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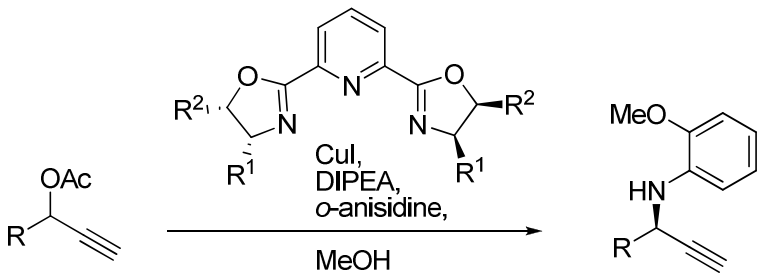
CHAPTER 3

Enantioselective Copper-Catalyzed Propargylic Amination*



ABSTRACT: *A proper copper catalyst* with a chiral pyridine-2,6-bisoxazoline (pybox) ligand was used to convert a variety of propargylic acetates with different side chains (R = Ar, Bn, Alkyl) into their amine counterparts in very high yield and with good selectivity (up to 88% *ee*). (see scheme; DIPEA=diisopropylethylamine).

* Part of this chapter has been published: Detz, R. J.; Delville, M. M. E.; Hiemstra, H.; van Maarseveen, J. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 3777-3780.

3.1 INTRODUCTION

3.1.1 CHIRAL CLICKPHINE

Since the pioneering work of Noyori, Knowles, and Horner in the late 1960s,[1] much progress has been made in the field of *asymmetric* transition metal catalysis. This allowed the syntheses of many different enantiomerically pure chemicals, but the quest for new catalysts to meet synthetic challenges continues. Having established a practical route for the synthesis of achiral ClickPhine P,N ligands,[2] our next objective was the introduction of a chiral center enabling us to perform asymmetric catalysis. Taking into account the structure of ClickPhine, there are roughly three ways of introducing chirality into the ligand.

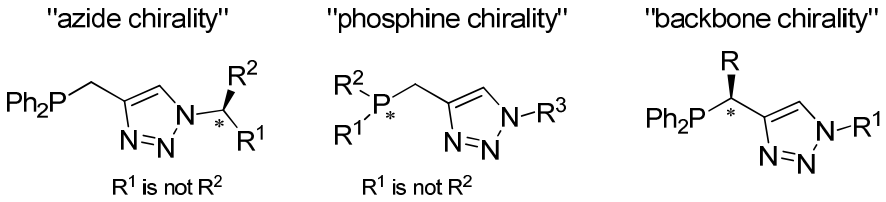
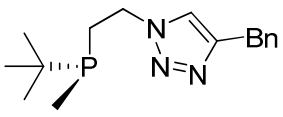


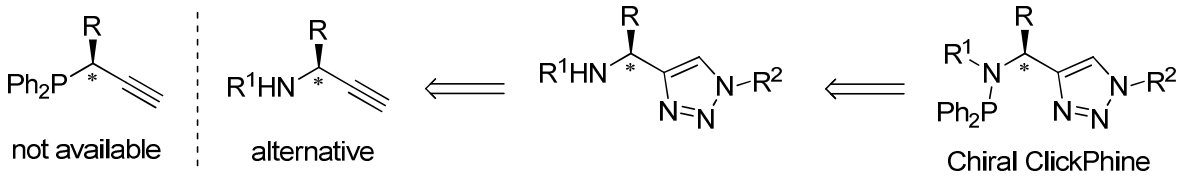
Figure 3.1 Three different types of chirality in ClickPhine

The first and most simple way, is the use of a chiral azide (Figure 3.1). The synthetic route towards this type of chirality is straightforward, but an obvious disadvantage is the fact that this stereocenter is far away from the catalytic center. Another opportunity is a chiral phosphorus atom. Now the chiral center is in close proximity to the reaction center. This idea was taken up by Kann and co-workers.[3] They made a library of P-chirogenic P,N ligands, called ChiraClick ligands, and screened some in the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate in THF. While in most cases the conversion was good to quantitative, the enantioselectivity was low, generally in the range of 8-12%.



ChiraClick
Kann *et al.* (2006)

Utilization of a chiral backbone is the third possibility and to our opinion a very promising and certainly challenging route. As a consequence, the synthesis of a chiral backbone precursor became our primary topic of interest. The chiral propargylic phosphine depicted in Scheme 3.1 closely resembles the propargylic phosphine used in the achiral ligands. The synthesis of this type of chiral propargylic phosphine is unfortunately not well documented in literature and we therefore choose for another target molecule.

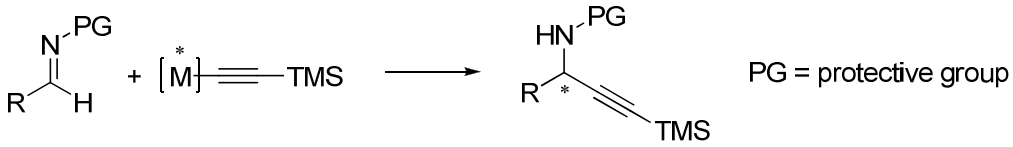


Scheme 3.1 From chiral propargylic amines to chiral ClickPhine ligands

Altering the original structure of the achiral P,N ligand was in this way unavoidable. We envisaged that a chiral propargylic amine would be a suitable starting material for the synthesis of enantiopure ClickPhine ligands. This amine could, after the copper-catalyzed azide-alkyne cycloaddition, be decorated with a phosphine arriving at triazole-based aminophosphine P,N ligands. Besides the nitrogen-bonded phosphorus, these ligands will have a larger bite angle, since the bridge between the coordinating N- and P-atom is one atom longer, giving a six-membered ring structure in a metal complex. To retain the simplicity of the synthesis and modification of the ligands, the route to the chiral propargylic amine should be straightforward and short.

3.1.2 Chiral Propargylic Amines

During the last decade, considerable progress has been made in the asymmetric synthesis of chiral propargylic amines. The most important synthetic route is still based on the enantioselective addition of terminal alkynes to imines (Scheme 3.2).[4]

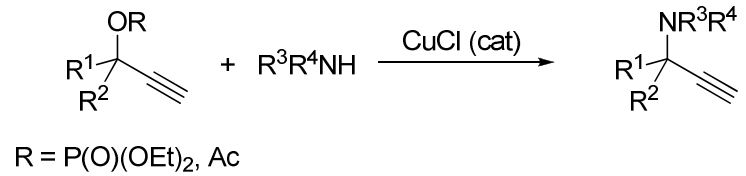


Scheme 3.2 Addition of terminal alkynes to imines

To broaden the scope and applicability of methods for the preparation of optically active propargylic amines, we envisioned the direct functionalization of the propargyl moiety. Products with a terminal acetylene would enable direct further functionalization, *e.g.* the 1,3-dipolar cycloaddition reaction with an azide, without the need of prior removal of the commonly used trimethylsilyl protecting group.

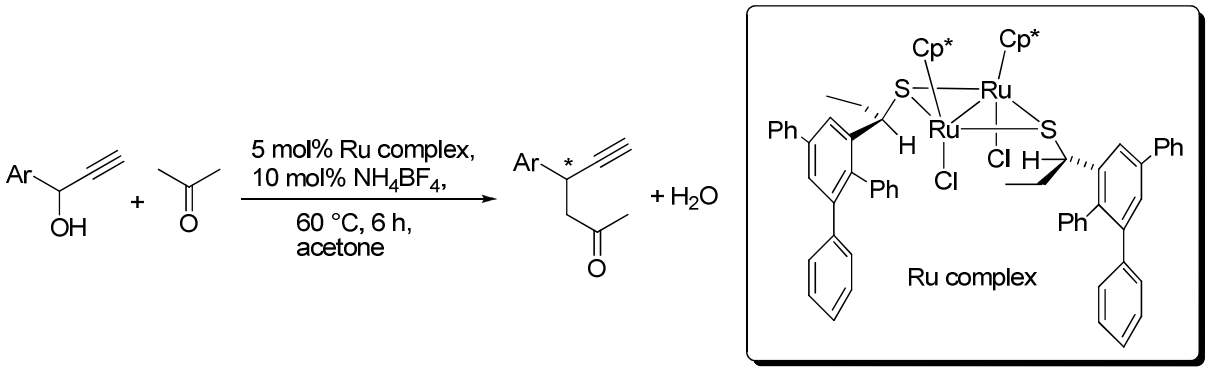
Propargylic substitution with transition metals is a poorly developed reaction type, in contrast to allylic substitution (see Chapter 1, §1.3) for a detailed overview about catalyzed propargylic substitution). A fundamental substitution reaction of propargylic alcohol derivatives is the Nicholas reaction, which occurs via a stoichiometric cobalt-alkyne complex.[5] In this reaction a broad range of nucleophiles (carbon, oxygen, nitrogen, and sulfur) can react with the dicobalt octacarbonyl-stabilized propargylic cation. Nishibayashi *et al.* reported a ruthenium-catalyzed process in which a wide variety of nucleophiles, such as alcohols, amides, thiols, phosphines, and amines, can be used. Nevertheless, amines of high basicity were not applicable under these conditions.[6] Although successful with alcohols and satisfactory with amides, the $TiCl_4$-mediated substitution reaction of propargylic esters did not

proceed with primary and secondary amines.[7] Murahashi and co-workers demonstrated the highly efficient preparation of several propargylic amines by a copper-catalyzed substitution reaction (Scheme 3.3).[8] Rhenium, gold, rhodium, and iron complexes were also reported recently to be effective catalysts for propargylic amination.[9]



Scheme 3.3 Murahashi's copper-catalyzed propargylic amination

Remarkably, enantioselective examples of propargylic substitution reactions are rare.[10] Nishibayashi and co-workers 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 94% ee, Scheme 3.4). However, other nucleophiles did not lead to good enantioselectivity. Because these are as far as we know the only literature examples of asymmetric propargylic substitutions, the asymmetric propargylic amination reaction was unknown, when we started our investigations.



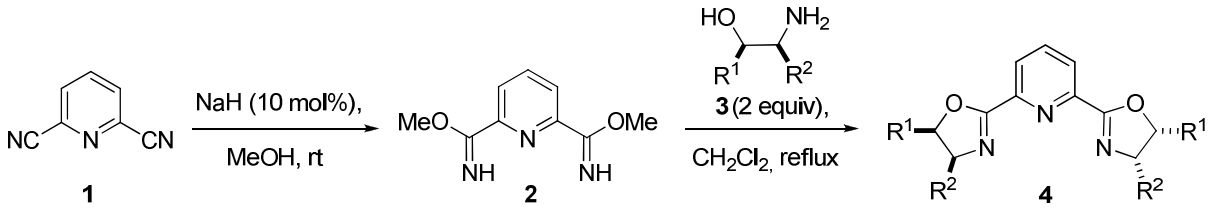
Scheme 3.4 Asymmetric propargylic substitution by a chiral ruthenium complex

3.2 Enantioselective Propargylic Amination

3.2.1 Pyridine-2,6-Bisoxazolines

Inspired by the results of Murahashi and co-workers, we decided to study an enantioselective version of the copper-catalyzed propargylic amination of propargylic esters. The correct choice of the chiral ligand is essential for the selectivity and reactivity, and also important, for the employability of the method. A commercially available set of ligands is preferred, but if modification is required, the synthetic route should be short. The pyridine-2,6-bisoxazoline (pybox) ligands address both of these criteria and, compared to phosphorus containing ligands, are stable towards air oxidation. Copper(I) complexes of chiral pybox

ligands are well established in asymmetric catalysis.[11] For our studies, a collection of pybox ligands was synthesized.



Scheme 3.5 Synthesis of pybox ligands

The synthetic route to the pybox ligands (Scheme 3.5) was published by Müller and Bolèa in 2001 and consists of only two practical steps.[12] Commercially available pyridine-2,6-dicarbonitrile **1** was quantitatively converted to diimidate **2** with a catalytic amount of NaH in methanol. Condensation of crude diimidate **2** with amino alcohol **3** in refluxing CH_2Cl_2 afforded pybox ligand **4** in good yield after chromatography or recrystallization. *Via* this procedure we synthesized pybox ligands **4a**, **4f**, and **4h**, and these, together with five commercially available pybox ligands (**4b**-**e**, **4g**), were subjected to our screening conditions for the copper(I)-catalyzed propargylic amination (Figure 3.2).

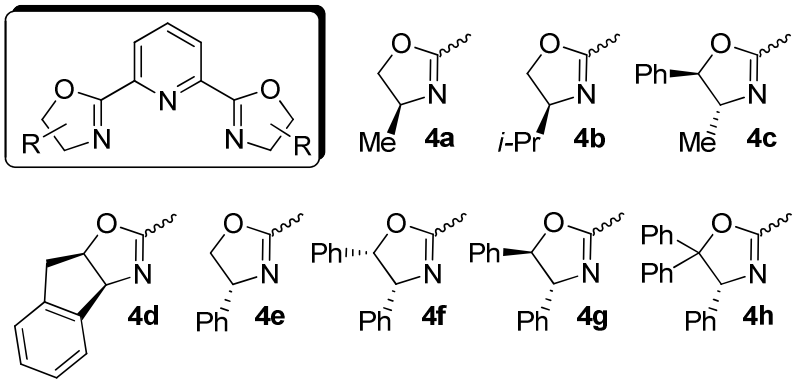
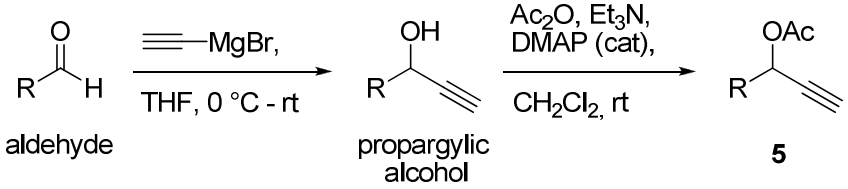


Figure 3.2 Set of pybox ligands

3.2.2 SUBSTRATE SYNTHESIS

As substrates for the propargylic amination we chose for propargylic esters (**5**), like Murahashi,[8] and in particular the most simple type: α-branched propargylic acetates. These substrates were either prepared by acetylation of commercially available propargylic alcohols or obtained from the corresponding aldehydes via addition of ethynyl magnesium bromide and subsequent esterification (Scheme 3.6).



Scheme 3.6 Synthesis of substrates for the propargylic amination

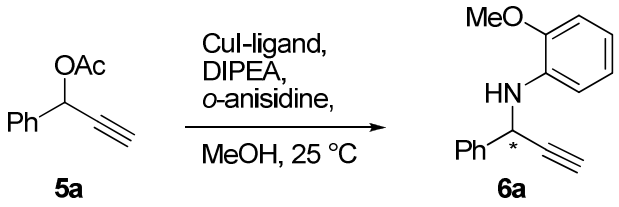
3.3 OPTIMIZATION STUDY

The ligand screening conditions were chosen after some initial experiments based on Murahashi's conditions. These experiments showed that, after treatment of 1-phenylprop-2-ynyl acetate with aniline at 50 °C in THF, and using CuI as the catalyst, some product was formed. Addition of diisopropylethylamine (DIPEA) further increased the yield and allowed a lower reaction temperature. When using methanol as the solvent a faster and cleaner reaction was observed. The synthetic relevance of the procedure would be much greater if it would lead to a primary propargylic amine and therefore functionalization of the nitrogen with a removable group would be an advantage. For this purpose we decided to use *o*-anisidine instead of aniline, because oxidative removal of the *o*-anisidyl group is well documented.[13]

3.3.1 LIGAND SCREENING

With our set of chiral pybox ligands and the pre-optimized reaction conditions in hand, we could start a screening in an attempt to induce enantioselectivity for the amination of racemic 1-phenylprop-2-ynyl acetate (**5a**). Initial experiments with pybox ligands **4a-e** were encouraging (Table 3.1, entries 1-5). In all cases propargylamine **6a** was obtained in high yield, and asymmetric induction was observed, although to a low extent.

Table 3.1 Survey of pybox ligands for the propargylic amination.[a]



5a **6a**

entry	ligand	yield (%)[b]	config.[c]	*ee* (%)[d]
1	**4a**	94	*R*	25
2	**4b**	93	*R*	17
3	**4c**	97	*R*	12
4	**4d**	74	*R*	28
5	**4e**	99	*S*	42
6	**4f**	97	*S*	76
7	**4g**	97	*S*	19
8	**4h**	97	*S*	61

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and the ligand (0.024 mmol) were stirred in methanol (2 mL) at 25 °C. Reactions were complete within 1 h. [b] Isolated yield after chromatography. [c] The absolute configuration was determined by comparison of the optical rotation with a literature value.[13] [d] Enantioselectivity is determined by chiral HPLC of the isolated product.

Gratifyingly, the use of ligand **4f**, which has the aromatic substituents in a *cis* relationship at the 4- and 5-positions of the two oxazoline rings, led to an increase in enantioselectivity (entry 6). The use of ligands **4g** or **4h** did not lead to a further improvement (entries 7 and 8). As could be expected, when the catalysis was performed with the other enantiomer of the pybox ligand (eg. **ent-4f**) the reaction gave access to the opposite enantiomer of the product (**6a**). The absolute configuration of amine **6a** was determined by comparison of the optical rotation with the literature value.[13] We assumed that the absolute configuration of comparable products obtained by this reaction was the same.

3.3.2 VARYING THE COPPER SALT

Further optimization of the reaction conditions with ligand **4f** revealed that other copper salts such as CuCl, $[Cu(CH_3CN)_4]PF_6$, and CuOTf•benzene gave similar results (Table 3.2, entries 1-4). Interestingly, also copper(II) acetate gave the product in high yield and with good selectivity (entry 5). The reaction mixture with CuI was more homogeneous than with CuCl and this, together with the slightly higher yield, led us decide to continue the screening with CuI as the copper source.

Table 3.2 Effect of the Cu salt on the propargylic amination of **5a** with pybox ligand **4f**.[a]

entry	Cu salt	yield (%)[b]	*ee* (%)[c]
1	CuI	97	76
2	CuCl	93	77
3	$[Cu(CH_3CN)_4]PF_6$	76	74
4	CuOTf•benzene	99	73
5	$Cu(OAc)_2$	99	73

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), Cu salt (0.02 mmol), and **4f** (0.024 mmol) were stirred in methanol (2 mL) at 25 °C. Reactions were complete within 1.5 h. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. Tf = trifluoromethanesulfonyl

3.3.3 SOLVENT SCREENING

The reaction showed to be highly solvent dependent (Table 3.3). High enantioselectivity and a high reaction rate were only observed with polar protic solvents (entries 1-4), the best being methanol. The conversions in some typical organic solvents were near quantitative although longer reaction times were required, and the selectivity dropped drastically (entries 5-7). Performing the reaction in an aprotic polar solvent, such as DMSO, resulted in many side products and gave the desired product in only 23% yield (entry 8). The applicability of solvent mixtures was studied too (entries 9-12), and, although the enantioselectivity did not improve, some remarkable observations were made. First of all, the addition of water (entry 9) and even acetic acid (entries 10 and 11) had no negative influence on the yield of the

reaction, underlining the robustness of the reaction. The decrease in enantioselectivity in these reactions is probably caused by a change in basicity due to inactivation of DIPEA, as the *ee* values are in the same range as for the reaction without additional base (Table 3.4, entry 2).

Table 3.3 Effect of the solvent on the propargylic amination of **5a** with pybox ligand **4f**.[a]

entry	solvent	time (h)	yield (%)[b]	*ee* (%)[c]
1	MeOH	1	97	76
2	MeOH (3 Å M.S.)	1	84	72
3	EtOH	1.5	99	60
4	CF_3CH_2OH	1.5	95	74
5	PhMe	25	99	21
6	CH_2Cl_2	25	97	34
7	THF	29	99	36
8	DMSO	1.5	23	58
9	MeOH/H_2O (19:1)	1.5	95	64
10	MeOH/AcOH (9:1)	2.5	99	56
11	CH_2Cl_2/AcOH (100:1)	24	90	23
12	MeOH/CH_2Cl_2 (1:1)	1	99	72
13	$HOCH_2CH_2OH$	24	36[d]	62
14	H_2O	24	59[d]	5

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **4f** (0.024 mmol) were stirred in the indicated solvent (2 mL) at 25 °C. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [d] An extraction step is performed before chromatography.

The solubility of the free ligand **4f** is very low in methanol and no clear solution was obtained during complex formation. These solubility problems could have a negative effect on the enantioselectivity, and therefore, we investigated the use of a mixture of methanol and dichloromethane, in which complex formation was homogeneous (entry 12). The slightly lower enantioselectivity found for this reaction does not totally disapprove our concerns, but shows us that further improvement via this way is unlikely.

We suspected a dependence of the dielectric constant of the solvent on the enantioselectivity of the reaction and two more solvents were investigated to study their influence. In ethylene glycol (entry 13), which has a slightly higher dielectric constant than MeOH, the reaction was

very slow, but the enantioselectivity was comparable with the reaction in ethanol, which has a lower dielectric constant than MeOH. The reaction in water (very high dielectric constant, entry 14), or better on water, was also sluggish and afforded the product in almost racemic form. If there is any dependence of the dielectricity of the solvent on the reaction's selectivity, methanol seems optimal.

3.3.4 BASE DEPENDENCE

The addition of a base seemed to be crucial in terms of both the yield and the selectivity (Table 3.4). At a first glance, the base appeared to be only a rate-accelerating component; however, in its absence the enantioselectivity dropped by 20% (entries 1 and 2). Stronger bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or cesium carbonate, had a detrimental effect on both the yield and the selectivity of the reaction (entry 3 and 4). Better results were obtained using other bases, with the tertiary amines giving the best results (entries 5-8).

Table 3.4 Effect of the base on the propargylic amination of **5a** with pybox ligand **4f**.[a]

entry	base	time (h)	yield (%)[b]	*ee* (%)[c]
1	DIPEA	1	97	76
2	none	4	93	56
3	DBU	0.5	2	7
4	Cs_2CO_3	0.5	8	33
5	NaOAc	2	84	68
6	di-*t*-Bu-Pyr	5	89	57
7	Proton Sponge	2	97	73
8	Et_3N	1	99	75

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), the indicated base (0.80 mmol), CuI (0.02 mmol), and **4f** (0.024 mmol) were stirred in methanol (2 mL) at 25 °C. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product.

3.3.5 TEMPERATURE EFFECTS

At lower temperatures the enantioselectivity was improved further at the expense of an increase in reaction time (Table 3.5). At higher temperature (40 °C, entry 1) the yield slightly decreased probably due to transesterification of the acetate with methanol liberating the propargylic alcohol as a side-product. To avoid cleavage of the acetate group a more hindered leaving group might be used, which will be discussed in the next chapter (Chapter 4, Paragraph 4.4).

Table 3.5 Effect of temperature on the propargylic amination of **5a** with pybox ligand **4f**.[a]

entry	T (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	40	0.5	93	72
2	25	1	97	76
3	0	3	99	82
4	–20	24	97	85
5	–40	48	99	86

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **4f** (0.024 mmol) were stirred in methanol (2 mL) at the indicated temperature. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product.

3.3.6 VARIATION OF THE REACTION STOICHIOMETRY

In an attempt to further improve the enantioselectivity the ratios between the reagents and/or catalyst were varied (Table 3.6). Lowering the amount of catalyst increased the time to achieve full conversion (entries 1, 2 and 6). The enantioselectivity was slightly lower at lower

Table 3.6 Effect of the ratio between the reagents on the propargylic amination of **5a** with pybox ligand **4f**.[a]

entry	Cu salt	time (h)	T (°C)	yield (%)[b]	*ee* (%)[c]
1	CuI (1 mol%)	20	–20	57[c]	82
2	CuI (2 mol%)	20	–20	68[c]	84
3[d]	CuI (2 mol%)	20	–20	n.d.	83
4	CuI (3 mol%)	22	0	n.d.	82
5[e]	CuI (3 mol%)	23	0	n.d.	81
6	CuI (5 mol%)	20	–20	95[c]	85
7	CuI (10 mol%)	24	–20	97	85
8	CuI (10 mol%)	1	25	97	76
9[f]	CuI (10 mol%)	1	25	86	74

[a] Reaction conditions: **5a** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI, and ligand **4f** were stirred in methanol (2 mL), unless noted otherwise. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [c] No full conversion was observed. [d] Reaction performed in 1 mL methanol. [e] Reaction performed with 1.6 mmol of DIPEA. [f] Reaction performed with 0.24 mmol of *o*-anisidine and DIPEA. n.d. = not determined

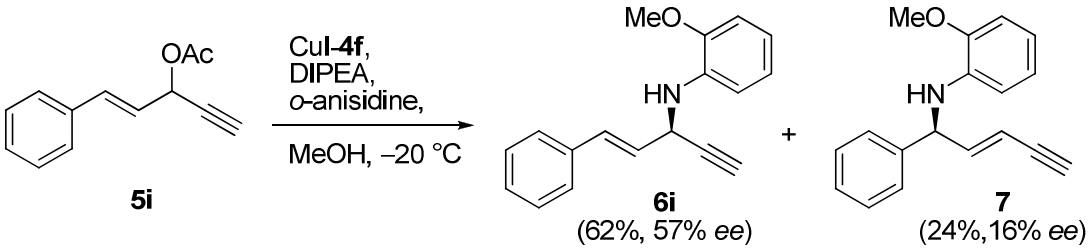
catalyst loadings, although with 5 mol% of catalyst no pronounced difference, compared with 10 mol% of catalyst, was observed (entries 6 vs 7). Doubling the concentration did not show any improvement in the enantioselectivity (entries 2 vs 3). Also, the addition of 8 equivalents of DIPEA (entry 5), instead of 4 equivalents (entry 4), gave no substantial change in the selectivity. Lowering the amount of DIPEA as well as the amount of *o*-anisidine (both 1.2 equiv) in the reaction mixture gave no distinct difference in the enantioselectivity, although the yield was slightly reduced (entries 8 vs 9).

The optimization study revealed that the pre-optimized reaction conditions were already well chosen and that with pybox ligand **4f** at lower temperatures the best results were obtained for substrate **5a**. Addition of base, DIPEA, did improve both the reaction rate as well as the enantioselectivity. At lower catalyst loading the yield slightly decreased while the selectivity remained unchanged. This finding is especially important if reactions will be scaled up to grams or even kilograms.

3.4 SUBSTRATE SCOPE

Having established an optimal reaction protocol, we explored the scope and the generality of the method for different propargylic acetates (Table 3.7). All substrates with an aromatic group at the propargylic position were converted into the corresponding amine in high yield (80-97%) and with high enantioselectivity (74-88% *ee*; entries 1-8). Slightly higher *ee* values were observed with more electron-rich aromatic substrates (compare entries 2 and 3, and entries 4 and 5). The pyridyl containing substrate **5f**, which could interfere with the ligand upon coordination to the copper with the basic pyridyl nitrogen atom, was also converted into the amine with high enantioselectivity (entry 6). Single step recrystallization of propargylic amines **6g** and **6h**, containing a naphthyl sidechain, afforded essentially enantiomerically pure compounds (entries 7 and 8). Propargylic amine **6a** was more difficult to recrystallize to a single enantiomer. The colorless crystals that formed were identified as a racemate; the propargylic amine **6a** was obtained in almost enantiomerically pure form (99% *ee*) from the mother liquor. Another recrystallization step provided optically pure **6a** in 46% yield.

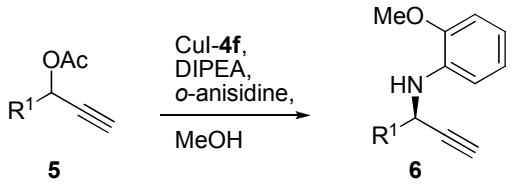
The reaction became more complex when cinnamyl derivative **5i** was used (Table 3.7, entry 9, and Scheme 3.7). In this case, two major products were isolated: **6i** with the amino group at

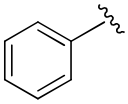
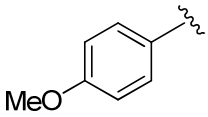
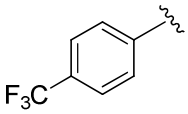
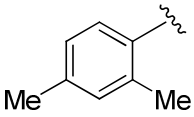
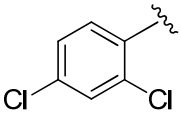
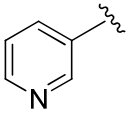
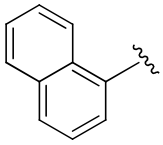
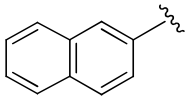
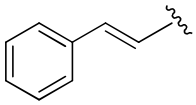
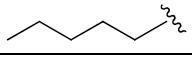


5i **6i** (62%, 57% *ee*) **7** (24%,16% *ee*)

Scheme 3.7 Propargylic amination with cinnamyl derivative **5i**

Table 3.7 Propargylic amination with various propargylic acetates.[a]



entry	R^1	time (h)	product	yield (%)[b]	*ee* (%)[c]
1		21	**6a**	97	85 (99)
2		19	**6b**	97	83
3		18	**6c**	84	80
4		20	**6d**	91	88
5		40	**6e**	88	79
6		23	**6f**	80	74
7		22	**6g**	91	85 (99)
8		23	**6h**	96	86 (99)
9		48	**6i**[d]	62	57
10[e]		24	**6j**	27	40
11[e]		21	**6k**	76	13

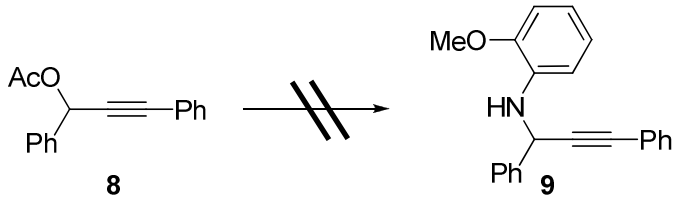
[a] Reaction conditions: propargylic acetate **5** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **4f** (0.024 mmol) were stirred in methanol (2 mL) at −20 °C, unless noted otherwise. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product; the *ee* value after recrystallization is given in brackets. [d] See Scheme 3.7. [e] The reaction was performed at 40 °C.

the propargylic position as expected (62%, 57% ee), and an analogue, **7**, in which the amino substituent is located at the alternative allylic position next to the phenyl moiety (24%, 16% *ee*).

Substrates with aliphatic side chains were less reactive and a higher temperature (40 °C) was necessary for sufficient conversion. At this temperature the rate of transesterification of the acetate with methanol increases which leads to more propargylic alcohol formation, lowering the yield of the propargylic amine. The catalytic process seems to be unsatisfactory with aliphatic substrates: only low enantioselectivity was observed (Table 3.7, entries 10 and 11).

3.4.1 INTERNAL ACETYLENE

As reported by Murahashi and co-workers,[8] no reaction occurred with an internal acetylene **8** (Scheme 3.8). This result serves as evidence for the necessity of the terminal acetylenic hydrogen atom, which is one of the shortcomings of this method. For our purpose, however, the terminal acetylenic hydrogen atom is essential for reaction in the 1,3-dipolar cycloaddition reaction with an azide to arrive at the final P,N ligands.



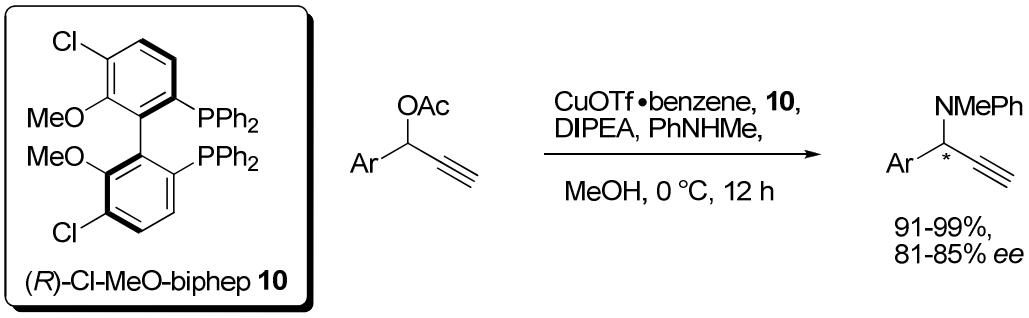
Scheme 3.8 Propargylic amination with internal acetylene **8**

3.4.2 PRACTICAL REMARKS

The method described is highly practical as commercially available reagents and solvents are used. The reaction is robust and the presence of air oxygen and moisture play minor roles. Although most experiments were performed with an excess of base (4 equiv) and *o*-anisidine (2 equiv), it was shown that a slight excess of both reagents (1.2 equiv) also gave good conversion and selectivity (86% yield, 74% ee) at room temperature (Table 3.6, entry 9). An experiment carried out on a 5.0 mmol (substrate) scale proceeded in a similar fashion, even with lower catalyst loading (0.05 equiv).

3.5 RECENT RESULTS FROM THE LITERATURE

With the experience that the ruthenium catalyst system was not suitable for the preparation of optically active propargylic amines, Nishibayashi and his co-workers considered to use another approach, also inspired by the Murahashi method. Shortly after our paper, describing the work collected in this chapter, was accepted, Nishibayashi communicated their achievements to us, resulting in back-to-back publication of our and Nishibayashi's work.[14] Recently, this work on the copper-catalyzed asymmetric propargylic substitution was highlighted by Ljungdahl and Kann.[15] The major difference between Nishibayashi's and our method is the structure of the chiral ligand (Scheme 3.9).



Scheme 3.9 Nishibayashi's enantioselective propargylic amination

Instead of a pybox ligand, they used a chiral diphosphine ligand, (R)-Cl-OMe-biphep **10**, which afforded propargylic amines in yields and with selectivities in the same range as for our method. Interestingly, to obtain high enantioselectivity, the use of a disubstituted amine, *e.g. N*-methylaniline, is required. As a consequence the method is less straightforward for the preparation of primary propargylic amines in high optical purity due to the *N*-Me bond, which is practically impossible to cleave. The cleavage of the anisidyl moiety, used in our method, will be discussed in Chapters 4 and 6.

A disadvantage of both Nishibayashi's and our method is the intolerance for substrates with non-aromatic side chains. In the next part of this chapter, our efforts to improve the enantioselective propargylic amination of propargylic esters bearing aliphatic side chains are disclosed. The efforts made in the field of transition-metal-catalyzed propargylic substitution, and especially the asymmetric examples, were recently highlighted by Ljungdahl and Kann.

3.6 A New Pybox Ligand for New Sustrates

Encouraged by our previous results, we screened some other pybox ligands to see if higher enantioselectivity was obtained for substrate **5k**, bearing a *n*-pentyl group, using the reaction conditions as reported before (Table 3.1). Surprisingly, reaction with pybox ligand **4a** afforded propargylic amine **6k** in good yield and in 66% *ee* at room temperature. To increase the selectivity we envisioned that ligands **4i** and especially **4j** would be worthwhile to test, after the good results obtained with bisfunctionalized ligand **4f** for substrates bearing an aromatic group (Figure 3.3).

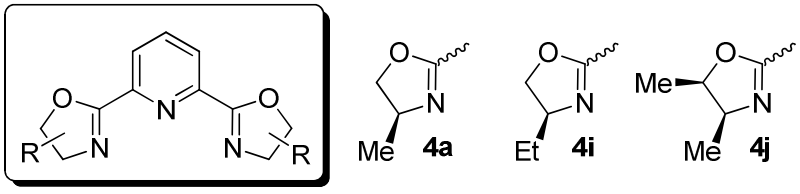
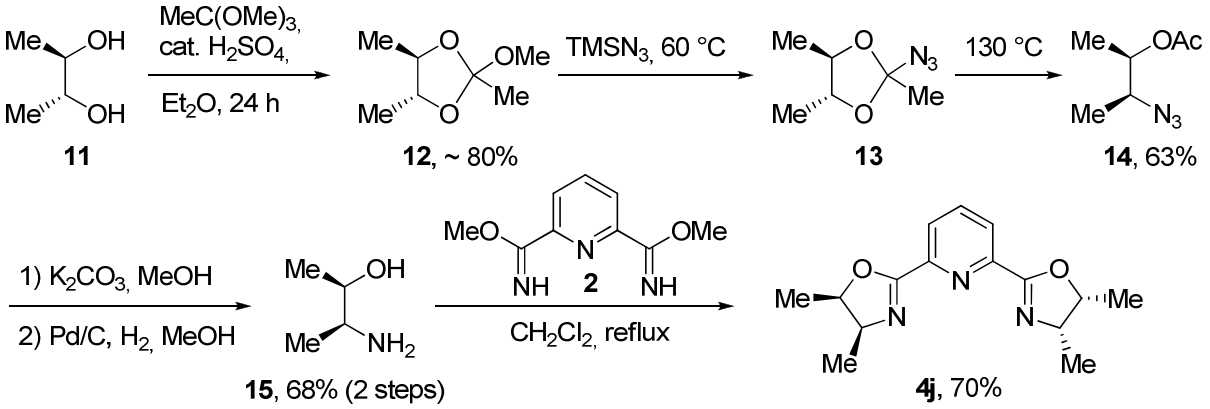


Figure 3.3 More pybox ligands

The chirality of most pybox ligands known in the literature is derived from commercially available enantiopure amino alcohols. The synthesis of ligand **4j** is challenging, because the

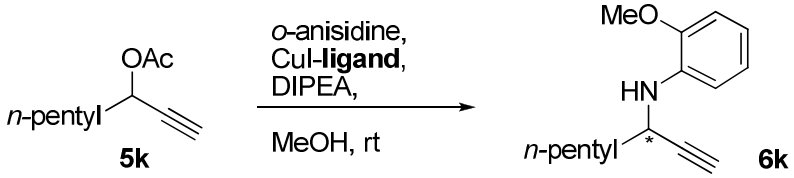
required amino alcohol first had to be synthesized before condensation with the pyridine diimidate **2** (see Scheme 3.5). For the synthesis of amino alcohol **15**, we followed the only published route described by Hartmann and Heine in 1979.[16] Orthoacetate **12** was prepared after treatment of commercially available (*2R*,*3R*)-(−)-2,3-butanediol **11** with trimethyl orthoacetate in diethyl ether in the presence of catalytic sulphuric acid (Scheme 3.10).



Scheme 3.10 Synthesis of pybox ligand **4j**

Stirring crude orthoacetate **12** in azidotrimethylsilane at 60 °C gave intermediate **13**, which was cleanly converted into azido acetate **14** upon heating at 130 °C. Saponification afforded the azido alcohol, which after hydrogenation gave desired amino alcohol **15**. Condensation of **15** with pyridine diimidate **2** afforded the new and promising DiMe-pybox ligand **4j** in good yield after column chromatography.

Table 3.8 Enantioselectivity dependence of ligands for the propargylic amination.[a]

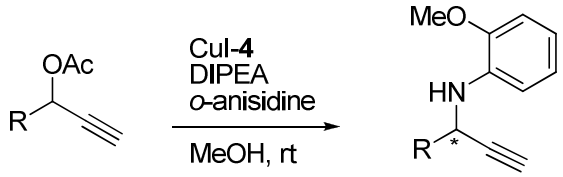


entry	ligand	config.[b]	*ee* (%)[c]	entry	ligand	config.[b]	*ee* (%)[c]
1	**4a**	+	66	6[d]	**4d**	+	21
2	**4i**	+	52	7	**4e**	+	23
3[d]	**4b**	+	22	8	**4f**	–	13
4	**4j**	+	64	9[d]	**4g**	–	21
5	**4c**	+	56	10	**4h**	+	1

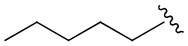
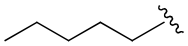
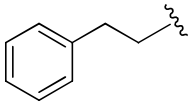
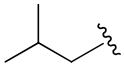
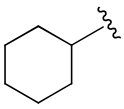
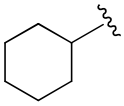
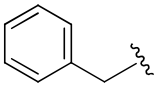
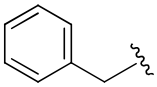
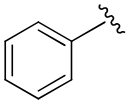
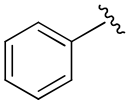
[a] Reaction conditions: **5k** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and ligand (0.024 mmol) were stirred in methanol (2 mL) at room temperature, unless noted otherwise. [b] Configuration is no optical rotation sign, only to illustrate if opposite enantiomers were formed according to chiral HPLC. [c] *Ee* was determined by chiral HPLC. [d] Reaction was performed at 40 °C.

Regrettably, the extra methyl group in the new ligand **4j** gave no higher enantioselectivity (Table 3.8, entry 4). Apparently, the pybox ligand **4a** with the least bulky group was the most selective ligand for this transformation. With this finding at hand, we explored the scope of the enantioselective propargylic amination of other substrates with aliphatic side chains.

Table 3.9 Propargylic amination with various propargylic acetates.[a]



5 **6**

entry	ligand	R	time (h)	product	yield (%)[b]	*ee* (%)[c]
1	**4a**		24	**6k**	76	66
2	**4j**		24	**6k**	67	64
3	**4a**		24	**6l**	84	67
4	**4a**		48	**6m**	80	82
5	**4a**		24	**6j**	77	82
6	**4a**		24	**6n**	96	85
7	**4j**		24	**6n**	63	86
8	**4a**		48	**6o**	66	88
9	**4j**		48	**6o**	60	89
10	**4a**		1	**6a**	94	25
11	**4f**		1	**6a**	97	76

[a] Reaction conditions: propargylic acetate **5** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and pybox ligand (0.024 mmol) were stirred in methanol (2 mL) at room temperature. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product.

3.7 ALIPHATIC SUBSTRATES

The usefulness of the method is greatly enhanced if the procedure can be applied to substrates with aliphatic side chains, which are interesting because of their resemblance with natural α-amino acids. As pybox ligand **4a** gave a reasonable *ee* value for substrate **5k** with a linear aliphatic side chain (Table 3.8, entry 1), it was worthwhile to explore its behavior in the asymmetric synthesis of other, more hindered, propargylic acetates (Table 3.9). In some cases we have also depicted the results obtained when diMe-pybox was used. Phenethyl-substituted propargylic amine **5l** was obtained in comparable yield and selectivity as **5k** (entry 2).
We were pleased to see that more steric hindrance near the reacting center caused an even higher level of asymmetric induction as is shown for products **6j**, **6m**, **6n**, and **6o** (entries 3-6). The importance of the ligand for these type of reactions, is illustrated by comparison of entries 7 and 8: while with diPh-pybox **4f** product **6a** was obtained with 76% *ee*, Me-pybox **4a** gave only 25% *ee*.

3.8 QUATERNARY SUBSTRATES

Interestingly, the procedure is also successful for the amination of quaternary propargylic acetates (Table 3.10). The asymmetric synthesis of these α,α-dibranched propargylic amines is limited to only a few methods affording a narrow set of structural motifs.[17] With our method chiral α,α-dibranched propargylic amines become available. Especially products such as **17c**, which contain an aromatic ring and a methyl group as the substituents, are of importance. Known routes towards this type of products are scarce, and provide the products, although in high optical purity (78% *de* and 98% *de*), in very low yields (resp. 11% and 31%).[17e,h] Some of these α,α-dibranched propargylic amines are part of biologically active compounds, *e.g.* the illustrated Cathepsin S inhibitor (Figure 3.4).[18]

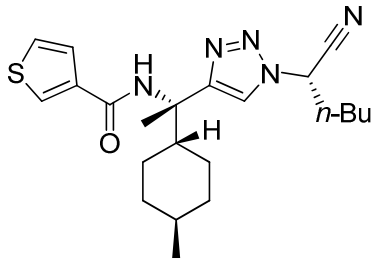
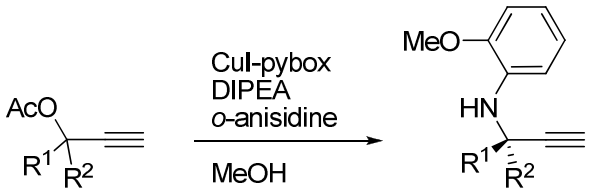


Figure 3.4 Cathepsin S inhibitor

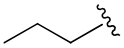
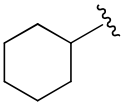
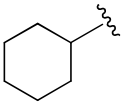
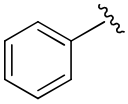
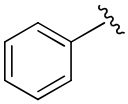
The difference between a methyl and a propyl moiety appeared to be insufficient for obtaining high enantioselectivity in the copper-catalyzed propargylic amination, as is shown for substrate **16a** (Table 3.10, entry 1). Amine **17a** was obtained in good yield (79%), but in low optical purity (21% *ee*) using Me-pybox **4a**. As Me-pybox **4a** was found to give the highest selectivies for substrates with aliphatic sidechains, no other ligands were screened. Desired product **17b** was obtained in similar yields and selectivities using either Me- or diMe-

pybox (entries 2 and 3). For substrates containing an aromatic ring as substituent diPh-pybox ligand **4f** gave the best results and afforded propargylic amine **17c** in very high yield and with good selectivity (entry 5).

Table 3.10 Propargylic amination with quaternary propargylic acetates.[a]



16 **17**

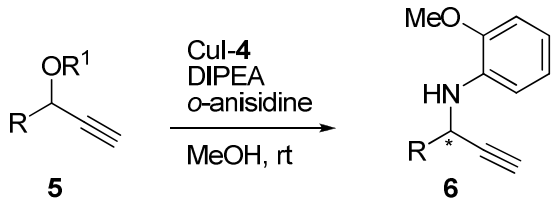
entry	ligand	R^1	R^2	T (°C)	time (h)	product	yield[b] (%)	*ee*[c] (%)
1	**4a**		Me	20	20	**17a**	79	21[d]
2	**4a**		Me	20	24	**17b**	64	43
3	**4j**		Me	20	24	**17b**	62	54
4	**4a**		Me	20	3	**17c**	78	8
5	**4f**		Me	0	4	**17c**	96	78

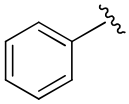
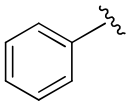
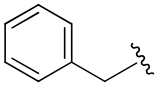
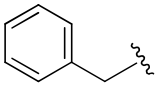
[a] Reaction conditions: propargylic acetate **16** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and pybox ligand (0.024 mmol) were stirred in methanol (2 mL). [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [d] No baseline separation was achieved with the chiral HPLC analysis.

3.9 INFLUENCE OF THE LEAVING GROUP

A problematic issue of the substitution reaction is the cleavage of the acetyl moiety under the basic reaction conditions. The acetate group is sensitive for transesterification (such as by methanol) giving the propargylic alcohol as a side-product. This phenomenon occurred more rapidly at higher temperatures and lowered the yield for the substrates that gave only good conversion at room temperature. To avoid cleavage of the acetate group, a more sterically hindered ester group can be used. The use of a benzoate or pivaloate ester gave the products in higher yields and no formation of propargylic alcohol was observed. The enantioselectivity remained the same, although the results with the substrates modified with the benzoate ester were not reproducible.

Table 3.10 Dependence of the leaving group on both yield and selectivity.[a]



entry	ligand	R	R^1	time (h)	product	yield (%)[b]	*ee* (%)[c]
1	**4f**		Ac	1	**6a**	97	76
2	**4f**		Bz	23	**6a**	98	75
3	**4a**		Ac	24	**6j**	77	82
4	**4a**		Bz	23	**6j**	89	79
5	**4a**		Ac	48	**6o**	66	88
6	**4a**		Piv	140	**6o**	66[d]	88

[a] Reaction conditions: propargylic ester **5** (0.20 mmol), *o*-anisidine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and pybox ligand (0.024 mmol) were stirred in methanol (2 mL) at room temperature. [b] Isolated yield after chromatography. [c] Enantioselectivity is determined by chiral HPLC of the isolated product. [d] No full conversion was observed and 24% of the starting material was recovered.

3.10 Conclusions

We have described the first example of an enantioselective copper-catalyzed propargylic amination reaction. Propargylic amines were prepared in high yields and high optical purities from a variety of readily available propargylic esters. The procedure is practical and does not require the exclusion of air and moisture. Enantiomerically pure propargylic amines (>99% *ee*) could be obtained in some cases by recrystallization of the products.

3.11 Towards Chiral ClickPhine

The initial goal of the synthesis of optically pure propargylic amines, mentioned in the beginning of this chapter, was the need for a proper chiral building block for the synthesis of

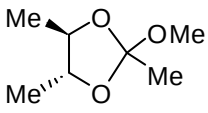
optically pure ClickPhine ligands. However, the discovery and exploration of this novel asymmetric propargylic substitution reaction took most of our interest and time. Before we will report on the synthesis of the chiral ligands in chapter 6, we will first discuss challenges, interesting findings, and some applications of the enantioselective copper-catalyzed propargylic substitution in the next two chapters.

3.12 ACKNOWLEDGEMENTS

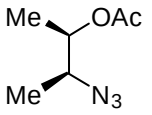
Z. Abiri, M. M. E. Delville, and R. le Griel are kindly acknowledged for their contribution to this chapter. The valuable discussions with dr. T. Marcelli and M. J. Wanner were very appreciated.

3.13 EXPERIMENTAL SECTION

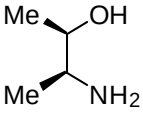
General Remarks – The general information is described in Chapter 2. Optical rotations ($[\alpha]^{20}_{D}$) were measured on a Perkin-Elmer 241 polarimeter. Chiral HPLC analysis was performed using a Meyvis-Gilson injector (model 231) and pump (model 307) with a Pharmacia LKB-VWM 2141 detector, and HP3395 integrator, or a Shimadzu LC-20AD with a Shimadzu SPD-M20A Diode Array detector.



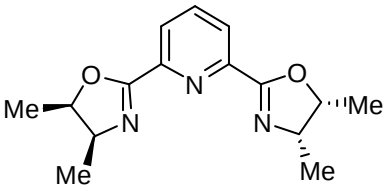
(4*R*,5*R*)-2-Methoxy-2,4,5-trimethyl-1,3-dioxolane (12). To a solution of commercially available (2*R*,3*R*)-butane-2,3-diol (2.0 mL, 22 mmol) in freshly distilled Et_2O (30 mL) was added 1,1,1-trimethoxyethane (5.6 mL, 44 mmol) and a catalytic amount of H_2SO_4 (60 µL, 1.1 mmol) at 0 °C. The mixture was stirred for 24 h allowing 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 3 times with Et_2O (50 mL). After evaporation of the solvent crude product **12** was obtained, which was used without further purification in the next step (contains 1,1,1-trimethoxyethane and triethylamine). ^{1}H NMR (400 MHz); δ (ppm) = 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 (d, *J* = 6.0 Hz, 3H).



(2*R*,3*S*)-3-Azidobutan-2-yl acetate (14).[16] To crude product **14** (5.5 g, ~50% w/w pure, max. 19.4 mmol) was added trimethylsilylazide (10 mL). The mixture was warmed for 7 h at 60 °C. After full conversion to intermediate **13** (followed by NMR), the mixture was heated for 13 h at 130 °C turning red. NMR analysis indicated the formation of **14** and the evaporation of most other reagents. Flash chromatography (PE/EtOAc 3:1) gave a clear yellowish liquid (2.01 g, 66%). ^{1}H NMR (400 MHz); δ (ppm) = 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 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 170.3, 72.8, 60.0, 20.1, 15.1, 14.9; FTIR (film, cm^{-1}); 2109 (s, azide), 1736 (s).



(2*R*,3*S*)-3-Aminobutan-2-ol (15).[16] To a solution of **14** (2.00 g, 12 mmol) in MeOH (120 mL) was added an excess of K_2CO_3 (8.3 g, 60 mmol). After stirring for 2 hours 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) affording the azido alcohol (1.22 g, 88%): $[\alpha]^{20}_D$ +59 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz); δ (ppm) = 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 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 70.2, 62.8, 18.4, 13.9; FTIR (film, cm^{-1}); 3371 (br s, OH), 2097 (s, azide). To a solution of the azido alcohol (300 mg, 2.7 mmol) in MeOH (3 mL) was added Pd/C (10% w/w, 0.14 g). After stirring for 5 hours at room temperature under H_2 atmosphere (balloon), the reaction mixture was filtrated over celite and the celite was rinsed with some fresh MeOH. Subsequent evaporation of the MeOH gave amino alcohol **15** as a colorless oil (0.18 g, 75%). ^{1}H NMR (400 MHz); δ (ppm) = 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 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 70.3, 62.8, 18.4, 13.9; FTIR (film, cm^{-1}); 3400 (br s, NH_2/OH).



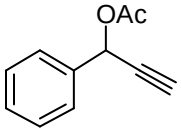
2,6-Bis((4*S*,5*R*)-4,5-dimethyl-4,5-dihydrooxazol-2-yl)pyridine (4j). Amino alcohol **15** (180 mg, 2.0 mmol) was added to a suspension of **2** (193 mg, 1.0 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at reflux for 18 hours. After evaporation of solvent, the residue was purified by flash chromatography (CH_2Cl_2 with 1% Et_3N to CH_2Cl_2 with 1% Et_3N and 1% MeOH) affording DiMe-pybox ligand **4j** as a white powder (196 mg, 72%): $[\alpha]^{20}_D$ −172 (c 0.5, $CHCl_3$). ^{1}H NMR (400 MHz); δ (ppm) = 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 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (101 MHz); δ (ppm) = 162.0, 147.5, 137.3, 125.6, 80.0, 63.9, 15.7, 15.0; HRMS (FAB+) m/z: calcd. (MH^+) 274.1556, found 274.1557.

General method for the synthesis of not commercially available pybox ligands. Dimethyl pyridine-2,6-bis(carbimidate)[12] (0.265 g, 1.37 mmol) was suspended in dry CH_2Cl_2 (5 mL). The amino-alcohol (2.75 mmol) was added and the mixture was refluxed until full conversion was reached (approximately 24 hours). The solvent was evaporated and the remaining solid was purified by flash chromatography (CH_2Cl_2 + 1-4% MeOH (+ 1% Et_3N)) and/or recrystallization from MeOH or EtOAc. NMR spectra were corresponding with literature.[19,20]

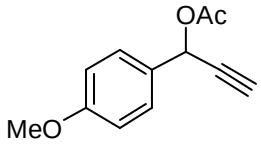
General method for the synthesis of propargylic acetates. The aldehyde (or ketone) (7.3 mmol) was dissolved in dry THF (20 mL) and added to a solution of ethynylmagnesium bromide in THF (0.5 M in THF, 22.0 mL, 11.0 mmol) at 0 °C. After 3 hours the reaction mixture was quenched in a mixture of saturated NH_4Cl-solution (50 mL) and ice (50 mL). After the evaporation of THF, diethylether (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 evaporated 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 obtain total

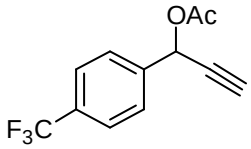
conversion. CH_2Cl_2 was evaporated using a laboratory evaporator. The mixture was purified by silica gel column chromatography.



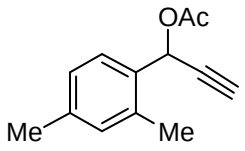
1-Phenylprop-2-ynyl acetate (5a).[21] To a solution of commercially available 1-phenylprop-2-ynyl alcohol (1.0 mL, 8.2 mmol) in dry CH_2Cl_2 (20 mL) acetic anhydride (1.0 mL, 11 mmol) was added under nitrogen atmosphere. After addition of Et_3N (1.5 mL, 11 mmol) the solution was stirred at ambient temperature for 21 hours. The reaction mixture was concentrated under vacuum and product **5a** was obtained after column chromatography (CH_2Cl_2/PE 5:1) as a colorless liquid (1.37 g, 96%). ^{1}H NMR (400 MHz); δ (ppm) = 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 (s, 3H, OAc).



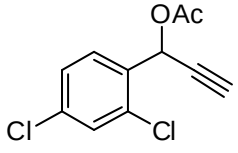
1-(4-Methoxyphenyl)prop-2-ynyl acetate (5b). The general procedure was followed starting with 16.5 mmol (2.00 mL) of *p*-anisaldehyde, using 17.3 mmol of ethynylmagnesium bromide in a total amount of 48 mL THF. After silica gel chromatography (CH_2Cl_2/PE 1:1) product **5b** was obtained (3.14 g, 93% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.47 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H, MeO), 2.65 (d, *J* = 2.3 Hz, 1H), 2.09 (s, 3H, AcO); ^{13}C NMR (101 MHz); δ (ppm) = 169.8 (COO), 160.2, 129.4, 128.7, 114.1, 80.5 (C≡), 75.2 (CH≡), 65.1 (CH-OAc), 55.3 (CH_3O), 21.1; FTIR (film, cm^{-1}); 3286 (s), 2937-2829 (w), 2129 (w), 1740 (vs), 1464 (w), 1370 (vs), 1228 (vs); HRMS (FAB+) m/z: calcd. (MH^+) 205.0865, found 205.0864.



1-(4-(Trifluoromethyl)phenyl)prop-2-ynyl acetate (5c). The general procedure was followed. After silica gel chromatography (CH_2Cl_2/PE 5:1) product **5c** was obtained (1.0 g, 56% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.66 (s, 4H), 6.49 (s, 1H), 2.69 (s, 1H), 2.14 (s, 3H, AcO); ^{13}C NMR (101 MHz); δ (ppm) = 169.5 (COO), 140.3, 131.2 (q, *J* = 32.6 Hz), 128.0, 125.7 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272 Hz, CF_3), 79.5 (C≡), 74.0 (CH≡), 64.5, 20.9; FTIR (film, cm^{-1}); 3301 (m), 2100 (w), 1747 (s), 1421 (s), 1373 (s), 1327 (vs), 1227 (vs); HRMS (EI+) m/z: calcd. (M^+) 242.0555, found 242.0554.

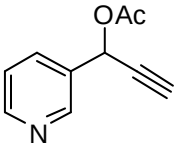


1-(2,4-Dimethylphenyl)prop-2-ynyl acetate (5d). The general procedure was followed. After silica gel chromatography (PE/CH_2Cl_2 4:1) product **5d** was obtained (1.1 g, 74% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.51 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 6.53 (d, *J* = 2.2 Hz, 1H), 2.62 (d, *J* = 2.3 Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.11 (s, 3H, Ac); ^{13}C NMR (101 MHz); δ (ppm) = 169.8 (COO), 139.2, 136.2, 131.8, 131.7, 128.1, 127.1, 80.4 (C≡), 75.2 (CH≡), 63.4, 21.2, 21.1, 19.1; FTIR (film, cm^{-1}) 3287 (s) 3017-2925 (m) 2124 (w) 1742 (vs) 1454 (m) 1370 (s) 1227 (vs); HRMS (FAB+) m/z: calcd. (MH^+) 203.1072, found 203.1075.

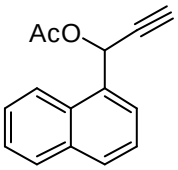


1-(2,4-Dichlorophenyl)prop-2-ynyl acetate (5e). The general procedure was followed. After silica gel chromatography (PE/CH_2Cl_2 4:1) product **5e** was obtained (1.4 g, 77% yield): mp 56-57 °C. ^{1}H NMR (400 MHz); δ (ppm) = 7.71 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.32 (dd, *J* = 2.1 Hz, 8.4 Hz, 1H), 6.67 (d, *J* = 2.3 Hz, 1H), 2.67 (d, *J* = 2.3 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 169.2 (COO), 135.8, 134.1, 132.6, 130.3, 129.7, 127.5, 78.8 (C≡), 76.0 (CH≡), 62.0, 20.7; FTIR (film, cm^{-1});

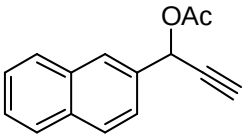
3297 (m), 2128 (w), 1748 (vs), 1473 (m), 1370 (m), 1221 (vs); HRMS (EI+) m/z: calcd. (M^+) 241.9901, found 241.9907.



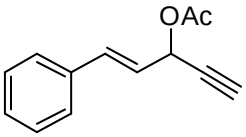
1-(Pyridin-3-yl)prop-2-ynyl acetate (5f). The general procedure was followed. After silica gel chromatography (gradient elution; CH_2Cl_2/EtOAc 10:1 to 1:10) product **5f** was obtained (230 mg, 18% yield). ^{1}H NMR (400 MHz); δ (ppm) = 8.74 (d, *J* = 1.3 Hz, 1H), 8.59 (d, *J* = 3.7 Hz, 1H), 7.84 (m, 1H), 7.31 (dd, *J* = 4.8 Hz, 7.9 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 2.69 (d, *J* = 2.3 Hz, 1H), 2.09 (s, 3H, AcO); ^{13}C NMR (101 MHz); δ (ppm) = 164.7 (COO), 145.5, 144.5, 130.5, 118.8, 74.4 (C≡), 71.5 (CH≡), 58.4, 16.1; FTIR (film, cm^{-1}) 3290 (m), 2100 (w), 1743 (vs), 1586 (w), 1557 (w), 1429 (m), 1371 (m), 1224 (vs); HRMS (EI+) m/z: calcd. (M^+) 175.0633, found 175.0633.



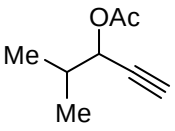
1-(Naphtalen-1-yl)prop-2-ynyl acetate (5g). The general procedure was followed. After silica gel chromatography (gradient elution; PE/CH_2Cl_2 4:1 to 3:1) product **5g** was obtained (1.1 g, 67% yield). ^{1}H NMR (400 MHz); δ (ppm) = 8.19-7.48 (m, 7H), 7.10 (d, *J* = 2.3 Hz, 1H), 2.72 (d, *J* = 2.3 Hz, 1H), 2.14 (d, *J* = 2.8 Hz, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 169.9 (COO), 134.1, 131.8, 130.6, 130.2, 129.0, 126.9, 126.7, 126.2, 125.3, 123.7, 80.3 (C≡), 76.1 (CH≡), 63.8, 21.1; FTIR (film, cm^{-1}) 3287 (m), 2157 (w), 1740 (vs), 1369 (w), 1224 (vs); HRMS (FAB+) m/z: calcd. (MH^+) 225.0916, found 225.0915.



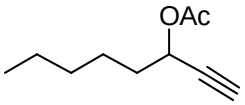
1-(Naphtalen-2-yl)prop-2-ynyl acetate (5h). The general procedure was followed. After silica gel chromatography (PE/CH_2Cl_2 4:1) product **5h** was obtained (1.0 g, 64% yield): mp 65-66 °C. ^{1}H NMR (400 MHz); δ (ppm) = 8.02-7.51 (m, 7H), 6.63 (d, *J* = 2.2 Hz, 1H), 2.73 (d, *J* = 2.2 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 169.7 (COO), 133.7, 133.5, 133.0, 128.7, 128.3, 127.7, 127.2, 126.8, 126.5, 125.0, 80.3 (C≡), 75.7 (CH≡), 65.5, 21.1; FTIR (film, cm^{-1}) 3285 (m), 3059 (w), 2120 (w), 1741 (vs), 1440 (w), 1369 (w), 1224 (vs); HRMS (FAB+) m/z: calcd. (MH^+) 225.0916, found 225.0915.



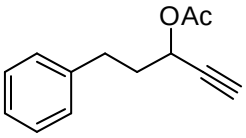
(*E*)-1-Phenylpent-1-en-4-yn-3-yl acetate (5i). The general procedure was followed. After silica gel chromatography (gradient elution; PE/CH_2Cl_2 4:1 to 3:1) product **5i** was obtained (1.2 g, 81% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.43-7.29 (m, 5H), 6.89 (d, *J* = 15.7 Hz, 1H), 6.24 (dd, *J* = 6.5 Hz, 15.7 Hz, 1H), 6.06 (d, *J* = 6.5 Hz, 1H), 2.66 (d, *J* = 2.2 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 169.7 (COO), 135.6, 134.9, 128.7, 128.6, 127.0, 123.3, 79.4 (C≡), 75.4 (CH≡), 64.0, 21.1; FTIR (film, cm^{-1}); 3289 (m), 3028 (w), 2125 (w), 1741 (vs), 1449 (w), 1371 (w), 1227 (vs); HRMS (FAB+) m/z: calcd. (MH^+) 201.0196, found 201.0191.



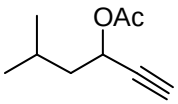
4-Methylpent-1-yn-3-yl acetate (5j). The general procedure was followed. After silica gel chromatography (gradient elution; PE/CH_2Cl_2 4:1 to 3:1) product **5j** was obtained (0.5 g, 49% yield). ^{1}H NMR (400 MHz); δ (ppm) = 5.18 (dd, *J* = 2.2 Hz, 5.7 Hz, 1H), 2.42 (d, *J* = 2.2 Hz, 1H), 2.10 (s, 3H, Ac), 2.01-1.96 (m, 1H), 1.02-0.98 (m, 6H); ^{13}C NMR (101 MHz); δ (ppm) = 170.0 (COO), 79.9 (C≡), 74.0 (CH≡), 68.7, 32.1, 20.9, 18.0, 17.4; FTIR (film, cm^{-1}) 3292 (m), 2969-2877 (m) 2114 (w) 1744 (vs) 1469 (m) 1373 (s) 1235 (vs).



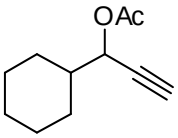
Oct-1-yn-3-yl acetate (5k). The general procedure was followed. After silica gel chromatography (PE/CH_2Cl_2 4:1) product **5k** was obtained (0.7 g, 57% yield). ^{1}H NMR (400 MHz); δ (ppm) = 5.34-5.32 (m, 1H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.09 (s, 3H), 1.79-1.74 (m, 2H), 1.46-1.43 (m, 2H), 1.32-1.29 (m, 4H), 0.91-0.88 (m, 3H); ^{13}C NMR (101 MHz); δ (ppm) 169.9 (COO), 81.3 (C≡), 73.4 (CH≡), 63.8, 34.5, 31.2, 24.6, 22.5, 21.0, 13.9; FTIR (film, cm^{-1}); 3294 (m), 2957-2864 (m), 2123 (w), 1744 (vs), 1467 (w), 1372 (m), 1235 (vs).



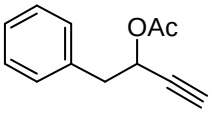
5-Phenylpent-1-yn-3-yl acetate (5l). The general procedure was followed, starting with 7.4 mmol of aldehyde. After silica gel chromatography (PE/CH_2Cl_2 1:1) product **5l** was obtained (1.0 g, 67% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.32-7.27 (m, 2H), 7.23-7.18 (m, 3H), 5.35 (dt, *J* = 2.2 Hz, *J* = 6.6 Hz, 1H), 2.79 (t, *J* = 7.9 Hz, 2H), 2.51 (d, *J* = 2.2 Hz, 1H), 2.17-2.06 (m, 2H), 2.08 (s, 3H).



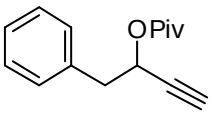
5-Methylhex-1-yn-3-yl acetate (5m). The general procedure was followed. After silica gel chromatography (PE/CH_2Cl_2 3:1) product **5m** was obtained (0.65 g, 47% yield). ^{1}H NMR (400 MHz); δ (ppm) = 5.41-5.36 (m, 1H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.08 (s, 3H), 1.83-1.76 (m, 1H), 1.71-1.60 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 6H).



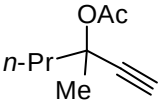
1-Cyclohexylprop-2-ynyl acetate (5n). The general procedure was followed, starting with 7.6 mmol of aldehyde. After silica gel chromatography (PE/CH_2Cl_2 1:1) product **5n** was obtained (1.36 g, 99% yield). ^{1}H NMR (400 MHz); δ (ppm) = 5.18 (dd, *J* = 2.2 Hz, 6.2 Hz, 1H), 2.42 (d, *J* = 2.2 Hz, 1H), 2.07 (s, 3H), 1.86-1.62 (m, 6H), 1.26-1.06 (m, 5H).



1-Phenylbut-3-yn-2-yl acetate (5o). The general procedure was followed, starting with 9.0 mmol of phenylacetaldehyde. After silica gel chromatography (PE/EtOAc 3:1) product **5o** was obtained (0.89 g, 53% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.30-7.27 (m, 5H, Ph), 5.53 (dt, *J* = 2.2 Hz, 6.8 Hz, 1H), 3.11 (m, 2H, CH_2) 2.48 (d, *J* = 2.2 Hz, 1H), 2.08 (s, 3H, OAc); ^{13}C NMR (101 MHz); δ (ppm) 170.0 (COO), 135.8, 129.2, 128.7, 127.2, 80.8 (C≡), 74.5 (CH≡), 64.4, 41.1, 21.0; FTIR (film, cm^{-1}); 3287 (m), 1740 (s), 1371 (m), 1231 (s), 1024 (m).

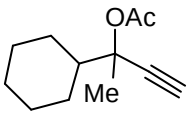


1-Phenylbut-3-yn-2-yl pivalate (5oPiv). The general procedure was followed, starting with 6.2 mmol of phenylacetaldehyde, and using pivaloyl chloride instead of acetic anhydride. After silica gel chromatography (PE/CH_2Cl_2 1:1) product **5oPiv** was obtained (0.77 g, 54% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.32-7.25 (m, 5H, Ph), 5.53 (dt, *J* = 2.1 Hz, 6.9 Hz, 1H), 3.12 (d, *J* = 6.9 Hz, CH_2) 2.46 (d, *J* = 2.1 Hz, 1H), 1.17 (s, 9H).

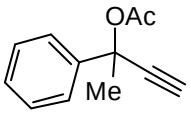


3-Methylhex-1-yn-3-yl acetate (16a). The general procedure was followed, starting with 9.0 mmol of 2-pentanone, and 3 equivalents of Et_3N and Ac_2O were used. After silica gel chromatography (PE/EtOAc 3:1) product **16a** was obtained (0.65 g, 47% yield), not totally pure, but used as this in the catalysis. ^{1}H NMR (400 MHz); δ (ppm) = 2.56 (s, 1H, C≡CH), 2.04 (s, 3H, OAc), 1.99-1.89 (m, 1H), 1.85-1.75 (m, 1H), 1.68 (s, 3H), 1.61-1.45 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz); δ (ppm) 169.6 (OC=O), 84.1 (C≡), 75.0, 73.2 (CH≡),

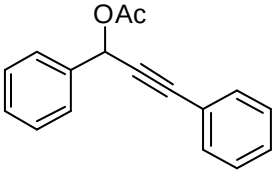
43.6, 26.5, 22.1, 17.5, 14.1; FTIR (film, cm^{-1}); 3267 (w), 2963 (s), 1733 (vs), 1368 (s), 1238 (vs), 1136 (m), 1020 (m).



2-Cyclohexylbut-3-yn-2-yl acetate (16b). The general procedure was followed, starting with 6.0 mmol of 1-cyclohexylethanone. After silica gel chromatography (PE/EtOAc 3:1) product **16b** was obtained (0.70 g, 61% yield), not totally pure, but used as this in the catalysis. ^{1}H NMR (400 MHz); δ (ppm) = 2.57 (s, 1H, C≡CH), 2.05 (s, 3H, OAc), 2.01-1.93 (m, 1H), 1.92-1.76 (m, 4H), 1.72-1.66 (m, 1H), 1.66 (s, 3H), 1.33-1.13 (m, 5H); ^{13}C NMR (101 MHz); δ (ppm) 169.5 (OC=O), 83.4 (C≡), 78.3, 74.0 (CH≡), 46.9, 27.4, 27.0, 26.4, 26.31, 26.27, 23.5, 22.1; FTIR (film, cm^{-1}); ~3300 (m, br), 2936 (s), 2854 (m), 1749 (s), 1452 (m), 1369 (m), 1236 (s).



2-Phenylbut-3-yn-2-yl acetate (16c). The general procedure was followed (acetylation), starting with commercially available 2-phenyl-3-butyn-2-ol (6.8 mmol). After silica gel chromatography (PE/DCM 1:1 to pure DCM) product **16c** was obtained (1.27 g, 99% yield). ^{1}H NMR (400 MHz); δ (ppm) = 7.60-7.57 (m, 2H), 7.39-7.29 (m, 3H), 2.82 (s, 1H, C≡CH), 2.09 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (101 MHz); δ (ppm) 168.7 (OC=O), 142.2, 128.5, 128.0, 124.9, 83.1 (C≡), 75.7 (CH≡), 75.4, 32.2, 21.8; FTIR (film, cm^{-1}); 3284 (m), 1752 (vs), 1368 (m), 1235 (vs), 1063 (s).

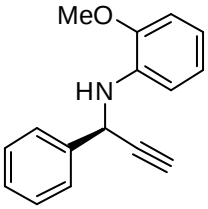


1,3-Diphenylprop-2-ynyl acetate (8).[22] To a solution of phenylacetylene (1.09 mL, 9.9 mmol) in THF at −78 °C a solution of *n*-BuLi (1.6 M in hexane, 6.25 ml, 10.0 mmol) was added slowly, followed by slow addition of benzaldehyde (1.0 mL, 9.9 mmol). After stirring overnight at room temperature the reaction mixture was quenched in saturated NH_4Cl-solution (50 mL) and ice (50 mL). The solvent was evaporated using a laboratory evaporator, followed by extraction of the water layer with diethylether (5 × 20 mL). The combined organic layers were washed with saturated NaCl-solution (50 mL). After separation of phases the organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude product was used without further purification in the acetylation step. A solution of the propargylic alcohol (max. 9.9 mmol), acetic anhydride (1.2 mL, 12.9 mmol) and triethylamine (1.8 mL, 12.9 mmol) in dry CH_2Cl_2 (20 mL) was stirred overnight at room temperature. CH_2Cl_2 was evaporated using a laboratory evaporator. After silica gel chromatography (PE/CH_2Cl_2 4:1) product **8** was obtained (2.0 g, 79% yield). NMR spectra were corresponding with literature.[3]

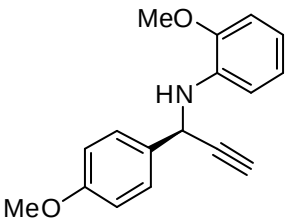
General procedure A. Propargylic amination with ligand 4f. Copper iodide (3.8 mg, 0.020 mmol) and 2,6-bis((4R,5S)-4,5-diphenyl-4,5-dihydrooxazol-2-yl)pyridine (**4f**) (12.5 mg, 0.024 mmol) were suspended in methanol (1.4 mL). The mixture was stirred for 20 minutes before addition of a solution of the propargylic acetate (0.20 mmol) in methanol (0.3 mL). The suspension is cooled to −20 °C. After 10 minutes 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 finished the reaction 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 with ligand 4a. See general procedure A. In this procedure pybox ligand **4a** was used instead of ligand **4f**. The reaction mixture was stirred at ambient temperature (18-25 °C) and the ligand did dissolve in methanol, together with the CuI, forming a clear red solution.

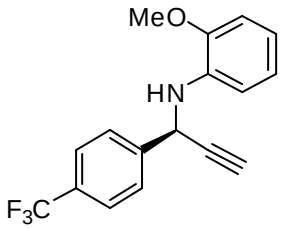
Racemic reaction. The racemic samples were obtained using the general procedure B with TBTA as the ligand instead of the chiral pybox ligand.



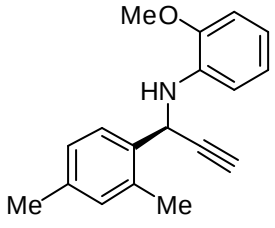
(*S*)-2-Methoxy-*N*-(1-phenylprop-2-ynyl)aniline (6a). Copper iodide (48 mg, 0.25 mmol) and pybox ligand **4f** (156 mg, 0.30 mmol) were stirred in MeOH (40 mL) for 30 minutes. To the acquired red solution, which contains small white particles of probably excess ligand, **5a** (0.87 g, 5.0 mmol) in MeOH (4 mL) was added. The mixture was cooled to −18 °C (ice/salt) followed by addition of a cooled solution of *o*-anisidine (1.1 mL, 10 mmol) and DIPEA (3.5 mL, 20 mmol) in MeOH (6 mL). The reaction mixture was stirred for 21 h at −18 °C. After evaporation and silica gel column chromatography (CH_2Cl_2/PE 1:2) the product was obtained as a yellow oil (1.15 g, 97% yield, 85% *ee*). After two crystallization steps (crystals of racemate) (EtOAc/PE, one weekend at −18 °C), the mother liquor contained the highly optical enriched product **6a** giving, after evaporation, an orange oil (0.97 g, 81% yield, 99% *ee*): $[\alpha]^{20}_D$ +100 (c 1.0, $CHCl_3$), lit.[13] $[\alpha]^{25}_D$ +75.6 (c 1.0, $CHCl_3$). The product solidified after one week at −18 °C and was recrystallized from heptane after addition of a seed crystal providing yellow crystals (0.55 g, 46% yield, >99.5% *ee*); mp (racemate) 75 °C, mp (single enantiomer) 32 °C. HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 13 min (minor isomer) and 20 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.64- 7.61 (m, 2H, *m*-Ph), 7.42-7.34 (m, 3H, *o*,*p*-Ph), 6.88-6.75 (m, 4H, anisidyl), 5.30 (dd, *J* = 7.1 Hz, *J* = 2.1 Hz, 1H, CH), 4.68 (br d, *J* = 7.0 Hz, 1H, NH), 3.83 (s, 3H, OMe), 2.47 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 139.3, 136.3, 128.9, 128.2, 127.4, 121.2, 118.0, 111.6, 109.7, 83.3, 73.0, 55.5, 49.6; FTIR (film, cm^{-1}); 3417 (w), 3287 (m), 1601 (m), 1509 (s), 1454 (m), 1426 (m), 1242 (s), 1221 (m), 1125 (m), 1027 (m); Anal. calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.23; H, 6.46; N, 5.89; HRMS (FAB+) m/z: calcd. (MH^+) 238.1232, found 238.1238.



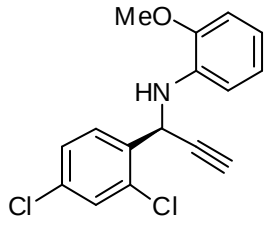
(*S*)-2-Methoxy-*N*-(1-(4-methoxyphenyl)prop-2-ynyl)aniline (6b). General procedure A was followed. Compound **5b** (41 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 19 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 5:1) afforded product **6b** as a colorless oil (52 mg, 97% yield, 83% *ee*): $[\alpha]^{20}_D$ +75 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 9:1 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 8.2 min (minor isomer) and 15.8 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.53 (m, 2H), 6.93-6.72 (m, 6H), 5.24 (br s, 1H, CH), 4.61 (br s, 1H, NH), 3.82 (s, 6H, 2 x OMe), 2.45 (d, *J* = 2.2 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 159.5, 147.2, 136.3, 131.4, 128.5, 121.1, 117.9, 114.1, 111.5, 109.6, 83.4, 72.8, 55.42, 55.37, 48.9; FTIR (film, cm^{-1}); 3283 (m), 1601 (m), 1509 (s), 1454 (m), 1245 (s), 1175 (m), 1125 (m), 1029 (m); HRMS (FAB+) m/z: calcd. (MH^+) 268.1338, found 268.1328.



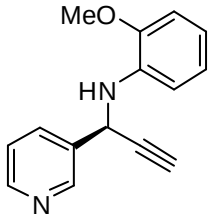
(*S*)-2-Methoxy-*N*-(1-(4-(trifluoromethyl)phenyl)prop-2-ynyl)aniline (6c). General procedure A was followed. Compound **5c** (48 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 18 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 5:1) afforded product **6c** as a colorless oil (51 mg, 84% yield, 80% *ee*): $[\alpha]^{20}_D$ +52 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 9:1 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 6.8 min (minor isomer) and 12.3 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.76 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 6.90-6.79 (m, 3H), 6.70 (dd, *J* = 7.8 Hz, *J* = 1.4 HZ, 1H), 5.38 (br s, 1H, CH), 4.77 (br s, 1H, NH), 3.87 (s, 3H, OMe), 2.52 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.4, 143.4, 135.9, 130.5 (q, *J* = 32.5 Hz), 127.7, 125.9 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.2 Hz), 121.1, 118.5, 111.7, 109.8, 82.4, 73.8, 55.6, 49.3; FTIR (film, cm^{-1}); 3297 (m), 1602 (m), 1509 (s), 1456 (m), 1428 (m), 1326 (s), 1243 (m), 1223 (m), 1166 (s), 1125 (s), 1067 (s), 1019 (m); HRMS (FAB+) m/z: calcd. (MH^+) 306.1106, found 306.1116.



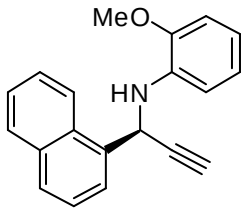
(*S*)-*N*-(1-(2,4-Dimethylphenyl)prop-2-ynyl)-2-methoxyaniline (6d). General procedure A was followed. Compound **5d** (40 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 20 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 2:1) afforded product **6d** as a white solid (48 mg, 91% yield, 88% *ee*): mp 69-74 °C; $[\alpha]^{20}_D$ +89 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 5.9 min (minor isomer) and 6.9 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.52 (d, *J* = 7.8 Hz, 1H), 7.09-7.06 (m, 2H), 6.93-6.89 (m, 1H), 6.83-6.76 (m, 3H), 5.35 (m, 1H), 4.55 (d, *J* = 5.4 Hz, 1H, NH), 3.83 (s, 3H, OMe), 2.44 (d, *J* = 2.3 Hz, 1H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz); δ (ppm) = 147.2, 138.0, 136.6, 136.1, 134.3, 131.8, 127.3, 127.2, 121.3, 117.7, 111.2, 109.7, 83.4 (-C≡), 72.6 (CH≡), 55.5, 46.9, 21.2, 18.9; FTIR (film, cm^{-1}); 3285 (m), 1601 (m), 1509 (s), 1454 (m), 1425 (m), 1236 (s), 1221 (m), 1125 (m), 1029 (m); HRMS (FAB+) m/z: calcd. (MH^+) 266.1545, found 266.1541.



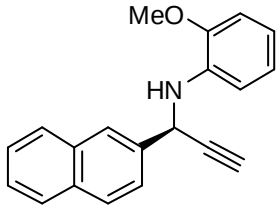
(*S*)-*N*-(1-(2,4-Dichlorophenyl)prop-2-ynyl)-2-methoxyaniline (6e). General procedure A was followed. Compound **5e** (49 mg, 0.20 mmol) was added to the catalyst suspension and cooled to –20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 40 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 2:1) afforded product **6e** as an orange oil (54 mg, 88% yield, 79% *ee*): $[\alpha]^{20}_D$ +67 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 6.3 min (minor isomer) and 7.9 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.69 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 2.1 Hz, 1H), 7.28 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H), 6.87-6.74 (m, 3H), 6.58 (dd, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H), 5.59 (dd, *J* = 6.5 Hz, *J* = 2.3 Hz, 1H, CH), 4.78 (br d, *J* = 6.4 Hz, 1H, NH), 3.87 (s, 3H, OMe), 2.48 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.2, 135.72, 135.65, 134.6, 134.0, 129.8, 129.5, 127.8, 121.2, 118.4, 111.3, 109.8, 81.9, 73.2, 55.6, 46.7; FTIR (film, cm^{-1}); 3296 (m), 1601 (m), 1509 (s), 1455 (m), 1243 (s), 1222 (m), 1127 (m), 1029 (m); HRMS (EI+) m/z: calcd. (M^+) 305.0374, found 305.0373.



(*S*)-2-Methoxy-*N*-(1-(pyridin-3-yl)prop-2-ynyl)aniline (6f). General procedure A was followed. Compound **5f** (35 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 23 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (EtOAc/PE 1:1) afforded product **6f** as an orange oil (42 mg, 88% yield, 74% *ee*): $[\alpha]^{20}_{D}$ +67 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 85:15 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 19 min (minor isomer) and 32 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 8.87 (br s, 1H), 8.60 (br d, *J* = 4.0 Hz, 1H), 7.94 (dd, *J* = 7.9 Hz, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 7.9 Hz, *J* = 4.8 Hz, 1H), 6.88-6.73 (m, 4H, anisidyl), 5.35 (dd, *J* = 7.5 Hz, *J* = 1.9 Hz, 1H, CH), 4.68 (br d, *J* = 7.4 Hz, 1H, NH), 3.84 (s, 3H, OMe), 2.51 (d, *J* = 2.3 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 149.6, 149.2, 147.4, 135.8, 135.0 (2x), 123.7, 121.1, 118.6, 111.8, 109.9, 82.0, 73.9, 55.6, 47.6; FTIR (film, cm^{-1}); 3285 (m), 1601 (m), 1509 (s), 1455 (m), 1423 (m), 1246 (s), 1223 (m), 1125 (m), 1026 (m); HRMS (FAB+) m/z: calcd. (MH^+) 239.1184, found 239.1184.

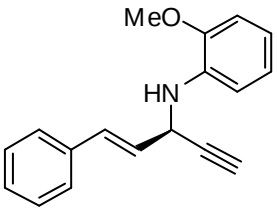


(*S*)-2-Methoxy-*N*-(1-(naphthalen-1-yl)prop-2-ynyl)aniline (6g). General procedure A was followed. Compound **5g** (45 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 22 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 3:1) afforded product **6g** as a white solid (52 mg, 91% yield, 85% *ee*). After recrystallization (EtOAc/PE) colourless needles were obtained (>99% *ee*): mp 148 °C; $[\alpha]^{20}_{D}$ +118 (c 1.0, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 0.8 mL/min, λ = 254 nm: 14.5 min (major isomer) and 15.9 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 8.16-8.14 (m, 1H), 8.01 (d, *J* = 7.1 Hz, 1H), 7.94-7.88 (m, 2H), 7.56-7.50 (m, 3H), 6.96-6.91 (m, 2H), 6.85-6.80 (m, 2H), 5.96 (br d, *J* = 3.3 Hz, 1H, CH), 4.80 (br d, *J* = 4.1 Hz, 1H, NH), 3.80 (s, 3H, OMe), 2.55 (d, *J* = 2.2 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 136.4, 134.2, 134.1, 130.9, 129.3, 129.0, 126.7, 126.0, 125.6, 125.5, 123.6, 121.3, 118.0, 111.3, 109.8, 83.1, 73.5, 55.4, 47.2; FTIR (film, cm^{-1}); 3287 (m), 1601 (m), 1509 (s), 1454 (m), 1426 (m), 1244 (s), 1221 (m), 1126 (m), 1028 (m); Anal. cacld. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.55; H, 6.10; N, 4.73; HRMS (FAB+) m/z: calcd. (MH^+) 288.1388, found 288.1383.

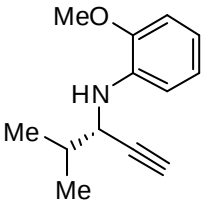


(*S*)-2-Methoxy-*N*-(1-(naphthalen-2-yl)prop-2-ynyl)aniline (6h). General procedure A was followed. Compound 5**h** (45 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 23 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 3:1) afforded product **6h** as a yellow oil (55 mg, 96% yield, 86% *ee*). After recrystallization (EtOAc/PE) yellowish crystals were obtained (>99% *ee*); $[\alpha]^{20}_{D}$ +21 (c 0.3, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 10 min (minor isomer) and 13 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 8.11 (s, 1H), 7.89-7.84 (m, 3H), 7.70 (dd, *J* = 8.5 Hz, *J* = 1.8 Hz, 1H), 7.53-7.49 (m, 2H), 6.90-6.74 (m, 4H, anisidyl), 5.46 (br d, *J* = 4.6 Hz, 1H, CH), 4.78 (br d, *J* = 5.7 Hz, 1H, NH), 3.84 (s, 3H, OMe), 2.53 (d, *J* = 2.2 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 136.7, 136.3, 133.4, 133.2, 128.8, 128.3, 127.8, 126.41, 126.35, 126.2, 125.3, 121.2, 118.1, 111.7, 109.7, 83.2, 73.4,

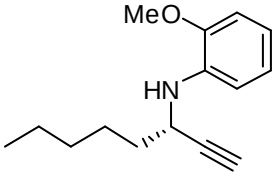
55.5, 49.8; FTIR (film, cm^{-1}); 3288 (m), 1601 (m), 1509 (s), 1454 (m), 1425 (m), 1241 (s), 1221 (m), 1126 (m), 1028 (m); HRMS (FAB+) m/z: calcd. (MH^+) 288.1388, found 288.1389.



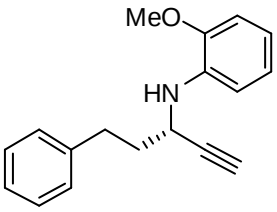
(*R*,*E*)-2-Methoxy-*N*-(1-phenylpent-1-en-4-yn-3-yl)aniline (6i). General procedure A was followed. Compound **5i** (40 mg, 0.20 mmol) was added to the catalyst suspension and cooled to −20 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 48 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 1:4) afforded product **6i** as a yellow oil (32 mg, 62% yield, 57% *ee*): $[\alpha]^{20}_D$ +26 (c 0.4, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 10 min (minor isomer) and 13 min (major isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.46-7.26 (m, 5H), 7.00-6.77 (m, 5H, anisidyl + alkene), 6.39 (dd, *J* = 15.8 Hz, *J* = 5.4 Hz, 1H, alkene), 4.97 (br d, *J* = 4.7 Hz, 1H, NCH), 4.55 (br s, 1H, NH), 3.88 (s, 3H, OMe), 2.48 (d, *J* = 2.1 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.5, 136.4, 136.0, 132.5, 128.7, 128.1, 126.9, 126.7, 121.2, 118.2, 111.9, 109.8, 82.4, 73.0, 55.6, 47.1; FTIR (film, cm^{-1}); 3289 (m), 1601 (m), 1509 (s), 1454 (m), 1427 (m), 1242 (s), 1222 (m), 1126 (m), 1028 (m), 968 (m); HRMS (FAB+) m/z: calcd. (MH^+) 264.1388, found 264.1389.



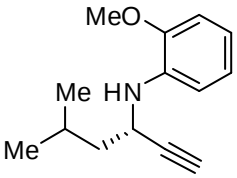
(*S*)-2-Methoxy-*N*-(4-methylpent-1-yn-3-yl)aniline (6j). General procedure B was followed. Compound **5j** (28 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 24 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 1:1) afforded product **6j** as a colourless oil (31 mg, 77% yield, 82% *ee*): $[\alpha]^{20}_D$ −146 (c 0.5, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 6.3 min (major isomer) and 9.6 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 6.91-6.87 (m, 1H), 6.80-6.69 (m, 3H), 4.40 (br d, *J* = 8.2 Hz, 1H, NH), 3.99-3.95 (m, 1H, CH), 3.85 (s, 3H, OMe), 2.21 (d, *J* = 2.2 Hz, 1H, C≡CH), 2.06 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 6H, CH_3); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 136.7, 121.3, 117.5, 111.3, 109.8, 83.3, 71.5, 55.6, 51.4, 32.4, 19.6, 18.0; FTIR (film, cm^{-1}); 3288 (m), 2961 (m), 1602 (m), 1510 (s), 1456 (m), 1428 (m), 1244 (s), 1221 (m), 1120 (m), 1029 (m); HRMS (FAB+) m/z: calcd. (MH^+) 204.1383, found 204.1381.



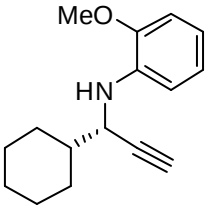
(*S*)-2-Methoxy-*N*-(oct-1-yn-3-yl)aniline (6k). General procedure B was followed. Compound **5k** (34 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 24 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 1:1) afforded product **6k** as a colourless oil (35 mg, 76% yield, 66% *ee*): $[\alpha]^{20}_D$ −85 (c 0.5, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 5.7 min (major isomer) and 6.8 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 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 (m, 3H, CH_3); ^{13}C NMR (101 MHz); δ (ppm) = 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; FTIR (film, cm^{-1}); 3408 (w), 3290 (m), 2934 (s), 2860 (m), 1603 (m), 1513 (s), 1456 (m), 1428 (m), 1248 (s), 1222 (s), 1030 (m); HRMS (FAB+) m/z: calcd. (MH^+) 232.1701, found 232.1697.



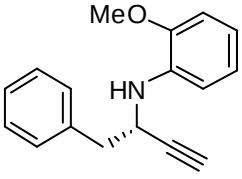
(*S*)-2-Methoxy-*N*-(5-phenylpent-1-yn-3-yl)aniline (6l). General procedure B was followed. Compound **5l** (40 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 24 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 1:2) afforded product **6l** (45 mg, 84% yield, 67% *ee*). HPLC conditions: Chiralcel AD (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 7.7 min (major isomer) and 9.1 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.33-7.19 (m, 5H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.81-6.67 (m, 3H), 4.36 (br s, 1H, NH), 4.11-4.07 (m, 1H, CH), 3.84 (s, 3H, OMe), 2.96-2.84 (m, 2H), 2.27 (d, *J* = 2.0 Hz, 1H, C≡CH), 2.22-2.14 (m, 2H).



(*S*)-2-Methoxy-*N*-(5-methylhex-1-yn-3-yl)aniline (6m). General procedure B was followed. Compound **5m** (31 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 48 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 2:3) afforded product **6m** (35 mg, 80% yield, 82% *ee*): $[\alpha]^{20}_D$ −88 (c 0.34, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 6.6 min (major isomer) and 12.6 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 6.94 (dt, *J* = 7.6 Hz, *J* = 1.4 Hz, 1H), 6.82-6.72 (m, 2H), 6.76 (dt, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 4.30 (br d, *J* = 7.5 Hz, 1H, NH), 4.20-4.15 (br m, 1H, CH), 3.87 (s, 3H, OMe), 2.23 (d, *J* = 2.1 Hz, 1H, C≡CH), 2.06-1.98 (m, 1H), 1.78-1.73 (m, 2H), 1.02 (t, *J* = 6.6 Hz, 6H, CH_3); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 136.6, 121.3, 117.6, 111.5, 109.8, 85.1, 70.5, 55.6, 45.0, 43.6, 25.2, 22.9, 21.3; FTIR (film, cm^{-1}); 3286 (m), 2956 (s), 2934 (m) 2869 (m), 1602 (s), 1512 (s), 1456 (s), 1247 (s), 1224 (s), 1029 (m); HRMS (FAB+) m/z: calcd. (MH^+) 218.1545, found 218.1548.

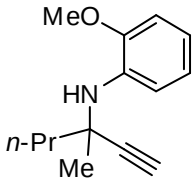


(*S*)-*N*-(1-Cyclohexylprop-2-ynyl)-2-methoxyaniline (6n). General procedure B was followed. Compound **5n** (36 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 24 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 1:2) afforded product **6n** (47 mg, 96% yield, 85% *ee*): $[\alpha]^{20}_D$ −116 (c 0.3, $CHCl_3$). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 6.0 min (major isomer) and 9.2 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 6.91-6.87 (m, 1H), 6.80-6.69 (m, 3H), 4.41 (br d, *J* = 8.0 Hz, 1H, NH), 3.97 (br t, *J* = 6.1 Hz, 1H, CH), 3.85 (s, 3H, OMe), 2.22 (d, *J* = 2.2 Hz, 1H, C≡CH), 1.97-1.90 (m, 2H), 1.83-1.69 (m, 4H), 1.36-1.18 (m, 5H); ^{13}C NMR (101 MHz); δ (ppm) = 147.3, 136.8, 121.2, 117.4, 111.2, 109.8, 83.8, 71.5, 55.6, 50.8, 42.1, 30.0, 28.7, 26.5, 26.2, 26.1; FTIR (film, cm^{-1}); 3408 (w), 3290 (m), 2934 (s), 2860 (m), 1603 (m), 1513 (s), 1456 (m), 1428 (m), 1248 (s), 1222 (s), 1030 (m); HRMS (FAB+) m/z: calcd. (MH^+) 244.1701, found 244.1697.

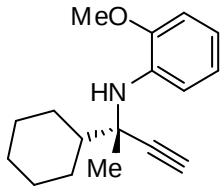


(*S*)-2-Methoxy-*N*-(1-phenylbut-3-yn-2-yl)aniline (6o). General procedure B was followed. Compound **5o** (38 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 48 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 2:3) afforded product **6o** as a colourless oil (33 mg, 66% yield, 88% ee): $[\alpha]^{20}_D$ −7 (c 0.5, $CHCl_3$). HPLC conditions: Chiralcel AD (4.6 x 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm, 9.1 min (major isomer), 10.9 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.35-7.31 (m,

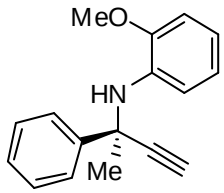
4H), 7.30-7.25 (m, 1H), 6.92-6.88 (m, 1H), 6.81-6.72 (m, 3H), 4.6 (br s, 1H, NH), 4.39-4.35 (m, X of ABX, 1H, CH), 3.81 (s, 3H, OMe), 3.20-3.15 (A of ABX, J_{ab} = 13.4 Hz, J_{ax} = 5.7 Hz, 1H), 3.12-3.07 (B of ABX, J_{ab} = 13.4 Hz, J_{bx} = 7.4 Hz, 1H), 2.26 (d, J = 2.1 Hz, 1H, C≡CH); ^{13}C NMR (101 MHz); δ (ppm) = 147.4, 137.0, 136.3, 129.8, 128.5, 127.0, 121.3, 117.9, 111.7, 110.0, 84.2, 71.9, 55.6, 46.7, 41.6; FTIR (film, cm^{-1}); 3427 (m), 1601 (m), 1511 (s), 1454 (m), 1246 (m), 1221 (m), 1125 (m), 1028 (m); HRMS (FAB+) m/z: calcd. (MH^+) 252.1383, found 252.1382.



2-Methoxy-N-(3-methylhex-1-yn-3-yl)aniline (17a). General procedure B was followed. Compound **16a** (31 mg, 0.20 mmol) was added to the catalyst solution before adding the *o*-anisidine/DIPEA mixture. After stirring for 20 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 2:3) afforded product **17a** (34 mg, 79% yield, ~21% ee). HPLC conditions: Chiralcel AD (4.6 x 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm, 5.2 min (major isomer), 5.4 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.30-7.27 (m, 1H), 6.90-6.84 (m, 1H), 6.80-6.77 (m, 1H), 6.74-6.71 (m, 1H), 4.4 (br s, 1H, NH), 3.83 (s, 3H, OMe), 2.38 (s, 1H, C≡CH), 1.90-1.85 (m, 1H), 1.80-1.76 (m, 1H), 1.66-1.49 (m, 2H), 1.58 (s, 3H, CH_3), 0.97 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (101 MHz); δ (ppm) = 147.6, 135.4, 120.7, 117.4, 114.1, 109.9, 87.3, 71.6, 55.7, 44.8, 28.0, 17.8, 14.4; FTIR (film, cm^{-1}); 3427 (w), 3284 (w), 2959 (m), 2935 (m), 2872 (w), 1602 (m), 1511 (s), 1457 (m), 1248 (s), 1222 (s), 1031 (m); HRMS (FAB+) m/z: calcd. (MH^+) 218.1545, found 218.1543.



(*S*)-*N*-(2-Cyclohexylbut-3-yn-2-yl)-2-methoxyaniline (17b). General procedure B was followed. Compound **16b** (31 mg, 0.20 mmol) was added to the catalyst solution (DiMe-pybox **4j** was used) before adding the *o*-anisidine/DIPEA mixture. After stirring for 20 hours, evaporation and silica gel chromatography (CH_2Cl_2/PE 3:5) afforded product **17b** (32 mg, 62% yield, 54% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 99.5:0.5 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. ^{1}H NMR (400 MHz); δ (ppm) = 7.34-7.31 (m, 1H), 6.88-6.84 (m, 1H), 6.80-6.78 (m, 1H), 6.72-6.68 (m, 1H), 4.39 (br s, 1H, NH), 3.84 (s, 3H, OMe), 2.41 (s, 1H, C≡CH), 2.17-2.11 (m, 1H), 1.88-1.80 (m, 4H), 1.72-1.68 (m, 1H), 1.52 (s, 3H, CH_3), 1.48-1.14 (m, 5H); ^{13}C NMR (101 MHz); δ (ppm) = 147.6, 135.4, 120.8, 117.2, 114.1, 109.7, 86.9, 72.4, 55.7, 54.7, 46.6, 28.2, 26.9, 26.8, 26.7, 26.6, 24.6; FTIR (film, cm^{-1}); 3428 (w), 3282 (m), 2922 (s), 2853 (m), 1602 (m), 1508 (s), 1453 (m), 1244 (m), 1222 (s), 1031 (m); HRMS (FAB+) m/z: calcd. (MH^+) 258.1858, found 258.1859.



(*S*)-2-Methoxy-*N*-(2-phenylbut-3-yn-2-yl)aniline (17c). General procedure A was followed with half the amounts. Compound **16c** (19 mg, 0.10 mmol) was added to the catalyst suspension and cooled to 0 °C before adding the *o*-anisidine/DIPEA mixture. After stirring for 4 hours the mixture was allowed to warm to room temperature. Evaporation and silica gel chromatography (CH_2Cl_2/PE 5:1) afforded product **17c** (24 mg, 96% yield, 78% *ee*). HPLC conditions: Chiralcel OD-H (4.6 × 250 mm), 98:2 heptane:HO*i*-Pr, 1.0 mL/min, λ = 254 nm: 5.9 min (major isomer) and 6.3 min (minor isomer). ^{1}H NMR (400 MHz); δ (ppm) = 7.61 (d, J = 7.7 Hz, 2H), 7.27-7.7.16 (m, 3H), 6.71 (dd, J = 7.7 Hz, J = 1.4 Hz, 1H), 6.60-6.51 (m, 2H), 6.26 (dd, J = 7.7 Hz, 1.7 Hz, 1H), 4.84 (br s, 1H, NH), 3.82 (s, 3H), 2.39 (s, 1H, C≡CH), 1.78 (s, 3H).

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