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Enantioselective Copper-Catalysed Propargylic Substitution: Synthetic Scope Study and Application in Formal Total Syntheses of (+)-Anisomycin and (−)-Cytoxazone

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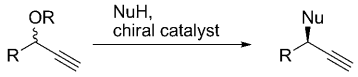
Abstract: A copper catalyst with a chiral pyridine-2,6-bisoxazoline (pybox) ligand was used to convert a variety of propargylic esters with different side chains (R = Ar, Bn, alkyl) into their amine counterparts in very high yields and with good enantioselectivities (up to 90% enantiomeric excess (*ee*)). Different amine nucleophiles were applied in the reactions and the highest enantioselectivities were obtained for aniline and its analogues. Interestingly, some carbon nucleophiles could also be used and with indoles excellent *ee* values were obtained (up to 98% *ee*). The versatility of the propargylic amines obtained was demonstrated by their further elaboration to formal total syntheses of the antibiotic (+)-anisomycin and the cytokine modulator (−)-cytoxazone.

Keywords: asymmetric catalysis · copper · homogeneous catalysis · propargylic substitution · synthetic methods

Introduction

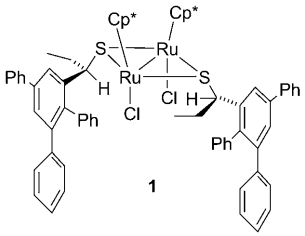
The propargylic moiety is a popular functionality in organic synthesis. The electron-rich triple bond, in combination with the fairly acidic character of the terminal acetylenic hydrogen atom, makes it a versatile entity for further chemical transformations.[1] In addition, various natural products, fine chemicals and pharmaceuticals containing propargylic subunits as components of their structures have been reported.[2] Unlike allylic substitution, which is one of the most reliable methods in organic synthesis, asymmetric transition-metal-catalysed propargylic substitution is a poorly developed reaction.[3,4] Several palladium-catalysed reactions with propargylic compounds are known, but these usually yield the corresponding allenic systems.[5]

Although some diastereoselective methods have been described,[6] only one example of an enantioselective propargylic substitution reaction (Scheme 1) is known. This method, developed in the group of Uemura, Hidai and Nishibayashi, uses a chiral diruthenium complex (**1**) to induce asymmetry in the C–C bond formation during the propargylation of aromatic compounds or acetone with propargylic alcohols (up to 95% enantiomeric excess (*ee*)).[7]



Scheme 1. Enantioselective transition-metal-catalysed propargylic substitution.

However, propargylic substitution reactions with heteroatom-centred nucleophiles, such as alcohols, amines, thiols and diphenylphosphine oxide, did not proceed enantioselectively in the presence of this diruthenium complex.[7c]



Recently, the first example of an enantioselective copper-catalysed propargylic amination, starting from the propargylic acetates **2** (Scheme 2), was discovered both by our group and by the group of Nishibayashi.[8] This new method, an enantioselective version of the propargylic substitution reaction originally reported by Murahashi et al.,[9] provides the propargylic amines **3** in very high yields and optical purities. The major difference between Nishibayashi's method and ours is the structure of the chiral ligand. Whereas Nishibayashi used a diphosphine ligand ((*R*)-Cl-OMe-biphep, **4**), we focussed on chiral 2,6-bis(oxazolinyl)pyridine-type (pybox, **5**) ligands.

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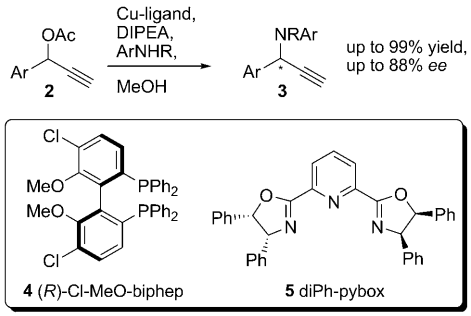


Scheme 2. Enantioselective copper-catalysed propargylic amination.

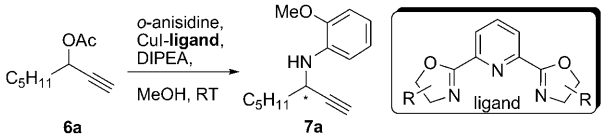
Whereas our system showed high yields and *ee* values with primary amines such as *o*-anisidine (Scheme 2, R = H), Nishibayashi's method gave the best results if secondary amines such as *N*-methylaniline (R = Me) were used.[8b,c] A disadvantage of both Nishibayashi's and our method is the incompatibility with substrates bearing non-aromatic side chains. However, in a recent paper, Nishibayashi et al. describe enantioselective copper-catalysed ring-opening reactions of racemic ethynyl epoxides with amines containing non-aromatic side chains.[8d]

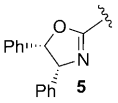
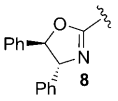
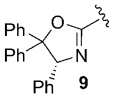
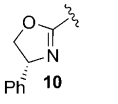
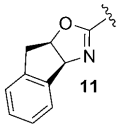
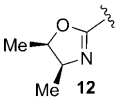
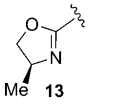
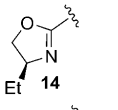
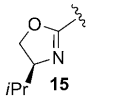
Herein, we disclose the results of our synthetic scope study starting from propargylic substrates bearing non-aromatic side chains in combination with the introduction of several nucleophiles such as anilines, but also aliphatic primary and secondary amines and some C-centred nucleophiles. The versatility of the obtained enantiomerically enriched propargylic amines is demonstrated by their further elaboration, leading to a formal total synthesis of the biologically active compound (+)-anisomycin.

Results and Discussion

Our previous study found that diPh-pybox (**5**) is the optimal ligand for propargylic substrates bearing aromatic side chains. With the propargylic acetate **6a**, bearing an *n*-pentyl group, diPh-pybox (**5**) gave poor stereoselectivity, affording the propargylic amine **7a** in only 13% *ee* under the optimised reaction conditions (Table 1, entry 1). After examination of ligands **8**–**11** it became apparent that aromatic substituents next to the oxazoline N atom are detrimental for the enantioselectivity (Table 1, entries 2–5). We speculated that substitution of the two phenyl groups in ligand **5** for two methyl groups to give diMe-pybox (**12**) might increase the enantioselectivity for aliphatic propargylic acetates. The synthesis of this ligand (see the Supporting Information) proved challenging because the required (2*R*,3*S*)-3-aminobutan-2-ol had to be synthesised. Gratifyingly, though, the reaction catalysed by the pybox ligand **12** afforded the propargylic amine **7a** in good yield and with 64% *ee* at room temperature. Removal of the methyl group adjoining the oxazoline O atom to give the ligand **13** gave a slightly further improved *ee* value of 66% (Table 1, entry 7). Replacement

Table 1. Screening of several pybox ligands.[a]



Entry	Ligand	*ee*[b] [%]
1	 **5**	13
2	 **8**	21
3[c]	 **9**	1
4	 **10**	23
5	 **11**	21
6[c]	 **12**	64
7	 **13**	66
8	 **14**	52
9[c]	 **15**	22

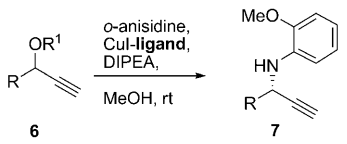
[a] Reaction conditions: **6** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol) and ligand (0.024 mmol) were stirred in methanol (2 mL) at room temperature, unless noted otherwise. [b] The *ee* value is determined by chiral HPLC of the isolated product. [c] Reaction is performed at 40 °C.

of the methyl groups in **13** by sterically more demanding groups gave lower enantioselectivities (Table 1, entries 8, 9). Apparently, the pybox ligand **13**, bearing the small methyl group, is the most selective ligand for this transformation.

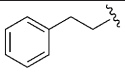
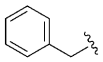
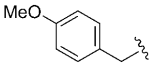
With this finding observed, we explored the scope of enantioselective propargylic aminations of substrates with more hindered aliphatic side chains (Table 2). In some cases we have also shown the results when diMe-pybox (**12**) was used. The phenethyl-substituted propargylic amine **7b** was obtained with yield and selectivity comparable to those seen with the phenyl-substituted **7a** (Table 2, entry 1).

We were pleased to see that branching near the propargylic C atom caused an increase in the asymmetric induction

Table 2. Propargylic aminations with several propargylic esters.[a]



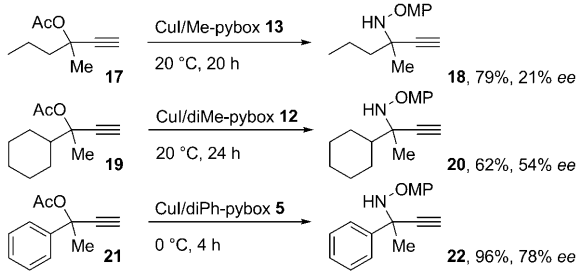
6 7

Entry	R	R^1	Ligand	Product	Yield[b] [%]	*ee*[c] [%]
1		Ac (**6b**)	**13**	**7b**	84	67
2		Ac (**6c**)	**13**	**7c**	80	82
3		Ac (**6d**)	**13**	**7d**	77	82
4		Bz (**6d2**)	**13**	**7d**	89	79
5		Ac (**6e**)	**13**	**7e**	96	85
6			**12**	**7e**	63	86
7		Ac (**6f**)	**13**	**7f**	66	88
8		Ac (**6f**)	**12**	**7f**	60	89
9		Piv (**6f2**)	**13**	**7f**	66[d]	88
10		Piv (**6g**)	**13**	**7g**	59[d]	90

[a] Reaction conditions: the propargylic ester **6** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol) and the pybox ligand (0.024 mmol) were stirred in methanol (2 mL) at room temperature typically for 24–48 h. [b] Isolated yield after chromatographic purification. [c] Enantioselectivity was determined by chiral HPLC of the isolated product. [d] No full conversion was observed and starting material (23–24%) was recovered. Bz = benzoyl, Piv = pivaloyl.

to the 79–90% *ee* range, as was shown for products **7c–g** (Table 2, entries 2–10). The acetate group proved sensitive to base-catalysed transesterification by the methanol solvent, thus giving the propargylic alcohol as a side product and lowering the yield. Use of the sterically more demanding benzoate or pivaloate esters gave the products in higher yields without sacrificing enantioselectivity and no transesterification was observed (Table 2, entries 4, 9 and 10).

Gratifyingly, the procedure also allows amination of quaternary propargylic acetates (Scheme 3). Currently, asymmetric synthesis of these α,α-dibranched propargylic amines



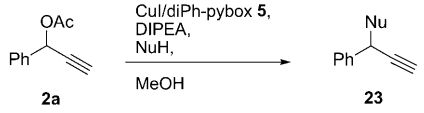
Scheme 3. Propargylic amination with quaternary propargylic acetates: the reactions were performed with the propargylic acetate (0.2 mmol), *o*-anisidine (H_2N–OMP, 0.4 mmol), DIPEA (0.8 mmol) and the indicated catalyst (10 mol%) in methanol.

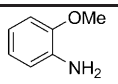
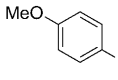
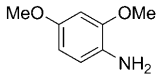
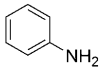
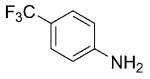
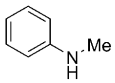
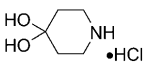
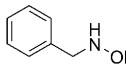
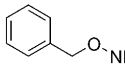
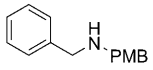
is limited to a few methods, thus giving access only to a narrow set of structural motifs.[10] In particular, products such as **22**, containing an aromatic ring and a methyl group as the substituents, are of importance. Known routes to products of this type are few and provide the products, although with high optical purities (78 and 98% *de*), in low yields (11 and 31%, respectively).[10e,h] The ability of the catalyst to discriminate between a methyl and a propyl moiety appeared to be limited, as was shown for substrate **17** (Scheme 3), which gave the amine **18** in good yield (79%) but in low optical purity (21% *ee*), in the presence of Me-pybox **13** as the optimal ligand. Replacement of the propyl group by a cyclohexyl moiety gave the product **20** with higher selectivity in the presence of either Me- or diMe-pybox (**13** or **12**, 54% *ee*). For substrates containing aromatic rings as substituents the diPh-pybox ligand **5** gave the best results and afforded the propargylic amine **22** in very high yield and with good selectivity (78% *ee*).

Nitrogen nucleophiles: After the study of several propargylic acetates in the enantioselective propargylic amination reaction (see above), the scope, with regards to the nitrogen nucleophile, was investigated (Table 3). *p*-Methoxyphenyl (PMP) is a commonly used protecting group for amines, so *p*-anisidine was included in our series under the optimal reaction conditions and with diPh-pybox (**5**) as the ligand (Table 2, entry 2). The observed enantioselectivity was slightly lower than seen with *o*-anisidine. Moreover, 2,4-dimethoxyaniline (Table 2, entry 3) also gave lower *ee* values than *o*-anisidine, so the latter system was chosen as the masked primary amine in our protocol. Results similar to those obtained with *o*-anisidine were also obtained both with aniline and with 4-(trifluoromethyl)aniline (Table 2, entries 4 and 5). Nitroanilines did not react properly and gave only small amounts of product among many side products (data not shown). In analogy with the Nishibayashi method,[8b] we applied *N*-methylaniline as the nucleophile: an *ee* value significantly lower than those obtained with the primary anilines was observed (Table 2, entry 6), underscoring the complementarity of the two methods.

Carreira et al. recently reported the use of 4-piperidone hydrate hydrochloride as an interesting masked primary amine in copper-catalysed three-component reactions of aldehydes, alkynes and amines.[11] Once the 4-piperidone is attached at the propargylic moiety, double dealkylation by use of an excess of a primary amine affords the unprotected propargylic amine. However, when 4-piperidone hydrate hydrochloride was applied in our reaction, the product was obtained in good yield but in almost racemic form (Table 2, entry 7). *N*-Benzylhydroxylamine, which also serves as a masked primary amine, gave the anticipated product in good yield. Although product **23h** showed an optical rotation, demonstrating an enantioselective reaction, all attempts to separate the enantiomers by chiral HPLC failed and no *ee* value could be determined. With *O*-benzylhydroxylamine, the product was obtained in good yield (74%), but with a low *ee* value (36% *ee*, Table 2, entry 9). On the other

Table 3. Propargylic amination with various nitrogen nucleophiles.[a]



Entry	NuH	t [h]	T [°C]	Product	Yield[b] [%]	ee[c] [%]
1		24	−20	**23a**	97	85
2		19	−20	**23b**	93	78
3		1.5	RT	**23c**	90	64
4		42	−20	**23d**	94	87
5		43	−20	**23e**	87	86
6		1	RT	**23f**	90	60
7		3	RT	**23g**	66	3
8		2	0	**23h**	77	n.d.
9		1.5	0	**23i**	74	36
10		24	−20	**23j**	94	68

[a] Reaction conditions: the propargylic acetate **2a** (0.20 mmol), the NuH (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol) and **5** (0.024 mmol) were stirred in methanol (2 mL). [b] Isolated yield after chromatographic purification. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. N.d. = could not be determined by chiral HPLC, PMB = *p*-methoxybenzyl.

hand, with *N*-benzyl-*N*-*p*-methoxybenzylamine, the desired product was obtained in high yield and with a moderate selectivity (Table 2, entry 10). This suggests that more hindered secondary aliphatic amines might provide products in even higher enantiopurity.

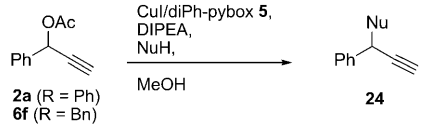
Removal of the *o*-anisidyl group was achieved in reasonable to high yields for most substrates, as is described later. It was nevertheless interesting to know whether other types of nitrogen nucleophiles would also lead to the desired products. In single-attempt experiments (not shown) a set of different nitrogen nucleophiles was tested under the optimal reaction conditions. *tert*-Butyl carbamate and di-*tert*-butyl iminodicarbonate were applied in the substitution reactions, 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.

Carbon nucleophiles: As is illustrated above, the copper-catalysed propargylic substitution reaction is rather sensitive with regard to the nitrogen nucleophile. The question arose of whether carbon nucleophiles could also 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. During the course of this work Fang and Hou reported the first example of Cu-catalysed asymmetric propargylic substitution in which enamines were used as carbon nucleophiles. With Nishibayashi's ligand **4** the substitution of several propargylic acetates bearing aromatic side chains with different aryl-substituted enamines resulted in the propargylic substituted products in high yields (40–95%) and with good enantioselectivities (67–91%).[12] Other examples of asymmetric substitutions at the propargylic moiety with carbon nucleophiles, reported by Nishibayshi et al., rely on a chiral thiolate-bridged diruthenium complex.[7] With its success in Nishibayashi's ruthenium-catalysed substitution in mind,[7c] the special π-nucleophilicity and biological relevance of indole prompted us to subject it to our reaction conditions. The first attempt at this novel copper-catalysed asymmetric Friedel–Crafts propargylation of indole gave very promising results. Treatment of 1-phenylprop-2-ynyl acetate (**2a**) with indole in the presence of diPh-pybox (**5**) gave the propargylated indole **24a** in high yield and with excellent selectivity (94% *ee*, Table 4, entry 1). Very delighted with this result, we subjected *N*-methylindole to the same conditions and obtained the product **24b** in high yield and with even higher selectivity (98% *ee*, Table 4, entry 2). *N*-Triisopropylsilylindole, which had given the best results in the ruthenium-catalysed propargylation, gave no product at all, which may be ascribed to steric hindrance (Table 4, entry 3).

With the propargylic acetate **6f**, containing an aliphatic side chain (R = Bn), and with indole as the nucleophile, no desired product was formed with either ligand **5** or **11** (Table 4, entry 4), even with a longer reaction time (144 h) and elevated temperatures (up to 50 °C).

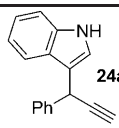
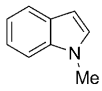
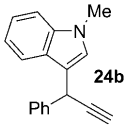
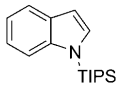
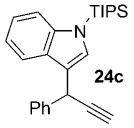
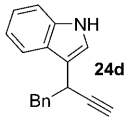
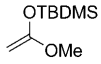
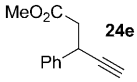
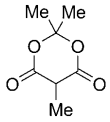
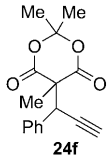
After the establishment of enantioselective copper-catalysed propargylic substitution with indoles, we envisaged that other carbon π-nucleophiles might also be applicable (Table 4, entries 5, 6). Unfortunately, the enol ester *tert*-butyl(1-methoxyvinyloxy)dimethylsilane gave a disappointing result and only a small amount of product was isolated (Table 4, entry 5). Interestingly, though, with 2,2,5-trimethyl-1,3-dioxane-4,6-dione the propargylic acetate was fully converted (Table 4, entry 6). Besides the anticipated product **24f**, compounds **25** and **26** (Scheme 4) were also identified in the ^{1}H NMR spectrum of a crude sample, indicating that an intriguing cascade of reactions had occurred. Probably, after the formation of **24f**, small amounts of methoxide, present in the basic reaction medium, could have attacked one of the ester functionalities (Scheme 4).

Table 4. Propargylic amination with various carbon nucleophiles.[a]

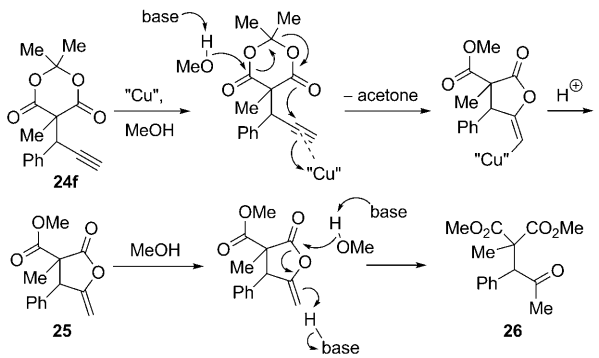


2a (R = Ph)
6f (R = Bn)

24

Entry	NuH	R	*T* [°C]	Product	Yield[b] [%]	*ee*[c] [%]
1		Ph	−20	 **24a**	71	94
2		Ph	−20	 **24b**	91	98
3		Ph	−20	 **24c**	n.r.	–
4[d]		Bn	up to 50	 **24d**	n.r.	–
5		Ph	RT	 **24e**	≈10	n.d.
6[e]		Ph	−20	 **24f**	64	6

[a] Reaction conditions: propargylic acetate (**2a**, 0.20 mmol), NuH (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol) and **5** (0.024 mmol) were stirred in methanol (2 mL) for 24 h. [b] Isolated yield after chromatographic purification. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [d] In this entry ligand **11** was also used, as well as the pivaloate ester **6f2**. [e] In this reaction only 0.22 mmol of the nucleophile was used, and after completion the reaction mixture was first quenched with sat. NH_4Cl (aq) and extracted, before chromatographic purification. n.r. = no product formation observed, n.d. = could not be determined by chiral HPLC, Bn = benzyl, TBDMS = *tert*-butyldimethylsilyl.

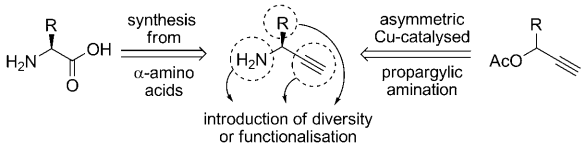


Scheme 4. Unexpected reaction cascade.

This could have liberated, after loss of acetone, a carboxylate anion, which in turn could have attacked the copper-activated alkyne moiety. After proteolysis, product **25**, which was identified by ^{1}H NMR analysis, would have been obtained. Another methanolysis step could have formed the dimethyl ester enolate, which could have isomerised to the ketone **26**. After a 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, the product **24f** could be isolated in good yield (64 %), although as a near racemate.

Applications

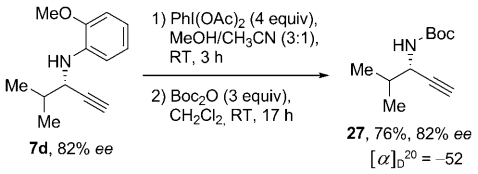
The establishment of the enantioselective copper-catalysed propargylic amination protocol motivated us to find new applications for the resulting optically active propargylic amines. Alkyne moieties are amenable to further functionalisation and conversion into natural products and biologically interesting molecules. This virtue, in combination with the ease of variation of the side chains (R), makes the new protocol a simple and versatile synthetic procedure. Optically active propargylic amines have been used before as starting materials, and compounds of this type are usually prepared by starting from α-amino acids (Scheme 5).[13] However, multiple steps are required and the procedures are prone to racemisation.[14] With our protocol a large array of substituents (R) is available. Because the absolute configuration of the product is determined by the pybox ligand, both enantiomers of which are available, complete stereocontrol of the product is possible.



Scheme 5. Synthesis of chiral propargylic amines.

When the substrate **6d** was converted into the propargylic amine **7d** (Table 2), a valine analogue was obtained. Oxidative removal of the anisidyl moiety with iodobenzene diacetate, as reported by Snapper et al.,[15] and subsequent N-protection with a *tert*-butoxycarbonyl (Boc) group gave the propargylic amine **27** in good yield (Scheme 6). The absolute configuration was determined by comparison of the optical rotation with a literature value ($[\alpha]_D^{20} = -59.9$, 96 % *ee*).[12b] The (*S*)-Me-pybox ligand **13** gave the (*S*)-valine analogue **27**, which is similar to the natural amino acid derived configuration.

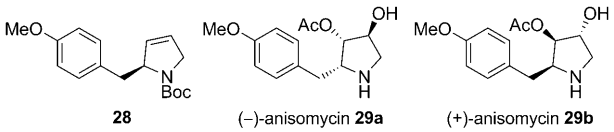
Anisomycin: Elaboration of the optically enriched products obtained by the copper-catalysed enantioselective propargylic amination into Boc-protected amines opens pathways for



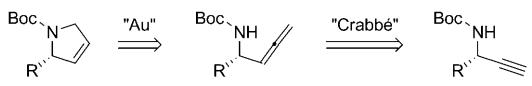
Scheme 6. Synthesis of an alkyne-containing amino acid (valine) analogue.

further transformations. Pyrrolidine rings are important structural motifs in many alkaloids, such as hygrine, nicotine and cocaine. Their biological activities make these alkaloids attractive synthetic targets. A formal total synthesis of anisomycin, which also contains a pyrrolidine system, is detailed below.

The antibiotic anisomycin was isolated from culture filtrates of two *Streptomyces* species (*S. griseolus* and *S. roseochromogenes*) in the early 1950s.[16] In the 1960s the structure was elucidated after a joint effort by several groups.[17] The natural product, (−)-anisomycin (**29a**), was found to block peptide bond formation specifically in eukaryotic ribosomes, and this made it a valuable tool in molecular biology.[18] In addition to its fungicidal activity,[15,18] anisomycin and some of its derivatives display high in vitro antitumor activity.[19] This diverse biological activity of anisomycin has stimulated many scientists to develop new routes for its synthesis, both in racemic and in enantiopure form.[20]



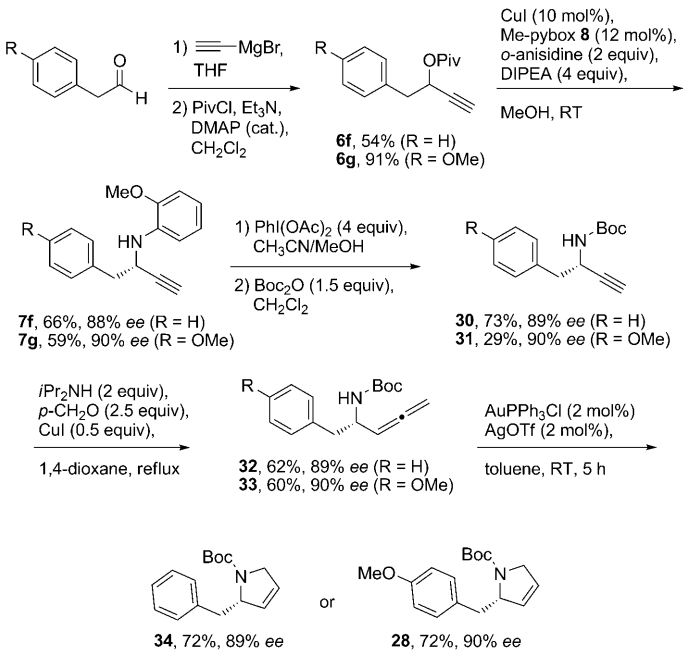
Retrosynthetically, anisomycin could be prepared from the 3,4-dehydropyrrolidine **28**, as described by Jegham and Das.[19d,k] To produce **28** from a starting propargylic amine would afford a formal synthesis of (+)-anisomycin (**29b**) now based on the enantioselective copper-catalysed propargylic amination. During the last five years the use of gold complexes in catalytic chemical transformations has undergone extensive growth.[21] Gold catalysis provides a new synthetic pathway by which to construct otherwise difficult to achieve complex chemical architectures in a mild manner. We envisaged that the 3,4-dehydropyrrolidine ring could be accessible through gold-catalysed ring closure of an aminoallene derived from an *N*-Boc-protected propargylic amine (Scheme 7). Access to this aminoallene could be provided



Scheme 7. Retrosynthetic scheme for the synthesis of 3,4-dehydropyrrolidines.

by the Crabbé reaction. Crabbé and co-workers found that terminal alkynes react with paraformaldehyde and diisopropylamine in the presence of copper(I) to form allenes.[22]

The enantioselective copper-catalysed propargylic amination reaction provided the benzyl-substituted propargylic amines **7f** and **7g** (Scheme 8) in good yields and with high



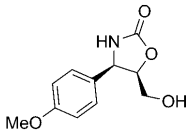
Scheme 8. Synthesis of *N*-Boc-protected 3,4-dehydropyrrolidines.

ee values. Even after prolonged reaction times no full conversion of the starting material was observed, which may be ascribed to catalyst deactivation. We were able to recover the starting materials together with the desired products. Oxidative removal of the anisidyl moiety of **7f** with iodobenzene diacetate followed by treatment with di-*tert*-butyl dicarbonate gave the Boc-protected propargylic amine **30** in good overall yield. Surprisingly, application of the same procedure to **7g** gave **31** 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. Subsequent subjection to Crabbé reaction conditions provided the allenic amines **32** and **33** in reasonable yields. The optical rotation of the allene **32** ($[\alpha]_D^{24} = +16$, $c = 1.3$, $CHCl_3$) was in good agreement with the literature value[28] ($[\alpha]_D^{26} = +20.0$, $c = 0.274$, $CHCl_3$) for the enantiopure compound. In a first cyclisation attempt with **32**, catalysed by a cationic gold complex prepared in situ, compound **34** was obtained in high yield (86%). In another attempt the starting material was totally recovered, indicating that the reaction was difficult to reproduce. It seems that on small scales the reaction is sensitive to traces of water and/or air oxygen, probably due to the very hygroscopic AgOTf. Altogether, the two *N*-Boc-protected 3,4-dehydropyrrolidines **34** and **28** were ob-

tained in satisfactory yields (72%), although higher conversions should be feasible.

With the synthesis of **28** we accomplished the formal synthesis of (+)-anisomycin **29b** in only seven steps. It is also noteworthy that the substituent at the 2-position can be varied easily, as is illustrated by the synthesis of **34**, allowing facile synthesis of anisomycin analogues.

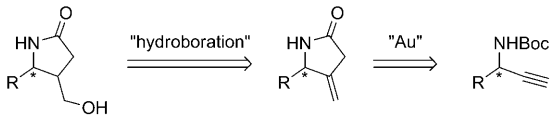
Cytoxazone: Since the isolation and structural elucidation of (−)-cytoxazone (**35**) by Osada and co-workers in 1998,[23] several groups have published total syntheses of this novel cytokine modulator.[24] The compound was isolated from cultures of Streptomyces species and interferes with the production of cytokines IL4 and IL10 and IgG through selective inhibition of the signalling pathway in Th2 cells.



(−)-cytoxazone (**35**)

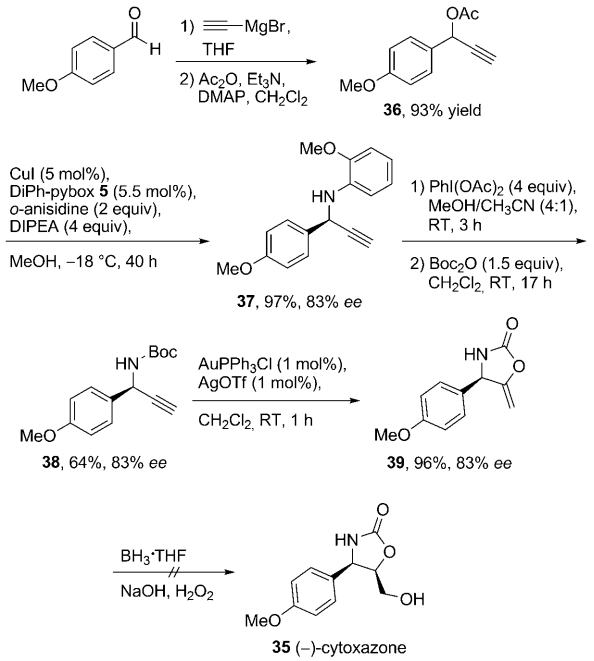
We envisioned a short synthetic route to oxazolidinones such as (−)-cytoxazone (**35**) by gold-catalysed cyclisation, as described by Shin et al.,[24d] of *N*-Boc-protected propargylic amines, prepared by enantioselective copper-catalysed propargylic amination (Scheme 9). Hydroboration would afford (−)-cytoxazone (**35**), or other interesting oxazolidinones.

As shown in Scheme 10, our new amination methodology was applied for a short synthesis of (−)-cytoxazone. Commercially available *p*-anisaldehyde was converted into the



Scheme 9. Retrosynthetic scheme for the synthesis of oxazolidinones.

propargylic acetate **36** upon treatment with ethynylmagnesium bromide and subsequent acetylation. The enantioselective copper-catalysed propargylic amination gave the propargylic amine **37** in high yield and enantioselectivity. After removal of the anisidyl moiety with iodobenzene diacetate, the primary amine was treated with di-*tert*-butyl dicarbonate to afford the Boc-protected propargylic amine **38** in good overall yield. At this point the cyclisation, catalysed by a cationic gold(I) complex prepared in situ from [Au(PPh_3)Cl] and AgOTf in toluene as reported by Shin et al.,[24d] provided us with the oxazolidinone **39** in excellent yield. The hydroboration of the double bond of **39**, although successful according to Shin et al., did not afford (−)-cytoxazone (**35**) in good yield in our hands and only traces of the desired compound were observed by NMR spectroscopy and LC-MS analysis of the crude product. Thus, although the total synthesis of (−)-cytoxazone (**35**) regrettably ended before the intended last step of the sequence, we had accomplished a short synthesis of enantioenriched oxazolidinones, such as **39**, in high overall yields (six steps to **39** in 55% yield).



Scheme 10. Formal total synthesis of (−)-cytoxazone.

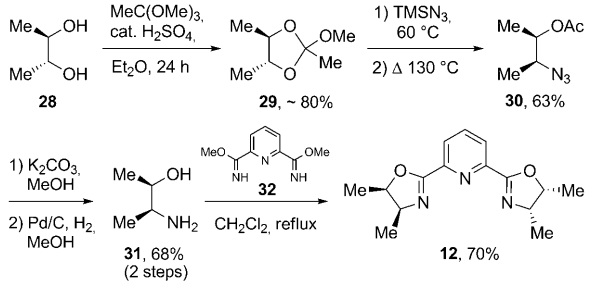
Conclusion

Several propargylic amines with non-aromatic side chains were prepared in reasonable to high yields (59–96%) and optical purities (64–90% *ee*) from a variety of readily available propargylic esters through the enantioselective copper-catalysed propargylic amination reaction. In addition, 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 yields and with high optical purities. 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. Indole and *N*-methylindole especially stand out in this series, giving high yields (up to 91%) and enantioselectivities (up to 98% *ee*). Some of the propargylic amines synthesised by our new protocol were converted into α-amino acid derivatives and further elaborated to provide formal total syntheses of the biologically active compounds (+)-anisomycin and (−)-cytoxazone.

Experimental Section

The Experimental Section gives general procedures and some examples. Further procedures and spectroscopic data for the new compounds described are collected in the Supporting Information, together with the general remarks and equipment used.

Synthesis of the ligand 12: The ligand **12** was prepared as shown in Scheme 11.



Scheme 11. Preparation of the ligand **12**.

(4*R*,5*R*)-2-Methoxy-2,4,5-trimethyl-1,3-dioxolane (29): 1,1,1-Trimethoxyethane (5.6 mL, 44 mmol) and a catalytic amount of H_2SO_4 (60 μL, 1.1 mmol) were added at 0 °C to a solution of commercially available (2*R*,3*R*)-butane-2,3-diol (2.0 mL, 22 mmol) in freshly distilled Et_2O (30 mL). The mixture was stirred for 24 h, being allowed to warm to room temperature. After addition of Et_3N (2 mL), the reaction mixture was poured into saturated aqueous $NaHCO_3$ (100 mL) and extracted three times with Et_2O (50 mL). After evaporation of the solvent, the crude product **29** was obtained and used in the next step without further purification (contains 1,1,1-trimethoxyethane and triethylamine). ^{1}H NMR (400 MHz): $\delta = 3.88$–3.85 (m, 1H), 3.77–3.72 (m, 1H), 3.31 (s, 3H; OCH_3), 1.56 (s, 3H; CH_3), 1.33 (d, $J = 6.0$ Hz, 3H), 1.27 ppm (d, $J = 6.0$ Hz, 3H).

(2*R*,3*S*)-3-Azidobutan-2-yl acetate (30):[25] Trimethylsilyl azide (10 mL) was added to the crude product **29** (5.5 g, ≈50% w/w pure, max. 19.4 mmol). The mixture was warmed for 7 h at 60 °C. After full conversion of the starting material (monitoring by NMR spectroscopy), the mixture was heated for 13 h at 130 °C, turning red. NMR analysis indicated the formation of **30** and the evaporation of most other reagents. Flash chromatography (petroleum ether (PE)/EtOAc 3:1) gave a clear yellowish liquid (2.01 g, 66%). ^{1}H NMR (400 MHz): $\delta = 4.95$–4.90 (m, 1H), 3.67–3.60 (m, 1H), 2.10 (s, 3H; OAc), 1.26 (d, $J = 6.8$ Hz, 3H), 1.25 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz): $\delta = 170.3$, 72.8, 60.0, 20.1, 15.1, 14.9 ppm; FTIR (film): $\tilde{\nu} = 2109$ (s, azide), 1736 cm^{-1} (s).

(2*R*,3*S*)-3-Aminobutan-2-ol (31):[25] K_2CO_3 (excess, 8.3 g, 60 mmol) was added to a solution of **30** (2.00 g, 12 mmol) in MeOH (120 mL). After the system had been stirred for 2 h at room temperature, the MeOH was evaporated. The residue was extracted with Et_2O (3×25 mL). Evaporation of the Et_2O fractions gave a clear yellowish liquid (1.23 g, 89%), which was further purified by flash chromatography (PE/EtOAc 4:1) to afford the azido alcohol (1.22 g, 88%): $[\alpha]_D^{20} = +59$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 3.86$–3.79 (m, 1H), 3.60–3.54 (m, 1H), 1.67 (br s, 1H; OH), 1.27 (d, $J = 6.8$ Hz, 3H), 1.21 ppm (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (101 MHz): $\delta = 70.2$, 62.8, 18.4, 13.9 ppm; FTIR (film): $\tilde{\nu} = 3371$ (br s, OH), 2097 cm^{-1} (s, azide).

Pd/C (10%, w/w, 0.14 g) was added to a solution of the azido alcohol (300 mg, 2.7 mmol) in MeOH (3 mL). After stirring for 5 h at room temperature under H_2 (balloon), the reaction mixture was filtrated over celite and the celite was rinsed with some fresh MeOH. Subsequent evaporation of the MeOH gave the amino alcohol **31** as a colourless oil (0.18 g, 75%). ^{1}H NMR (400 MHz): $\delta = 3.73$–3.67 (m, 1H), 3.02–2.95 (m, 1H), 1.95 (br s, 3H; NH_2/OH), 1.13 (d, $J = 6.4$ Hz, 3H), 1.05 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (101 MHz): $\delta = 70.3$, 62.8, 18.4, 13.9 ppm; FTIR (film): $\tilde{\nu} = 3400$ cm^{-1} (br s, NH_2/OH).

General method for the synthesis of the non-commercially available pybox ligands from amino alcohols[26,27]

2,6-Bis[(4*S*,5*R*)-4,5-dimethyl-4,5-dihydrooxazol-2-yl]pyridine (12): The amino alcohol **31** (180 mg, 2.0 mmol) was added to a suspension of dimethyl pyridine-2,6-bis(carbimidate)[28] (**32**, 193 mg, 1.0 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at reflux for 18 h. After evaporation of solvent, the residue was purified by flash chromatography (CH_2Cl_2 with 1% Et_3N to CH_2Cl_2 with 1% Et_3N and 1% MeOH) to afford the DiMe-pybox (**12**) ligand as a white powder (196 mg, 72%): $[\alpha]_D^{20} = -172$ ($c = 0.5$, $CHCl_3$); ^{1}H NMR (400 MHz): $\delta = 8.14$ (d, $J = 7.8$ Hz, 2H), 7.84 (d, $J = 7.8$ Hz, 1H), 4.96 (dq, $J = 6.6$ Hz, 9.3 Hz, 2H), 4.38 (dq, $J = 7.0$ Hz, 9.3 Hz, 2H), 1.40 (d, $J = 6.6$ Hz, 6H), 1.25 ppm (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (101 MHz): $\delta = 162.0$, 147.5, 137.3, 125.6, 80.0, 63.9, 15.7, 15.0 ppm; HRMS (FAB+) *m/z* calcd: 274.1556 $[M+H]^+$; found: 274.1557.

General method for the synthesis of propargylic acetates

The aldehyde (or ketone) (7.3 mmol) was dissolved in dry THF (20 mL) and added at 0 °C to a solution of ethynylmagnesium bromide in THF (0.5 M in THF, 22.0 mL, 11.0 mmol). After 3 h the reaction mixture was quenched in a mixture of saturated NH_4Cl solution (50 mL) and ice (50 mL). After the evaporation of THF, diethyl ether (50 mL) was added. The organic and water layer were separated and the organic layer was washed with saturated NaCl solution (50 mL). After separation of phases the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was used without further purification in the next step.

A solution of the propargylic alcohol (max. 7.3 mmol), acetic anhydride (0.9 mL, 9.5 mmol) and triethylamine (1.3 mL, 9.5 mmol) in dry CH_2Cl_2 (20 mL) was stirred overnight at room temperature. If necessary a catalytic amount of *N*-dimethylaminopyridine (DMAP) was added to achieve total conversion. CH_2Cl_2 was evaporated with a laboratory evaporator. The mixture was purified by silica gel column chromatography.

1-Phenylprop-2-ynyl acetate (2a):[29] Acetic anhydride (1.0 mL, 11 mmol) was added under nitrogen to a solution of commercially available 1-phenylprop-2-ynyl alcohol (1.0 mL, 8.2 mmol) in dry CH_2Cl_2 (20 mL). After addition of Et_3N (1.5 mL, 11 mmol) the solution was stirred at ambient temperature for 21 h. The reaction mixture was concentrated under vacuum and the product **2a** was obtained after column chromatography (CH_2Cl_2/PE 5:1) as a colourless liquid (1.37 g, 96%). ^{1}H NMR (400 MHz): $\delta = 7.55$–7.52 (m, 2H; *m*-Ar), 7.42–7.37 (m, 3H; *o*,*p*-Ar), 6.45 (d, $J = 2.2$ Hz, 1H; CH), 2.66 (d, $J = 2.3$ Hz, 1H; C≡CH), 2.12 ppm (s, 3H; OAc).

General Procedure A—propargylic amination in the presence of the ligand 5

Copper iodide (3.8 mg, 0.020 mmol) and 2,6-bis[(4*R*,5*S*)-4,5-diphenyl-4,5-dihydrooxazol-2-yl]pyridine (**5**, 12.5 mg, 0.024 mmol) were suspended in methanol (1.4 mL). The mixture was stirred for 20 min before addition of a solution of the propargylic acetate (0.20 mmol) in methanol (0.3 mL). The suspension was cooled to −20 °C. After 10 min of stirring at −20 °C, a cooled 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 the reaction was complete the mixture was allowed to warm to room temperature and concentrated in vacuo. Silica gel chromatography gave the pure propargylic amine.

General Procedure B—propargylic amination in the presence of ligands 8 or 12

See General Procedure A. In this procedure, the pybox ligands **8** or **12** were used instead of ligand **5**. The reaction mixture was stirred at ambient temperature (18–25 °C) and the ligand dissolved in methanol, together with the CuI, to form a clear red solution.

(*S*)-2-Methoxy-*N*-(oct-1-yn-3-yl)aniline (7a): General Procedure B was followed. Compound **6a** (34 mg, 0.20 mmol) was added to the catalyst solution before addition of the *o*-anisidine/DIPEA mixture. After the mixture had been stirred for 24 h, concentration and silica gel chromatography (CH_2Cl_2/PE 1:1) afforded the product **7a** as a colourless oil (35 mg, 76% yield, 66% *ee*): $[\alpha]_D^{20} = -85$ ($c = 0.5$, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6×250 mm), heptane/*i*PrOH 98:2, 1.0 mL min^{-1}, $\lambda = 254$ nm: 5.7 min (major isomer) and 6.8 min (minor isomer). ^{1}H NMR (400 MHz): $\delta = 6.93$–6.89 (m, 1H), 6.82–6.72 (m, 3H), 4.34 (br s, 1H; NH), 4.10 (br, 1H; CH), 3.86 (s, 3H; OMe), 2.22 (d, $J = 2.0$ Hz, 1H; C≡CH), 1.87–1.81 (m, 2H), 1.60–1.56 (m, 2H), 1.39–1.34 (m, 4H), 0.95–0.91 ppm (m, 3H; CH_3); ^{13}C NMR (101 MHz): $\delta = 147.2$, 136.5, 121.2, 117.6, 111.4, 109.7, 85.0, 70.6, 55.5, 45.2, 35.8, 31.6, 25.8, 22.7, 14.2 ppm; FTIR (film): $\tilde{\nu} =$ 3408 (w), 3290 (m), 2934 (s), 2860 (m), 1603 (m), 1513 (s), 1456 (m), 1428

(m), 1248 (s), 1222 (s), 1030 cm^{-1} (m); HRMS (FAB+): *m/z* calcd: 232.1701 $[M+H]^+$; found: 232.1697.

General method for the oxidative removal of the anisidyl moiety

(*S*)-*tert*-Butyl 4-methylpent-1-yn-3-ylcarbamate (27): A solution of **7d** (197 mg, 0.97 mmol) in acetonitrile (2.5 mL) was added by syringe pump over 30 min at room temperature to a solution of $PhI(OAc)_2$ (1.25 g, 3.88 mmol) in methanol (10 mL). After the addition, the reaction mixture was stirred for another 2 h, followed by addition of aqueous HCl (1.0 M, 10 mL). The mixture was stirred for 1.5 h. Afterwards, the mixture was extracted four times with CH_2Cl_2 (8 mL). The organic layers were backwashed once with aqueous HCl (0.1 M, 10 mL). The combined water layers were neutralised by addition of solid K_2CO_3 and a solution of Boc_2O (635 mg, 2.9 mmol) in CH_2Cl_2 (10 mL) was added. The biphasic mixture was basified to pH 11 by K_2CO_3 (s) addition and stirred for 17 h. The layers were separated and the water layer was extracted once with CH_2Cl_2 (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated to dryness. Silica gel column chromatography (CH_2Cl_2) gave **27** in good yield (145 mg, 76% yield, 82% *ee*): $[\alpha]_D^{20} = -52$ ($c = 0.5$, $CHCl_3$); lit.[13] ($[\alpha]_D^{20} = -59.9$, 96% *ee*); ^1H NMR (400 MHz): $\delta =$ 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 ppm (d, $J = 6.8$ Hz, 6H). Data correspond with the literature.[13c]

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