured into a flask containing a mixture of saturated NH$_4$Cl (aq, 25 mL) and ice (25 mL). The THF was evaporated under reduced pressure and afterwards the water layer was extracted twice with Et$_2$O (70 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated to dryness affording the propargylic alcohol as a yellow liquid. The crude propargylic alcohol (max. 13.3 mmol) was dissolved in dry CH$_2$Cl$_2$ (50 mL) in a schlenck under nitrogen atmosphere. Pivaloyl chloride (2.0 mL, 16.0 mmol) was added followed by addition of Et$_3$N (2.2 mL, 16 mmol) and DMAP (~15 mg) at 0 °C. The solution was stirred for 18 hours allowing to warm up to room temperature. After evaporation of the solvent, silica gel column chromatography (PE/EtOAc (5:1)) gave **12** in high yield (3.16 g, 91% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.19-7.15 (m, 2H), 6.85-6.81 (m, 2H), 4.46 (dt, *J* = 2.1 Hz, *J* = 6.8 Hz, 1H, CH), 3.79 (s, OMe), 3.03 (d, *J* = 6.8 Hz, 2H, CH$_2$), 2.43 (d, *J* = 2.1 Hz, 1H), 1.16 (s, 9H, *t*-Bu).
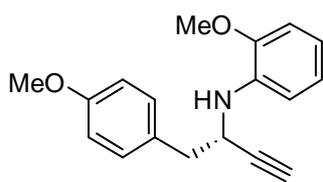
(S)-2-Methoxy-*N*-(1-(4-methoxyphenyl)but-3-yn-2-yl)aniline (14). Copper iodide (3.8 mg, 0.020 mmol) and pybox ligand **6** (5.9 mg, 0.024 mmol) were stirred in MeOH (1.5 mL) for 15 minutes. To the acquired red solution, a solution of **12** (52 mg, 0.2 mmol) in MeOH (0.2 mL) was added, followed by addition of a solution of *o*-anisidine (45 μL, 0.40 mmol) and DIPEA (139 μL, 0.80 mmol) in MeOH (0.3 mL). The reaction mixture was stirred for 72 h at room temperature. After evaporation and silica gel column chromatography (PE/EtOAc 10:1) **14** was obtained in reasonable yield and high *ee* (33 mg, 59% yield, 90% *ee*): [α]$^{24}_D$ −46 (c 1.0, CHCl$_3$). Next to the desired product 23% of starting material was recovered. HPLC conditions: Chiralcel AD (4.6 × 250 mm), 99:1 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm, 18.4 min (minor isomer), 20.3 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.26 (d, *J* = 8.4 Hz, 2H), 6.93-6.87 (m, 3H), 6.81-6.72 (m, 3H, anisidyl), 4.45 (br s, 1H, NH), 4.33 (br t (X of ABX), J_{ax} = 5.5 Hz, 1H, CH), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.15-3.09 (A of ABX, J_{ab} = 13.5 Hz, J_{ax} = 5.6 Hz, 1H), 3.08-3.02 (B of ABX, J_{ab} = 13.5 Hz, J_{bx} = 7.3 Hz, 1H), 2.26 (d, *J* = 1.4 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 158.7, 147.4, 136.2, 130.8, 129.0, 121.3, 117.9, 113.9, 111.7, 109.9, 84.3, 71.9, 55.6, 55.4, 46.9,

40.7; FTIR (film, cm^{-1}); 3402 (w), 3285 (m), 1602 (m), 1521 (s), 1456 (m), 1247 (s), 1223 (m), 1178 (m), 1126 (m), 1030 (m); HRMS (FAB+) m/z: calcd. (MH$^+$) 282.1494, found 282.1493.
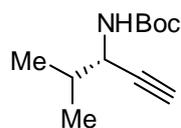
(*S*)-*tert*-Butyl 4-methylpent-1-yn-3-ylcarbamate (10). To a solution of PhI(OAc)$_2$ (1.25 g, 3.88 mmol) in methanol (10 mL) was added in 30 minutes using a syringe pump a solution of **3c** (197 mg, 0.97 mmol) in acetonitrile (2.5 mL) at room temperature. After the addition, the reaction mixture was stirred for another 2 hours, followed by addition of aqueous HCl (1.0 M, 10 mL). The mixture was stirred for 1.5 h. Afterwards, the mixture was extracted 4 times with CH$_2$Cl$_2$ (8 mL). The organic layers were backwashed once with aqueous HCl (0.1 M, 10 mL). The combined water layers were neutralized by addition of solid K$_2$CO$_3$ and a solution of Boc$_2$O (635 mg, 2.9 mmol) in CH$_2$Cl$_2$ (10 mL) was added. The biphasic mixture was basified to pH = 11 by K$_2$CO$_3$ (s) addition and stirred for 17 h. The layers were separated and the water layer was extracted once with CH$_2$Cl$_2$ (10 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated to dryness. Silica gel column chromatography (CH$_2$Cl$_2$) gave **10** in good yield (145 mg, 76% yield, 82% *ee*): [α]$^{20}_D$ −52 (c 0.5, CHCl$_3$), lit.[10] ([α]$_D$^{20} = −59.9, 96% *ee*). ^{1}H NMR (400 MHz); δ (ppm) = 4.71 (br s, 1H), 4.31 (br s, 1H), 2.24 (d, *J* = 2.4 Hz, 1H, C≡CH), 1.94-1.85 (m, 1H), 1.45 (s, 9H, *t*-Bu), 0.98 (d, *J* = 6.8 Hz, 6H). Data corresponds with literature.[26a]
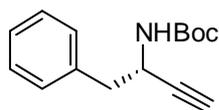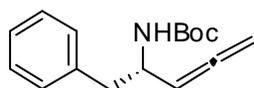
(*S*)-*tert*-Butyl 1-phenylbut-3-yn-2-ylcarbamate (15). To a solution of PhI(OAc)$_2$ (642 mg, 2.0 mmol) in methanol (10 mL) was added in 30 minutes using a syringe pump a solution of **13** (125 mg, 0.50 mmol) in acetonitrile (2 mL) at room temperature. After the addition, the reaction mixture is stirred for another 2 hours, followed by addition of aqueous HCl (1.0 M, 10 mL). The mixture was stirred for 1.5 h. Afterwards, the mixture was extracted 4 times with CH$_2$Cl$_2$ (10 mL). The organic layers were backwashed once with aqueous HCl (0.1 M, 10 mL). The combined water layers were neutralized by addition of solid K$_2$CO$_3$ and a solution of Boc$_2$O (218 mg, 1.0 mmol) in CH$_2$Cl$_2$ (10 mL) was added. The biphasic mixture was basified to pH = 11 by K$_2$CO$_3$ (s) addition and stirred for 17 h. The layers were separated and the water layer was extracted once with CH$_2$Cl$_2$ (10 mL). The combined organic layers were dried over anhydrous MgSO$_4$ and evaporated to dryness. Silica gel column chromatography (PE/CH$_2$Cl$_2$ (1:1) to pure CH$_2$Cl$_2$) gave **15** in good yield (89 mg, 73% yield, 89% *ee*): [α]$^{20}_D$ −9 (c 0.5, CHCl$_3$), lit.[23a] [α]$^{21}_D$ −10.6 (c 1.01, CHCl$_3$). ^{1}H NMR (400 MHz); δ (ppm) = 7.30-7.22 (m, 5H, Ph), 4.67 (br s, 2H, NH + CH), 3.00-2.96 (A of ABX, *J*$_{ab}$ = 13.3 Hz, *J*$_{ax}$ = 5.0 Hz, 1H) 2.94-2.89 (B of ABX, *J*$_{ab}$ = 13.3 Hz, *J*$_{bx}$ = 7.0 Hz, 1H), 2.26 (d, *J* = 1.7 Hz, 1H), 1.41 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = 154.7, 136.5, 129.9, 128.4, 127.0, 82.9, 80.1, 72.3, 44.0, 41.8, 28.4; FTIR (film, cm^{-1}); 3420 (w), 3303 (m), 2978 (m), 1698 (s), 1496 (s), 1167 (s). Analytical data corresponds with literature.[26]
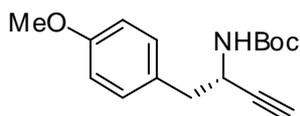
(*S*)-*tert*-Butyl 1-(4-methoxyphenyl)but-3-yn-2-ylcarbamate (16). To a solution of PhI(OAc)$_2$ (1.32 g, 4.09 mmol) in methanol (20 mL) was added by syringe pump in 30 minutes a solution of **14** (287 mg, 1.02 mmol) in acetonitrile (5 mL) at room temperature. After the addition, the reaction mixture was stirred for another 1.5 hours, followed by addition of aqueous HCl (1.0 M, 20 mL). The mixture was stirred for 1.5 h. Afterwards, the mixture was extracted 3 times with CH$_2$Cl$_2$ (20 mL). The organic layers were backwashed once with aqueous HCl (0.1 M, 20 mL). The combined water layers were neutralized by addition of solid K$_2$CO$_3$ and a solution of Boc$_2$O (334 mg, 1.53 mmol) in CH$_2$Cl$_2$ (20 mL) was added. The biphasic mixture was basified to pH = 11 by K$_2$CO$_3$ (s) addition and stirred for 17 h. The layers were separated and the water layer was extracted once with CH$_2$Cl$_2$ (20 mL). The combined organic

layers were dried over anhydrous MgSO$_4$ and evaporated to dryness. Silica gel column chromatography (PE/CH$_2$Cl$_2$ (1:1) to pure CH$_2$Cl$_2$) gave **16** in reasonable yield (82 mg, 29% yield, 90% *ee*): [α]$^{23}_D$ –5 (c 0.5, CHCl$_3$). ^{1}H NMR (400 MHz); δ (ppm) = 7.18 (d, *J* = 8.5 Hz, 2H, Ph), 6.86-6.82 (m, 2H, Ph), 4.73 (br s, 1H), 4.63 (br s, 1H), 3.79 (s, 3H, OMe), 2.96-2.91 (A of ABX, *J*$_{ab}$ = 13.4 Hz, *J*$_{ax}$ = 5.1 Hz, 1H) 2.89-2.84 (B of ABX, *J*$_{ab}$ = 13.4 Hz, *J*$_{bx}$ = 7.2 Hz, 1H), 2.27 (d, *J* = 2.2 Hz, 1H), 1.43 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = 158.7, 154.7, 130.9, 128.5, 113.8, 83.0, 80.1, 72.2, 55.3, 44.1, 40.9, 28.4; HRMS (FAB+) m/z: calcd. (MH$^+$) 276.1600, found 275.1599. NMR data corresponds with literature.[27]

(*S*)-*tert*-Butyl 1-phenylpenta-3,4-dien-2-ylcarbamate (17). To a suspension of CuI (16 mg, 0.085 mmol), *p*-CH$_2$O (13 mg, 0.42 mmol), and **15** (42 mg, 0.17 mmol) in 1,4-dioxane (8 mL) was added *i*Pr$_2$NH (48 μL, 0.34 mmol) and the mixture was stirred at reflux. After 22 hours, the mixture was allowed to cool to room temperature. A solution of ammonia (10%) in brine (4 mL) was added together with CH$_2$Cl$_2$ (5 mL) and the mixture was stirred for 10 minutes. After separation of the layers, the organic layer was washed subsequently with solution of ammonia (10%) in brine (4 mL), KHSO$_4$ (aq, 5 mL), H$_2$O (5 mL), and brine (5 mL). The organic layers was dried over anhydrous MgSO$_4$ and evaporated to dryness. Silica gel column chromatography (CH$_2$Cl$_2$) provided **17** (27 mg, 62%): [α]$^{24}_D$ +16 (c 1.3, CHCl$_3$), lit.[28] [α]$^{26}_D$ +20.0 (c 0.274, CHCl$_3$). ^{1}H NMR (400 MHz); δ (ppm) = 7.31-7.19 (m, 5H, Ph), 5.21 (dt, *J* = 6.5 Hz, *J* = 5.4 Hz, 1H, =CH), 4.84-4.81 (m, 2H, =CH$_2$), 4.58 (br s, 1H), 4.42 (br s, 1H), 2.97-2.89 (A of ABX, *J*$_{ab}$ = 13.3 Hz, *J*$_{ax}$ = 4.8 Hz, 1H) 2.86-2.81 (B of ABX, *J*$_{ab}$ = 13.3 Hz, *J*$_{bx}$ = 7.1 Hz, 1H), 1.41 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = 206.9, 155.2, 137.6, 129.8, 128.4, 126.6, 92.5, 79.3, 78.6, 49.7, 41.7, 28.5; FTIR (film, cm^{-1}); 3350 (w), 2978 (w), 1958 (w), 1698 (s), 1497 (m), 1169 (s); HRMS (FAB+) m/z: calcd. (MH$^+$) 260.1651, found 260.1655. NMR data corresponds with literature.[28]
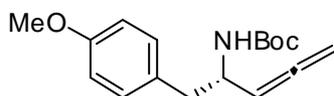
(*S*)-*tert*-Butyl 1-(4-methoxyphenyl)penta-3,4-dien-2-ylcarba-mate (18). To a suspension of CuI (25 mg, 0.13 mmol), *p*-CH$_2$O (20 mg, 0.65 mmol), and **16** (72 mg, 0.26 mmol) in 1,4-dioxane (12 mL) was added *i*Pr$_2$NH (73 μL, 0.52 mmol) and the mixture was stirred at reflux for 21 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (CH$_2$Cl$_2$) to give **18** as a white solid (45 mg, 60%): [α]$^{20}_D$ +25 (c 0.5, CHCl$_3$). ^{1}H NMR (400 MHz); δ (ppm) = 7.11 (d, *J* = 8.4 Hz, 2H, Ph), 6.84-6.80 (m, 2H, Ph), 5.21 (dt, *J* = 6.5 Hz, *J* = 5.4 Hz, 1H, =CH), 4.83-4.79 (m, 2H, =CH$_2$), 4.58 (br s, 1H), 4.36 (br s, 1H), 3.78 (s, 3H, OMe), 2.87-2.81 (A of ABX, *J*$_{ab}$ = 13.4 Hz, *J*$_{ax}$ = 5.2 Hz, 1H) 2.80-2.74 (B of ABX, *J*$_{ab}$ = 13.4 Hz, *J*$_{bx}$ = 7.1 Hz, 1H), 1.41 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = 206.9, 158.4, 155.2, 130.7, 129.6, 113.8, 92.5, 79.4, 78.5, 55.3, 49.8, 40.7, 28.5; FTIR (film, cm^{-1}); 3352 (m), 2977 (m), 1957 (m), 1703 (s), 1513 (s), 1247 (s), 1171 (s); HRMS (FAB+) m/z: calcd. (MH$^+$) 290.1756, found 290.1753.
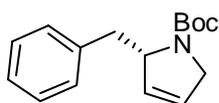
(*S*)-*tert*-Butyl 2-benzyl-2,5-dihydro-1*H*-pyrrole-1-carboxylate (19). In a schlenck under nitrogen atmosphere, Au(PPh$_3$)Cl (0.7 mg, 1.4 μmol) and AgOTf (0.4 mg, 1.4 μmol) were dissolved in toluene (0.46 mL). After 2 minutes **17** was added and the reaction mixture was stirred at room temperature. After 5 h the mixture was evaporated to dryness and subjected to silica gel column chromatography (CH$_2$Cl$_2$). This gave **19** in good yield (13 mg, 72%): [α]$^{20}_D$ +9 (c 0.28, CHCl$_3$). ^{1}H NMR (400 MHz); δ (ppm) = mixture of rotamers (0.55/0.45): 7.29-7.12 (m, 5H, Ph), 5.71-5.69 and 5.63-5.60 (m, 2H), 4.76 and 4.64 (br m, 1H), 4.17

(dd, J = 15.6 Hz, J = 2.0 Hz, 0.55H) and 4.04 (dd, J = 17.0 Hz, J = 1.6 Hz, 0.45H), 3.82 (dd, J = 15.6 Hz, J = 5.3 Hz, 0.55H) and 3.68 (dd, J = 15.4 Hz, J = 5.4 Hz, 0.45H), 3.21-3.12 (A of ABX, m, 1H), 2.93-2.87 (B of ABX, J_{ab} = 12.9 Hz, J_{bx} = 8.2 Hz, 0.45H) and 2.78-2.72 (B of ABX, J_{ab} = 12.9 Hz, J_{bx} = 8.5 Hz, 0.55H), 1.56 and 1.51 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = mixture of rotamers: 154.3, 138.0, 130.0 and 129.6, 129.7, 128.3 and 128.1, 126.4 and 126.2, 125.7 and 125.6, 79.8 and 79.4, 65.6 and 65.4, 53.9 and 53.6, 41.1 and 39.6, 28.8; FTIR (film, cm[-1]); 2974 (w), 2862 (w), 1698 (s), 1398 (s), 1173 (m), 1107 (m).
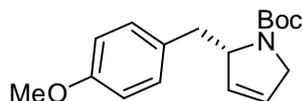
(*S*)-*tert*-Butyl 2-(4-methoxybenzyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (20). In a schlenck under nitrogen atmosphere, Au(PPh₃)Cl (0.56 mg, 1.1 µmol) and AgOTf (0.26 mg, 1.1 µmol) were dissolved in toluene (0.37 mL). After 2 minutes **18** (16 mg, 55 µmol) was added (dissolved in 0.3 mL toluene) and the reaction mixture was stirred at room temperature. After 5 h the mixture was evaporated to dryness and subjected to silica gel column chromatography (CH₂Cl₂ to 1% MeOH in CH₂Cl₂). This gave **20** in good yield (11.5 mg, 72%): [α]²⁰_D +154 (c 0.41, CHCl₃). ^{1}H NMR (400 MHz); δ (ppm) = mixture of rotamers (0.55/0.45): 7.09-7.04 (m, 2H, Ph), 6.88-6.80 (m, 2H, Ph), 5.72-5.62 (m, 2H), 4.76-4.60 (m, 1H), 4.19-4.02 (m, 1H), 3.80 (s, 3H), 3.82-3.79 and 3.72-3.68 (m, 1H), 3.11-3.05 (m, 1H), 2.91-2.71 (m, 1H), 1.58 and 1.53 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = mixture of rotamers: 158.2 and 158.1 (C_q), 154.3 and 154.2 (C_q), 130.9 and 130.7, 130.04 and 129.98 (C_q), 129.8 and 129.7 (=CH), 125.7 and 125.5 (=CH), 113.7 and 113.5, 80.7 and 79.7 (C_q), 65.7 and 65.4, 55.3, (MeO), 53.9 and 53.6 (NCH₂), 40.0 and 38.6, 28.78 and 28.72; HRMS (FAB+) m/z: calcd. (MH⁺) 290.1756, found 290.1753.
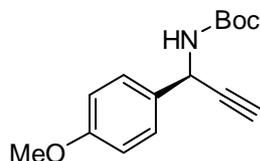
**(*S*)-*tert*-Butyl 1-(4-methoxyphenyl)prop-2-ynylcarbamate (25).** To a solution of PhI(OAc)₂ (515 mg, 1.60 mmol) in methanol (5 mL) was added by syringe pump in 30 minutes a solution of **24** (107 mg, 0.40 mmol) in acetonitrile (1 mL) at room temperature. After the addition, the reaction mixture was stirred for another hour, followed by addition of aqueous HCl (1.0 M, 10 mL). The mixture was stirred for 2 h. Afterwards, the mixture was extracted 3 times with CH₂Cl₂ (15 mL). The combined organic layers were backwashed once with aqueous HCl (0.1 M, 10 mL). The combined water layers were neutralized by addition of solid K₂CO₃ and a solution of Boc₂O (131 mg, 0.60 mmol) in CH₂Cl₂ (15 mL) was added. The biphasic mixture was basified to pH = 11 by K₂CO₃ (s) addition and stirred for 19 h. The layers were separated and the water layer was extracted once with CH₂Cl₂ (15 mL). The combined organic layers were dried over anhydrous MgSO₄ and evaporated to dryness. Silica gel column chromatography (CH₂Cl₂) gave **25** in good yield as a white solid (67 mg, 64% yield, 83% *ee*): [α]²⁰_D −15 (c 0.5, CHCl₃). ^{1}H NMR (400 MHz); δ (ppm) = 7.42 (d, J = 8.6 Hz, 2H, Ph), 6.89-6.85 (m, 2H, Ph), 5.59 (br s, 1H), 5.03 (br s, 1H), 3.80 (s, 3H, OMe), 2.48 (d, J = 2.4 Hz, 1H), 1.45 (s, 9H, *t*Bu); ^{13}C NMR (101 MHz); δ (ppm) = 159.5, 154.8, 131.0, 128.3, 114.1, 82.5, 80.8, 72.8, 55.4, 45.7, 28.4; FTIR (film, cm[-1]); 3281 (m), 2977 (m), 1692 (s), 1512 (s), 1247 (s), 1167 (s); HRMS (FAB+) m/z: calcd. (MH⁺) 262.1443, found 262.1440. NMR data corresponds with literature.[22d]
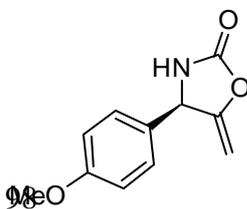
(*R*)-4-(4-Methoxyphenyl)-5-methyleneoxazolidin-2-one (26). The gold catalyst was prepared *in situ* by stirring Au(PPh₃)Cl (1.2 mg, 0.0025 mmol) and AgOTf (0.6 mg, 0.0025 mmol) in toluene (0.5 mL, dried on 4 Å mol.

sieves) for 5 minutes. A solution of **25** (64 mg, 0.25 mmol) in toluene (0.5 mL) was added to the catalyst solution and the mixture was stirred for 1 h at room temperature. Evaporation and column chromatography (1.0% MeOH in CH$_2$Cl$_2$) gave oxazolidinone **26** in excellent yield (49 mg, 96% yield, 83% *ee*): [α]$^{20}_D$ +47 (c 0.5, CHCl$_3$). HPLC conditions: Chiralcel OD (4.6 × 250 mm), 95:5 heptane:HOi-Pr, 0.8 mL/min, λ = 228 nm, 54 min (major isomer), 66 min (minor isomer); ^{1}H NMR (400 MHz); δ (ppm) = 7.26-7.22 (m, 2H, *m*-Ph), 6.92-6.89 (m, 2H, *o*-Ph), 6.29 (br s, 1H, NH), 5.36 (br s, 1H), 4.76-4.74 (m, 1H), 4.10-4.09 (m, 1H), 3.80 (s, 3H, OMe); ^{13}C NMR (101 MHz); δ (ppm) = 160.2, 156.8, 156.3, 130.9, 128.2, 114.6, 88.3, 59.5, 55.5; FTIR (film, cm^{-1}); 3240 (m), 1794 (s), 1753 (m), 1681 (m), 1514 (m), 1326 (m), 1252 (s), 1174 (s), 1026 (m), 987 (s); HRMS (FAB+) m/z: calcd. (MH$^+$) 206.0817, found 206.0817. NMR data corresponds with literature.[22d]
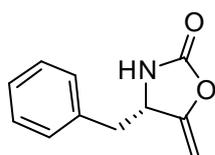
(*S*)-4-Benzyl-5-methyleneoxazolidin-2-one (27). The gold catalyst was prepared *in situ* by stirring Au(PPh$_3$)Cl (1.0 mg, 0.002 mmol) and AgOTf (0.5 mg, 0.002 mmol) in toluene (1 mL, dried on 4 Å mol. sieves) for 5 minutes. Compound **15** (50 mg, 0.20 mmol) was added to the solution and the mixture was stirred for 45 minutes at room temperature (TLC indicated total conversion after 5 minutes). Evaporation and column chromatography (gradient: 0.5% - 1.0% MeOH in CH$_2$Cl$_2$) gave oxazolidinone **27** in quantitative yield (38 mg, 99% yield, 89% *ee*): [α]$^{20}_D$ −137 (c 0.5, CHCl$_3$). HPLC conditions: Chiralcel OD (4.6 × 250 mm), 9:1 heptane:HOi-Pr, 0.8 mL/min, λ = 220 nm, 18.4 min (major isomer), 29.3 min (minor isomer); ^{1}H NMR (400 MHz); δ (ppm) = 7.30-7.26 (m, 3H, *m,p*-Ph), 7.21-7.18 (m, 2H, *o*-Ph), 6.09 (br s, 1H, NH), 4.77-4.75 (m, 1H, =CH$_2$), 4.61-4.56 (m X of ABX, 1H, CH), 4.23-4.21 (m, 1H, =CH$_2$), 3.04-2.99 (A of ABX, J_{ab} = 13.7 Hz, J_{ax} = 4.9 Hz, 1H) 2.91-2.85 (B of ABX, J_{ab} = 13.7 Hz, J_{bx} = 8.5 Hz, 1H); ^{13}C NMR (101 MHz); δ (ppm) = 156.1, 155.3, 135.5, 129.4, 129.0, 127.5, 87.2, 57.1, 42.7; FTIR (film, cm^{-1}); 3269 (m), 1771 (s), 1678 (s), 1191 (m), 982 (m), 700 (m); HRMS (FAB+) m/z: calcd. (MH$^+$) 190.0868, found 190.0865. NMR data corresponds with literature.[22d]

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