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

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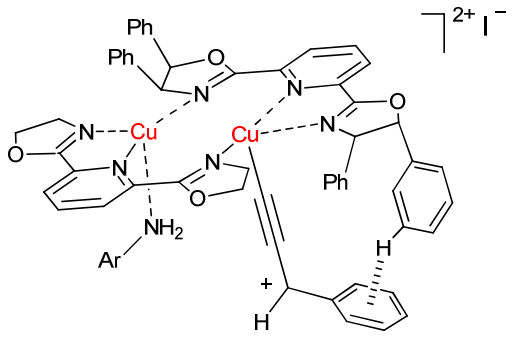
Publication date
2009

Document Version
Final published version

CHAPTER 5

Mechanistic Aspects of the Enantioselective Copper-Catalyzed Propargylic Amination*



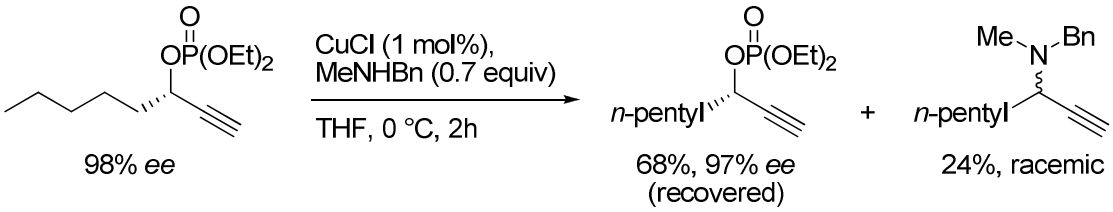
ABSTRACT: The mechanism of the enantioselective copper-catalyzed propargylic amination is discussed. Initial rate kinetics and ESI-MS experiments suggest the formation of higher copper aggregates. A study of the substrate and solvent dependence of the reaction revealed that CH-π interactions may play a role in the enantiodiscriminating step. Pathways for both mononuclear and multinuclear active copper complexes are considered. Finally, a catalytic cycle is presented together with a possible structure of a dinuclear copper complex. However, more experimental and theoretical results are required in order to understand the mechanism of the title reaction.

* 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.

5.1 INTRODUCTION

A detailed understanding of a chemical reaction can result from a study of its precise mechanism. Insight in every single elementary step of the mechanism requires extensive experimental and computational studies. For asymmetric catalysis the most significant step in the catalytic cycle is usually the step in which the enantiodiscrimination occurs. A clear picture of the important interactions between the catalytic species and the reagents can provide information on the scope and selectivity of a given reaction. In addition, mechanistic insight can lead to rational optimization and fine-tuning of the reaction. Proposals of mechanisms, and especially explanations for observed enantioselectivities, have been reported for various reactions, *e.g.* for the osmium-catalyzed asymmetric dihydroxylation[1] and the palladium-catalyzed allylic alkylation.[2,3]

In 1994, Murahashi *et al.* published a paper on the copper-catalyzed propargylic amination (See also Chapter 1, § 1.3.2).[4] The stereochemical aspects of this amination reaction were examined by treating an optically active propargylic phosphate with *N*-methylbenzylamine in the presence of a catalytic amount of CuCl (Scheme 5.1). Interestingly, the obtained product appeared to be racemic. Although this observation indicated the possible formation of an intermediate cationic, achiral, copper-complex, the role of the copper ion in these intermediates is not well understood.



Scheme 5.1 Stereochemical course of Murahashi's copper-catalyzed propargylic amination

Remarkably, the mechanistic aspects of transition metal-catalyzed propargylic substitutions are rarely examined. Only for a ruthenium-catalyzed propargylic substitution, reported by Nishibayashi *et al.*, a plausible mechanism has been proposed on the basis of experimental data. The reaction proceeds via an allenylidene diruthenium complex as key intermediate as illustrated in Chapter 1 (§ 1.3.3). The formation of such a complex was proven by isolation of the allenylidene intermediate and its characterization by X-ray crystallography.[5] Probably encouraged by this mechanistic study, the first examples of an enantioselective ruthenium-catalyzed propargylic substitution reaction were reported shortly thereafter.[6] The observed enantioselectivity of this reaction was explained by favorable π-π interactions between the phenyl rings of the chiral ligand and the allenylidene moiety (Chapter 1, § 1.4).

The motivation for our research toward the enantioselective copper-catalyzed propargylic amination is based on the idea that the achiral intermediate in the Murahashi reaction could be similar to the allenylidene intermediate described by Nishibayashi (Figure 5.1). At least, the copper ion could be in close proximity to the achiral intermediate. If this is true, a chiral,

enantiopure ligand, attached to the copper, may induce the anticipated enantioselectivity. Indeed, our concept works as is described in the previous two chapters, in which the scope and applications of the newly developed enantioselective copper-catalyzed propargylic amination reaction are discussed. The lack of reliable mechanistic knowledge about copper-catalyzed propargylic substitutions and the desire for better results with our method, prompted us to study the mechanism of the reaction more closely.

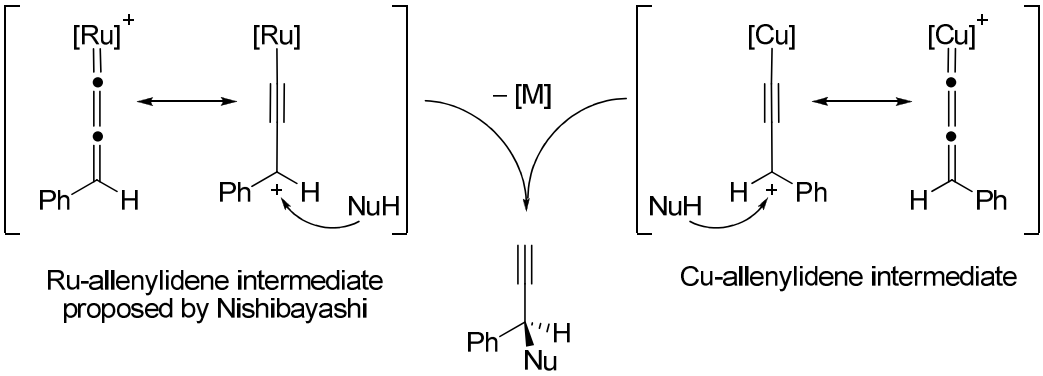
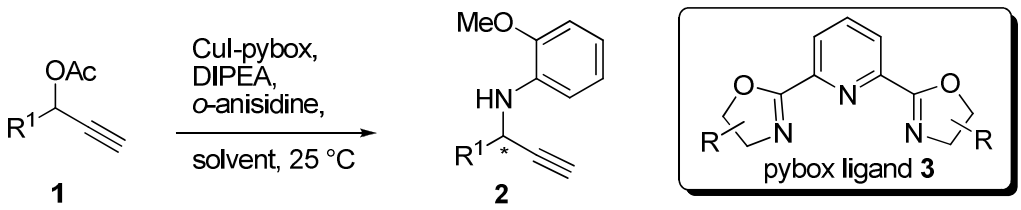


Figure 5.1 Proposed transition states for propargylic substitution.

5.2 SUMMARY OF THE PREVIOUS TWO CHAPTERS

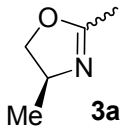
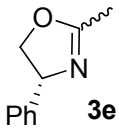
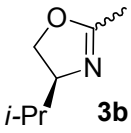
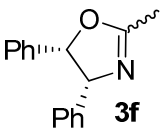
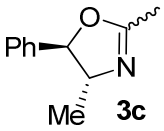
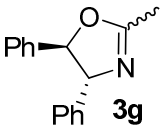
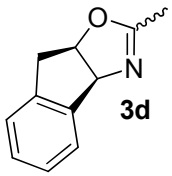
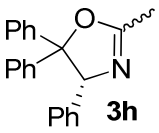
In order to establish a plausible mechanism for the copper-catalyzed propargylic amination (Scheme 5.2) we will recapitulate some of the results obtained during the study of the scope of the reaction (Chapter 3 and 4).



Scheme 5.2 Enantioselective copper-catalyzed propargylic amination

As expected, the most profound influence on the enantioselectivity of the reaction is displayed by the substitution pattern of the pyridine-2,6-bisoxazoline (pybox) ligand (Table 5.1). For the amination of phenyl-substituted propargylic acetate **1a** (R^1 = Ph), ligands with aromatic rings as substituents give the highest asymmetric induction. It seems to be important that the phenyl groups are positioned in a *cis* relationship at the 4- and 5-positions of the two oxazoline rings, as is illustrated by the relatively high enantioselectivities obtained with ligands **3f** and **3h** (76% and 61% *ee*, resp.).

Table 5.1 Survey of pybox ligands for the propargylic amination.[a]

	yield (%)[b]	config.	*ee* (%)[c]		yield (%)[b]	config.	*ee* (%)[c]
 **3a**	94	*R*	25	 **3e**	99	*S*	42
 **3b**	93	*R*	17	 **3f**	97	*S*	76
 **3c**	97	*R*	12	 **3g**	97	*S*	19
 **3d**	74	*R*	28	 **3h**	97	*S*	61

[a] Reaction (see Scheme 5.2) conditions: **1a** (R^1 = Ph, 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 chromatographic purification. [c] Enantioselectivity is determined by chiral HPLC of the isolated product.

Some observations from the optimization of the reaction conditions with ligand **3f** are worthwhile to summarize here as well. Varying the copper source has little or no effect on both the yield and enantioselectivity (see Chapter 3, Table 3.2), in sharp contrast to the results obtained for the different solvents. Although the conversion is high in most solvents (except for DMSO), we observe a strong enantioselectivity and rate dependence on the solvent (Table 5.2). In aprotic solvents like toluene, dichloromethane and THF, the reaction is slow and only slightly enantioselective. In protic solvents, such as methanol and 2,2,2-trifluoroethanol, the best results are obtained. Besides the solvent effect, also the presence and the type of base is crucial in terms of yield and enantioselectivity (Chapter 3, Table 3.4). The best results are obtained with tertiary amines, such as DIPEA.

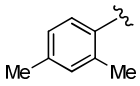
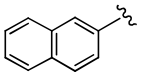
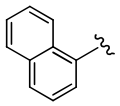
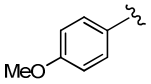
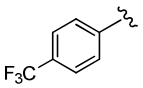
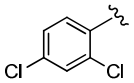
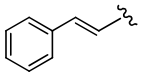
The data derived from the catalysis with a small set of substrates (Table 5.3) show an increase in selectivity if the π-system of the aromatic ring of the substrate is more electron-rich. With non-benzylic propargylic acetates (entries 9-11) the reaction becomes slower and less enantioselective. Interestingly, propargylic esters with an aliphatic side chain are converted into the corresponding propargylic amines with surprisingly high enantioselectivities (66-88% *ee*) with the use of Me-pybox **3a** (see Chapter 3, §3.7). The reactivity of these substrates is lower as compared to the benzylic alkynes and higher temperature and longer reaction times are required for good conversion. As reported by Murahashi and co-workers,[4] no reaction occurs with internal acetylenes.

Table 5.2 Solvent effects.[a]

entry	solvent	*ee* (%)
1	MeOH	76
2	CF_3CH_2OH	74
3	EtOH	60
4	DMSO	58
5	CH_2Cl_2	34
6	THF	36
7	PhMe	21
8	H_2O	5

[a] For the reaction with pybox **3f**. For all data see Chapter 3, Table 3.3.

Table 5.3 Substituent effects.[a]

entry	substituent	*ee* (%)
1		88
2		86
3		85
4		85
5		83
6		80
7		79
8		74
9		57
10		40
11		13

[a] For the reaction with pybox **3f**. For all data see Chapter 3, Table 3.7.

The evaluation of a series of primary and secondary amines as nucleophiles reveals that aniline and its derivatives give the best results affording the corresponding propargylic amines in high yield (up to 97%) and high optical purity (up to 87% *ee*). Other nitrogen nucleophiles, such as sulfonamides and carbamates, are not efficient reactants in the reaction. Carbon nucleophiles, *e.g.* indole and *N*-methylindole, give high yields (up to 91%) and enantioselectivities (up to 98% *ee*), whereas other π-nucleophiles, such as 2,2,5-trimethyl-1,3-dioxane-4,6-dione, give the desired product in almost racemic form.

5.3 New Experimental Data

To evaluate the stereochemical aspects of the enantioselective copper-catalyzed propargylic amination in more detail, the reaction has been followed in time by chiral HPLC analysis. An experiment under standard reaction conditions (as depicted in Table 5.1) at −20 °C reveals

that no enantioenrichment of the starting material, propargylic acetate **1a**, is observed during the reaction (Figure 5.2). The enantioselectivity of the product is slightly decreasing during the progress of the reaction. Probably, this drop in *ee* is explained by the very low concentration of the minor enantiomer of the product in the early phase of the reaction, which makes the determination of the amount of this compound by HPLC less accurate.

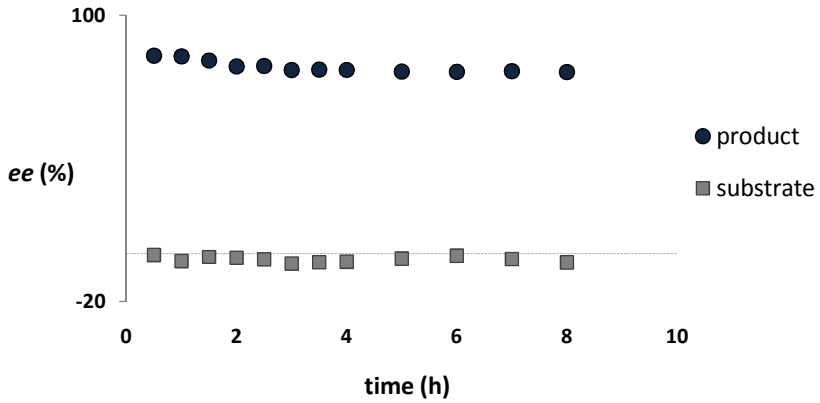


Figure 5.2 Enantioselectivity of the starting material (substrate) and the product followed in time. The conversion of the starting material after 8 h was 45%.

When the reaction is performed with enantiopure propargylic acetate **1a**, no racemization of the substrate is observed in line with the results of Murahashi (Scheme 5.1).[4] The use of either the (*R*)- or the (*S*)-1-phenylprop-2-ynyl acetate **1a** gives no difference in enantioselectivity of the product. In an experiment with enantiopure product **2a** (0.8 equiv) present from the start of the reaction, the enantiomeric excess after complete conversion of the starting material is slightly higher than in a reaction without additional enantiopure product. In a similar experiment with the minor enantiomer (0.8 equiv) of the product, the almost racemic product is obtained after full conversion of the propargylic acetate.

5.3.1 Initial-Rate Kinetics

In order to acquire more information we have studied the initial-rate kinetics of the reaction. Although the rate equation of the copper-catalyzed propargylic amination is probably complex, a simplified rate equation can be obtained if several assumptions are made. Under the standard reaction conditions there is an initial large excess of propargylic acetate (= substrate, 10 equiv), *o*-anisidine (20 equiv), and base (40 equiv) with respect to the copper ions. If the initial concentrations of these reagents are constant, it can be assumed that the rate of the reaction is depending only on the concentration of the copper-pybox complex. Based on the assumption that the ratio of the copper and the pybox ligand is one to one in the active complex, this affords the following simplified rate equations:

$$\text{rate} = k' [\text{Cu*}]^{a} \qquad (1) \qquad \text{or} \qquad \ln(\text{rate}) - \ln(k') = a \ln([\text{Cu*}]) \qquad (2)$$

In these equations *k'* is the pseudo-rate coefficient of the reaction and a is the reaction order of the copper-pybox complex Cu*. Consequently, the propargylic amination may be followed by NMR under the standard reaction conditions (100 mM in substrate) in CD_3OD changing only the copper/pybox concentration. Plotting the data according to equation 2 (ln(*k'*) is considered to be constant) the slope (a) equals 0.27 revealing that the order in Cu-pybox complex concentration is ca. 0.3 (Figure 5.3). It should also be noted that during these experiments the acetylenic hydrogen atom of the product did not appear in the ^1H NMR spectrum in agreement with the expected deuteration of this position.

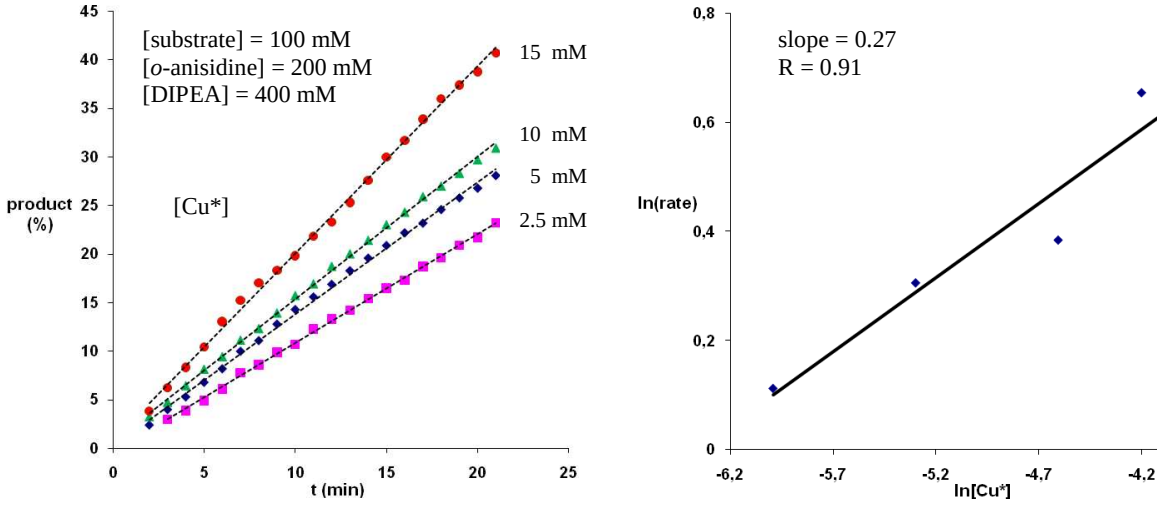


Figure 5.3 Initial-rate kinetics experiments: data (left), rate-order plot (right) showing 0.27 rate order dependence on [Cu*] under standard reaction conditions

5.3.2 ESI-MS EXPERIMENTS

As the next goal we have attempted to elucidate the composition of some of the copper-complexes in the reaction by direct infusion electrospray ionization mass spectrometry (ESI-MS). This technique has recently emerged as a powerful method to probe reaction mechanisms of condensed phase reactions.[7] It provides continuous snapshots of the ionic composition of the reaction medium, because the charged species present in the condensed phase are gently transferred to the gas phase prior to MS characterization. First a solution of CuI and diPh-pybox in MeOH was examined. Several species were observed, such as the pybox ligand with H^+ (*m*/*z* 522), Na^+ (*m*/*z* 544), and Cu^+ (*m*/*z* 584) bonded to it, amongst others (Figure 5.4). Although the pybox-Cu^+ species (*m*/*z* 584) was expected to give rise to the most intense signal, the typical cluster of isotopic pybox-Cu^+-pybox ions (*m*/*z* 1105-1115) were the major ions observed. Interestingly, we also observed species containing more than one Cu ion, such as pybox-CuI-Cu^+ (*m*/*z* 774), $(pybox)_2$CuI-Cu^+ (*m*/*z* 1295), and $(pybox)_2(CuI)_2$-Cu^+ (*m*/*z* 1485), all as reasonably abundant ions with characteristic distributions of the Cu isotopes. With the substrate, 1-phenylprop-2-ynyl acetate, added to the CuI-pybox solution, only a few new peaks arose in the mass spectrum. Two clear signals corresponded to complexes containing the product obtained after substitution of the acetate by methanol, pybox-(Cu-prodOMe)-Cu^+ (*m*/*z* 792) and pybox-(Cu-prodOMe)-Cu^+ (*m*/*z* 1503).

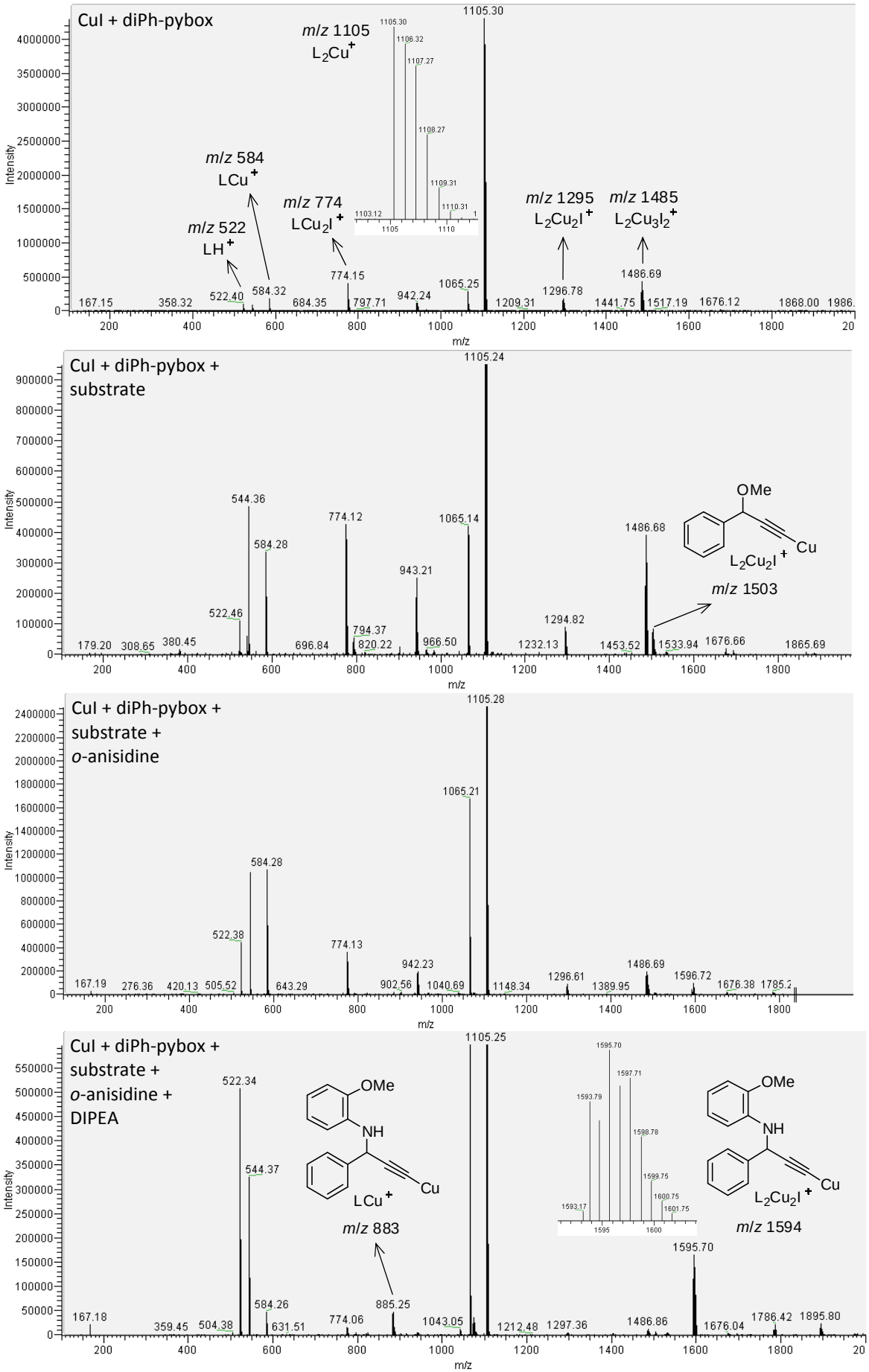


Figure 5.4 ESI(+)-MS of the copper-catalyzed propargylic amination with diPh-pybox **3f**

Also complexes with the acetylide of the substrate were detected although with very low intensities (*m*/*z* 820 and *m*/*z* 1531). Either these complexes are not well ionized or they are very reactive and react directly with any nucleophilic species in the neighborhood (in this case methanol). The four described complexes all indicated the formation of the copper acetylide species, even without the addition of base, illustrating that the acetylene is easily deprotonated.

The same measurements were performed with *o*-anisidine added to the solution. Now we observed an additional weak signal of a complex that supposedly consists of pybox-(Cu-product)-pybox-CuI-Cu^+ (*m*/*z* 1594), and an even less intense signal corresponding to pybox-(Cu-product)-Cu^+ (*m*/*z* 883). Both these signals became more intense if DIPEA was added together with *o*-anisidine. Under the basic conditions the copper-activated acetylenes are likely to be deprotonated affording more copper-acetylide complexes. Along with this, many of the iodides are replaced by anionic acetylides lowering the intensities of the signals from complexes with CuI (*m*/*z* 774, *m*/*z* 1295, and *m*/*z* 1485). The formation of larger complexes was also emphasized by the low intensity of the pybox-Cu^+ signal under these conditions.

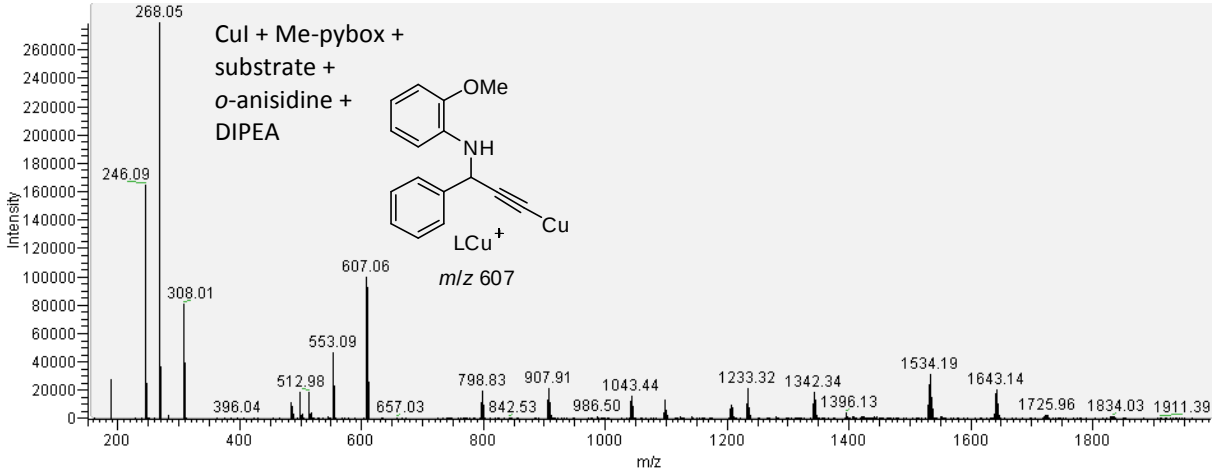


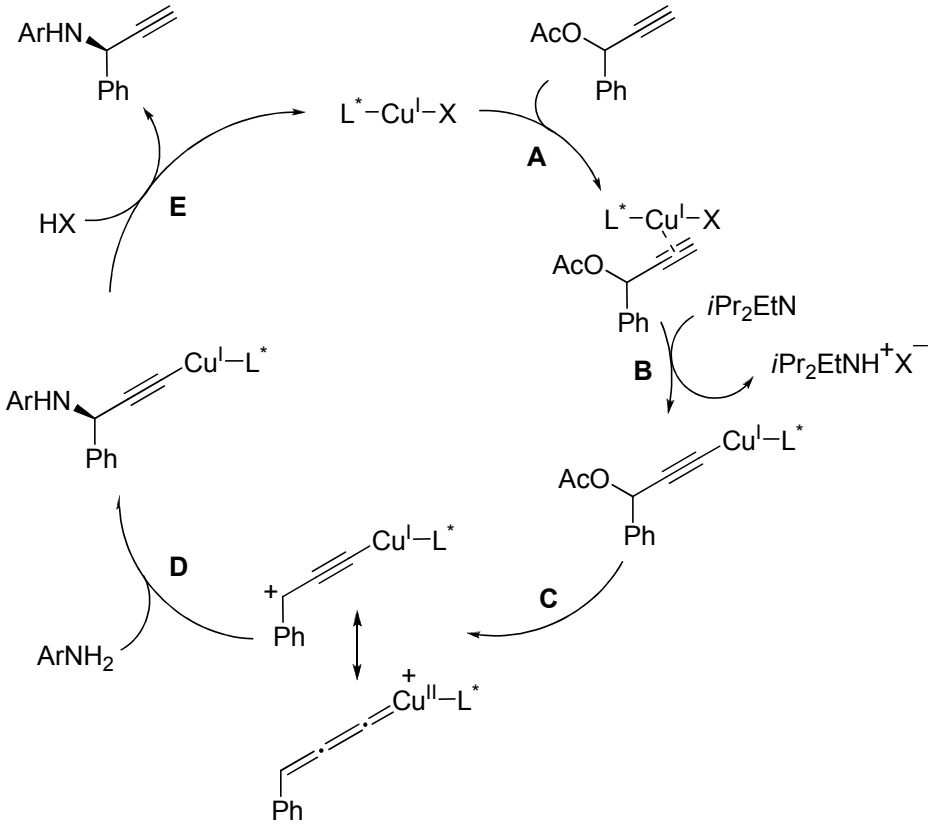
Figure 5.5 ESI(+)-MS of the copper-catalyzed propargylic amination with Me-pybox **3a**

In comparable experiments with the Me-pybox ligand **3a** (**3a**-Cu^+ *m*/*z* 308), the formation of one distinct complex was not observed. Instead, a plethora of complexes containing three or more copper ions were formed (Figure 5.5). In the region between *m*/*z* 700-1700, nine different signals with similar intensities were observed in the presence of DIPEA. This revealed, besides the peculiar role of the base, a difference in composition of the reaction mixture between the Me-pybox and diPh-pybox systems.

5.4 Discussion on the Reaction Mechanism

We start the discussion by proposing a simple mechanistic model based upon our own experimental results and other studies (Scheme 5.3).[4,8] The necessity of the presence of a

terminal acetylenic hydrogen atom and the exchange of the acetylenic hydrogen atom of the product for a deuterium atom in methanol-d_4 both strongly indicate the formation of a copper acetylide species. We suspect that the major complex observed in the ESI-MS measurements (*m*/*z* 1105) is a non-active state of the catalyst, with CuI_2^- as the likely counter anion (which is one of the observed ions in the negative ion ESI-MS). The addition of other ligands, such as the propargylic acetate, leads possibly to dissociation of this dimeric resting state affording the active monomeric copper catalyst. Prior to acetylide formation, the copper complex can form a π-complex with the alkyne (step **A**). The formation of this π-complex lowers the pK_a value of the acetylenic hydrogen atom, as described previously by Fokin and co-workers.[8] Deprotonation with a base gives the copper acetylide (step **B**).



Scheme 5.3 Proposed model of the catalytic cycle (Cu−L* = copper complex with chiral ligand)

Also in the ESI-MS experiments copper complexes containing the acetylide of the substrate, 1-phenylprop-2-ynyl acetate, are detected, although with low abundance (*m*/*z* 820 and *m*/*z* 1531). These measurements point out that the nature of the copper complex might be more complicated than expected. Nevertheless, we have to be careful with the interpretation of these mass spectrometry results, as it remains unclear whether the observed complexes are formed during the electrospray process or exist in the reaction mixture prior to introduction into the instrument. In addition, the mass spectra only provide an image of the well ionizable compounds, for example the substrate, 1-phenylprop-2-ynyl acetate (*m*/*z* 175), and the product, 2-methoxy-*N*-(1-phenylprop-2-ynyl)aniline (*m*/*z* 238), have not been observed. The

intial rate kinetics experiments showed no simple first order rate dependence on the copper concentration. For the moment, this phenomenon is assigned to the formation of inactive copper aggregates. For simplicity the active catalyst is in Scheme 5.3 considered to be a mononuclear copper species (*vide infra*).

The observed asymmetric induction is only possible if the chiral, but racemic, substrate is converted into a achiral intermediate which upon enantioselective attack of the amine affords the enantioenriched propargylic amine. This achiral intermediate can be formed by liberation of the acetate group from the copper acetylide intermediate (step **C**), as also proposed by Murahashi and co-workers.[4] This step is considered to be irreversible because no enantioenrichment of the substrate is observed during the reaction. When the reaction is performed with enantiopure propargylic acetate, no racemization of the substrate occurs, thus providing experimental support for the irreversibility of step **C** under the reaction conditions. The resulting electrophilic intermediate is stabilized by resonance involving the copper complex. Propargylic acetates bearing an aromatic ring as side chain will stabilize the cationic charge at the benzylic 3-position better than non-benzylic substrates, which explains the lower reactivity of the latter. Regrettably, we were unable to detect this key intermediate by ESI-MS, which can be ascribed to its high reactivity. Attack by the amine nucleophile (step **D**) most probably determines the regio- and enantioselectivity of the reaction. Despite of the electrophilic nature of the propargylic 1-position, the propargylic amine is formed exclusively, and not the allenic amine.

However, the experiment carried out in the presence of the minor enantiomer of the product from the start of the reaction, shows that the observed *ee* value is close to zero after total conversion of the starting material. This suggests that product formation (step **D**) is irreversible under the reaction conditions. The ESI-MS measurements reveal a high abundance of copper complexes containing the product acetylide (*m*/*z* 883 and *m*/*z* 1594). This suggests that the last step (step **E**), anion exchange or proteolysis, is relatively slow in the basic reaction medium. In protic solvents this step is probably faster, explaining the observed rate enhancement for this type of solvents. Finally, the product is released to complete the catalytic cycle.

5.4.1 MONONUCLEAR COPPER COMPLEX

In this mechanistic model the copper complex is specified in a very simplified manner, and by this means the most intriguing question is avoided: how is the enantioselectivity achieved? To answer this question, it is necessary to take a closer look at possible structures of the active copper complex. The general model for copper-pybox catalysis is based on the monomeric copper complex as the active catalytic species.[9] If such species are considered for our reaction (Figure 5.6), the copper-acetylide is most probably directed almost perpendicular to the copper-pybox plane as was also described by Finn and co-workers.[9d] The *trans*-pyridine position in this square pyramidal (or distorted trigonal bipyrimidal) complex is occupied by a solvent molecule (or amine). The steric hindrance of the aromatic rings of the ligand on one side of the complex forces the largest substrate substituent (the Ph moiety) to occupy the least shielded position. This gives the amine nucleophile the opportunity to attack the cationic

intermediate in an enantiodiscriminating manner. The major enantiomer observed has the *R*-configuration if (4*S*,5*R*)-diPh-pybox (*ent*-**3f**) is used. This indicates that the substituent of the substrate is positioned away from the substituents of the ligand affording the *R*-product by attack of the amine from the least hindered front side.

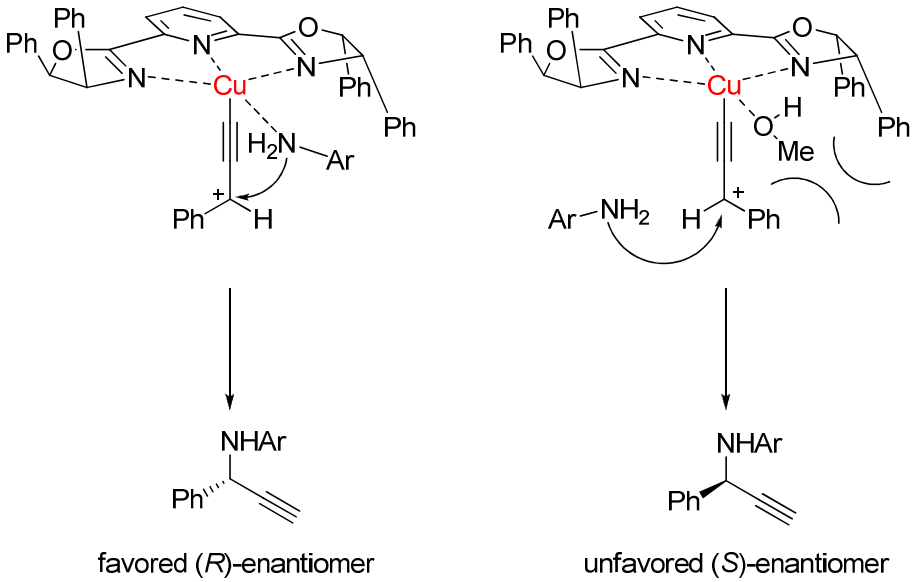


Figure 5.6 Enantiodiscriminating step for a proposed monomeric copper-complex

π-π INTERACTIONS

To explain the high enantioselectivity of the reaction, the chiral ligand should be in close proximity to the reacting center in order to shield one side of cationic intermediate effectively. Because the copper acetylide is linear and pointing away from the ligand, other interactions, in addition to repulsive interactions, may play a role. Attractive interactions from ligand to substrate, such as *π*-*π* interactions,[10] can also induce the necessary energy gain in the pre-organized transition state and yield the product in high optical purity.

During the last decade, *π*-*π* interactions have more often been invoked in order to explain the observed selectivities in transition metal catalyzed reactions.[1,3a,6b,11] Also in the copper-catalyzed propargylic amination with pybox ligand **3f**, *π*-*π* interactions may play a role. Such interactions are imaginable if the aromatic ring of the substrate is pointing towards the phenyl substituent of the ligand and causes a T shaped edge-to-face interaction, also known as CH-*π* interaction (Figure 5.7, type **A**).[12] This type of binding is fairly weak (~2 kcal/mol), and can probably not account solely for the observed selectivities. However, the total enthalpy may become appreciable as a result of the interplay of many *π*-*π* interactions (*e.g.* type **B** and **C**). The two most enantioselective pybox ligands, **3f** and **3h**, bear their aromatic groups in a *cis* orientation, allowing multiple *π*-*π* interactions (*e.g.* face-to-face interaction type **B**). In addition, the amine nucleophile, *e.g.* aniline, coordinated *trans* to the pyridine-nitrogen atom, can also participate in these stabilizing CH-*π* interactions (type **C**), which may explain the higher enantioselectivities found with aniline-type nucleophiles.

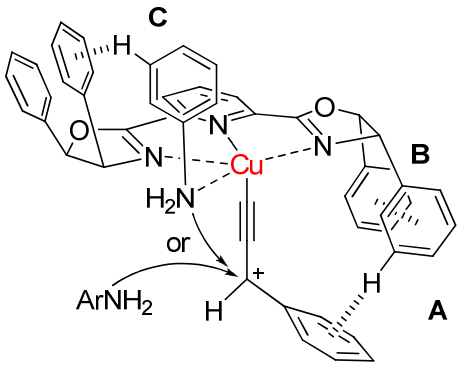


Figure 5.7 π-π interactions (**A**, **B**, and **C**) in the transition state of a monomeric copper-complex.

The data derived from the catalysis with a small set of substrates (Table 5.3) shows an increase in enantioselectivity if the π-system of the aromatic ring of the substrate is more electron-rich. This may be explained by a stronger π-π interaction between the substrate and the ligand. As depicted in Table 5.2, the highest enantioselectivity is obtained in protic dipolar solvents such as methanol. This phenomenon is also reported by Diederich *et al.* who states that the apolar binding strength increases consistently from apolar to dipolar aprotic solvents, to protic solvents.[7,13] According to Diederich water promotes the π-π interactions the most. By contrasts, our reaction is very slow in water and affords the propargylic amine in almost racemic form, although this may be a result of the inhomogeneous reaction mixture.

The exact geometry of the transition state of the catalytic process is unknown (in Figure 5.7 a possible intermediate structure is given). However, the amine nucleophile, either the one attached to the copper or one from the solution, attacks from the *Re*-face side, affording the *R*-enantiomer of the propargylic amine if (4*S*,5*R*)-diPh-pybox (*ent*-**3f**) is used.

5.4.2 Relevant Copper Complexes in Literature

From the literature it is known that most crystal structures of copper-alkyne complexes possess multiple copper atoms.[14] The acetylenic moiety can bind to the copper ions in several ways. Often coordination from a single acetylide to two or more copper ions is observed (Figure 5.8). Besides this, coordination of the acetylene to the copper is also possible with its π-system.[14b]

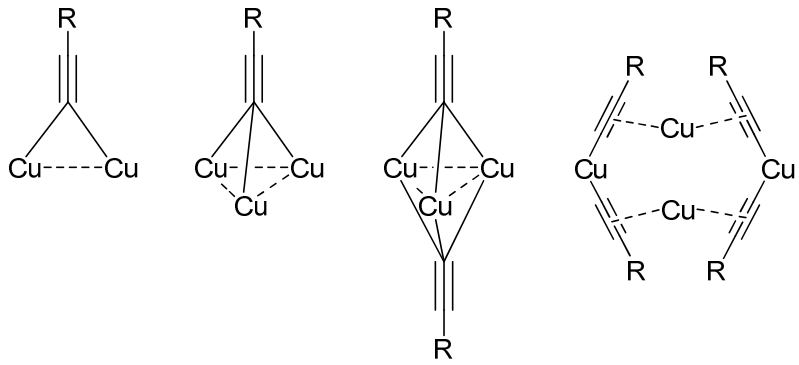
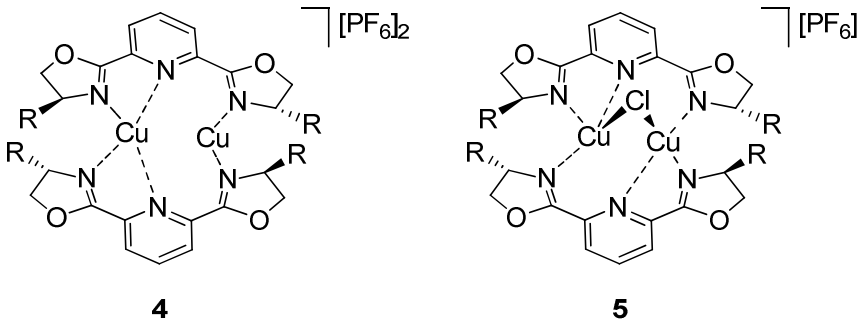


Figure 5.8 Coordination behavior in copper-acetylene complexes

Recently, Straub reported a computational study revealing that dinuclear and tetranuclear copper acetylide complexes are likely to give better results in the copper-catalyzed azide-alkyne cycloaddition than mononuclear complexes.[15] Also the experimental evidence indicates that the active copper complex in the cycloaddition reaction requires at least two metal centers, and one or more alkyne ligands (see also Chapter 1, § 1.2).[16]

Díez *et al*. reported that the common mechanistic proposal involving a unique active monomeric copper species is not fully satisfactory.[17] The formation of a certain type of copper complex is dependent on the copper precursor, and the ratio between the amounts of copper salt and ligand. Upon mixing *i*-Pr-pybox in a 1 to 1 ratio with $[Cu(CH_3CN)_4[PF_6]$ in CH_2Cl_2, they isolated a dinuclear complex (**4**, Figure 5.9), which retained its nuclearity after reaction with NaCl to produce the complex $[Cu_2Cl(i\text{-Pr-pybox})_2][PF_6]$ **5**.



4 **5**

Figure 5.9 Dimeric copper-pybox complexes

X-ray structure analysis of complex **4** revealed that the copper atoms have different coordination environments showing linear and distorted tetrahedral arrays. In a complex similar to **5** (counterion is $CuCl_2^-$ instead of PF_6^-) no significant differences between the two copper atoms were observed. Although, according to the NMR resonance signals, both complexes are C_2 symmetric in solution, at lower temperature the ^1H NMR signals of complex **5** (with $CuCl_2$ anion) become broad, proving a mixture of several species. Díez also stated that the occurrence of a monomeric species or an equilibrium involving mononuclear and binuclear complexes in solution cannot be ruled out. Nevertheless, a mechanism via a bi- or multinuclear copper complex as the active catalytic species has to be considered for our reaction based on these reports. In the next part of this chapter pathways for multinuclear active copper complexes will be described.

5.4.3 MULTINUCLEAR COPPER COMPLEX

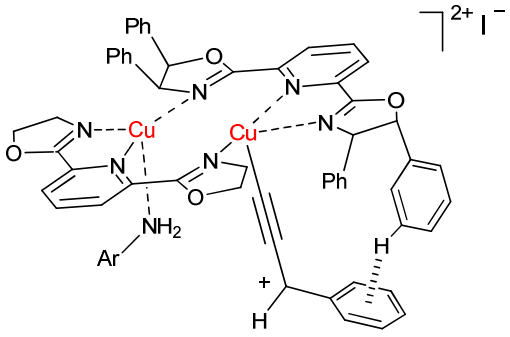
For the substrates with an aromatic side chain, the steric interactions seem to explain the observed selectivities, perhaps facilitated by π-π interactions (Figure 5.6 and 5.7). However, the poor enantioselectivities found for the propargylic acetates with aliphatic side chains, *e.g.* *i*-Pr (Table 5.3, entry 10), are not well explained by a model based on steric hindrance. Also the unexpectedly high enantioselectivities observed for this type of substrates with Me-pybox as the ligand are difficult to explain. It is unlikely that aliphatic interactions between the

substituents of the ligand and the substrate cause this high level of asymmetric induction, because other ligands with alkyl substituents, such as *i*-Pr-pybox **3b**, are less selective.

As reported in the literature, the copper complexes with acetylene and pybox ligands often consist of multiple copper ions and ligand molecules (see § 5.4.2). This suggests that a multinuclear copper complex may be the most active catalytic species in the enantioselective propargylic amination. As illustrated by the initial-rate kinetics experiments, the kinetics under the reaction conditions cannot be described as simple first order in copper concentration. At this point we can only speculate on the kinetics of the reaction, but the presence of an active multinuclear copper species is not unlikely in view of the results for the azide-alkyne cycloaddition reaction (*vide supra*). If the current opinion about the copper-catalyzed azide-alkyne cycloaddition is correct, the copper-pybox mixtures could also form multinuclear copper species that are reactive in the catalytic process.

As stated before, we have to be careful with the interpretation of the ESI-MS results. Nevertheless, the measurements do indicate the formation of multinuclear copper complexes. Furthermore, a clear dependence on the presence of DIPEA on the composition of the reaction mixture is observed. Presumably, this change in complex concentrations is the reason why the reaction with DIPEA proceeds faster and more selectively. Although the exact mechanism of action is not clear, DIPEA could be thought to increase the relative concentration of the more reactive and enantioselective complex, lowering the rate of competitive routes towards the product. With the less selective Me-pybox, an even higher abundance of multinuclear copper complexes is observed in the ESI-MS measurements.

The results obtained by the kinetics and ESI-MS experiments suggest the formation of higher copper aggregates. The question arises whether these complexes are only resting states or active catalytic species (or their precursors). Although it is too early to draw conclusions from the experimental data we have obtained so far, structures such as **6** and **7** can be imagined. The formation of **6** can be proposed based on complex **5** in Figure 5.9 (the substituents of the pybox in front have been omitted for clarity).



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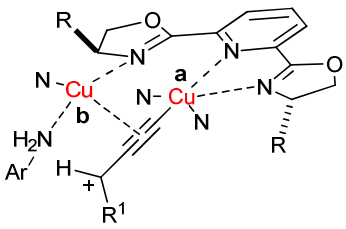

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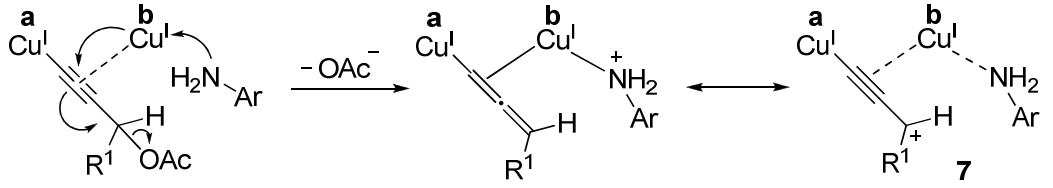
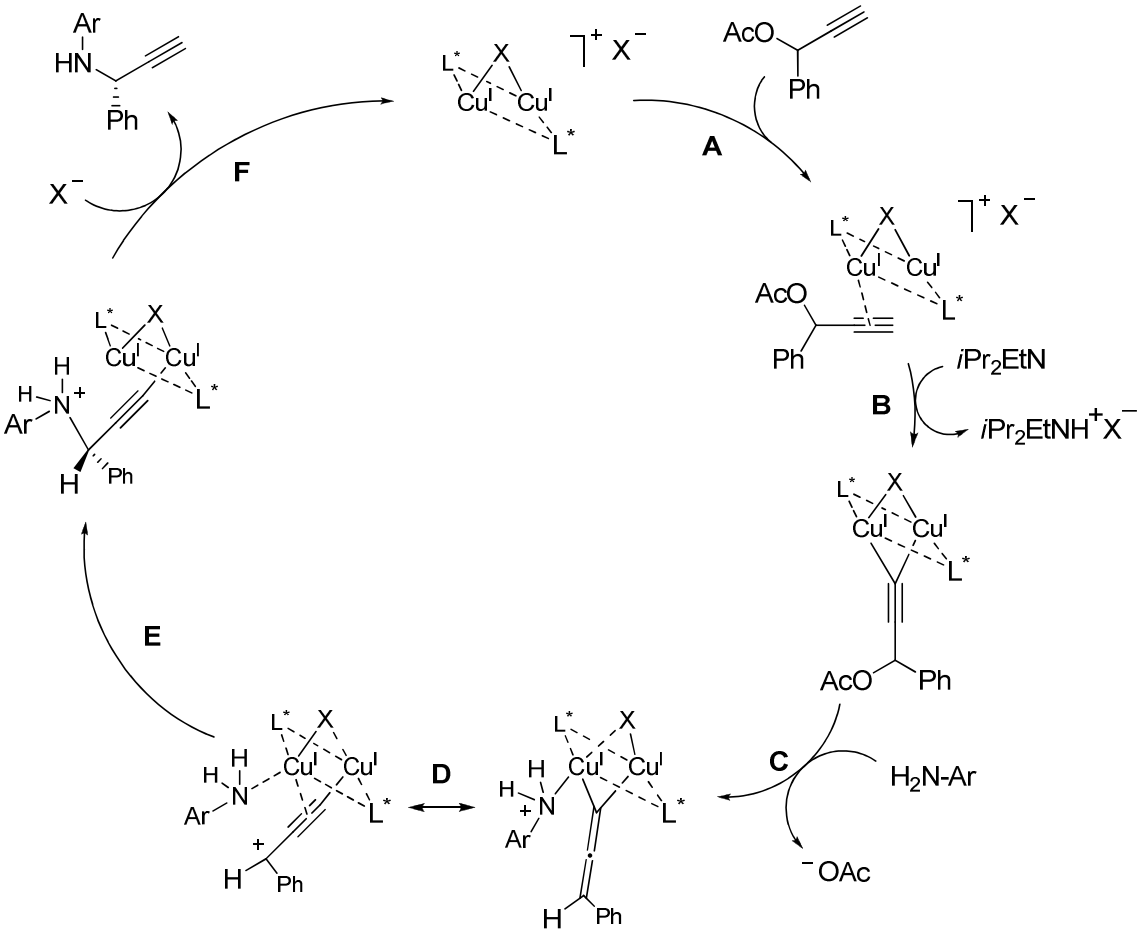
The chloride, or in our case an iodide ion is replaced by the substrate-acetylide, which coordinates probably to both copper ions (not shown in the illustration). Coordination of the amine nucleophile and liberation of the acetoxy anion leads to complex **6**. The phenyl substituent of the substrate should be folded underneath the pybox ligand depicted at the back, to give the amine the opportunity to attack from the *Re*-face side, explaining the observed absolute configuration of the product if (4*S*,5*R*)-diPh-pybox (*ent*-**3f**) is used. In this proposed transition state π-π interactions may play a stabilizing role.

In complex **7** the pybox ligand in front is omitted and only the coordinating nitrogen atoms are drawn. We depict in **7** the π-coordination of the acetylene to the second copper ion **b**. This suggests that upon entrance of the amine, the electron density at the second copper center is increased, donating more electron density into the π-system of the acetylene (Scheme 5.4). This interaction forces the acetoxy group to leave providing intermediate **7**. As mentioned above, the activated propargylic position and the amine are now in the appropriate distance to react with each other. All nucleophiles, that give good enantioselectivities with diPh-pybox **3f**, possess an aromatic ring for additional π-π interactions and are able to coordinate to the copper with a nitrogen atom (*e.g.* aniline, indole). This suggests the formation of a highly organized transition state in agreement with the observed high selectivity. Other nucleophiles, *e.g.* the carbon nucleophile 2,2,5-trimethyl-1,3-dioxane-4,6-dione, are deficient in one or both of these properties and afford the products with low or without enantioselectivity.



Scheme 5.4 Proposed mechanism of the liberation of the acetoxy group

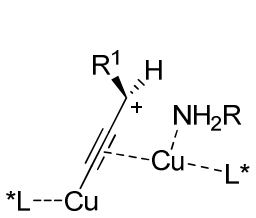
If the complex as described above is the active catalytic species, the previously described catalytic cycle (Scheme 5.3) needs to be modified. The most abundant copper species observed in the ESI-MS experiments (*m*/*z* 1105) and the supposed counterion CuI_2^- lead to a neutral complex, which can be taken as the starting point for a modified catalytic cycle (Scheme 5.5). The copper complex activates a nearby alkyne (step **A**), which upon deprotonation with DIPEA gives the copper acetylide species (step **B**). The acetylide is now depicted as bonded to two copper ions, as discussed above. As the amine enters, the acetate group is released (step **C**), affording a cationic intermediate, which is stabilized by resonance (step **D**). The resonance structure in which the cationic charge is depicted at the 3-position of the propargyl moiety, illustrates best how C-N bond formation may occur. The regio- and enantioselectivity of the reaction is most probably determined during the formation of the C-N bond (step **E**). After anion exchange, the product is released to complete the catalytic cycle (step **F**).



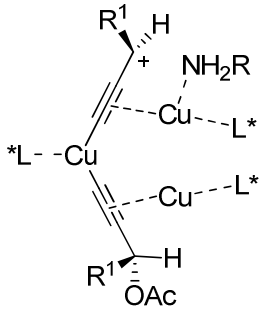
Scheme 5.5 Modified catalytic cycle for dinuclear copper catalyst (L* = (4*S*,5*R*)-diPh-pybox, X = counteranion, *e.g.* I or acetylide)

Finally, we will try to give an explanation for the high enantioselectivities observed with Me-pybox for the reaction with propargylic acetates bearing aliphatic side chains. Probably the most simple interpretation of this phenomenon is the occurrence of a different mechanism, or more specifically, the reaction proceeds via another type of copper complex. The coordination of the pybox ligand is not necessarily flat and rigid. The two pybox ligands in the crystal structure of Díez' complex **4** are, for example, twisted around the copper-copper axis and form a double-helical structure. If the copper complex contains the more crowded pybox ligands, such as diPh-pybox **3f**, the steric hindrance of the substituents hampers the formation of higher copper aggregates (*i.e.* more than two Cu ions) and the catalytic species may look predominantly like **7'**. When the ligand contains small substituents, like with Me-pybox, the ligand attached to a the third copper ion will fit and an even more reactive, trinuclear copper intermediate, like **8** may be formed. Although the substituents are small on each ligand, the combined chirality of all three ligands, accompanied by a possible chiral twist of the ligands, makes the copper environment suitable for high asymmetric induction in the propargylic amination of several substrates with aliphatic side chains. Nevertheless, the low selectivities found with the Me-pybox for the catalysis with the substrates bearing aromatic side chains is not well understood. Perhaps, the rigidity of the aromatic side chain interrupts the formation of a well-defined trinuclear complex affording the products via complex **7'**,

and/or via other complexes, in low enantiopurity. The complexity of the reaction mixture of this system, as observed in the ESI-MS experiments, probably implicates the existence of several reactive species.



7'



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Of course more experimental results are required in order to get better insight into the mechanistic aspects of the enantioselective copper-catalyzed propargylic amination. Several observations are still hard to explain, and the present discussion is only a beginning of the process of elucidating the mechanism of this remarkable reaction.

5.5 CONCLUSIONS

Mechanistic aspects of the enantioselective copper-catalyzed propargylic amination reaction have been discussed. Initial rate kinetics under the reaction conditions revealed that the catalysis cannot be described as a simple first order process in copper concentration. ESI-MS experiments indicated the formation of multinuclear copper complexes, which might be the active species in the catalysis. Although the nature of the active species is unknown, one of the first steps in the catalysis is the formation of a copper acetylide. After liberation of the acetate moiety, the acquired achiral intermediate is attacked by the amine nucleophile in an enantioselective fashion. In this step π-π interactions could play a role as indicated by the substrate and solvent dependence on the enantioselectivity with the diPh-pybox ligand. The catalysis with Me-pybox and propargylic acetates with aliphatic side chains, possibly occurs via a different active copper complex. More experimental results, *e.g.* crystallization of the copper pybox complexes for crystal structure determination, computational calculations on the proposed intermediate structures, more initial rate kinetics measurements, and broader substrate and nucleophile studies, are required in order to get a better insight into the mechanism of the enantioselective copper-catalyzed propargylic amination.

5.6 ACKNOWLEDGEMENTS

I would like to thank M. M. E. Delville for her efforts during her internship at MercaChem. Dr. G. Verspui and dr. P. Molenveld (MercaChem, Nijmegen) are kindly acknowledged for fruitful discussions. The collaboration with dr. T. Marcelli (Royal Institute of Technology, Stockholm, Sweden) and dr. S. Ingemann Jørgensen is very much appreciated.

5.7 EXPERIMENTAL SECTION

General Remarks – The general information is described in Chapter 2 and 3. ESI-MS measurements were performed on a Finnigan LXQ linear ion trap mass spectrometer.

Standard reaction for HPLC measurements. Copper iodide (3.8 mg, 0.020 mmol) and pybox **3f** (12.6 mg, 0.024 mmol) were stirred in MeOH (1.4 mL) for 20 minutes. To the acquired red solution, 1-phenylprop-2-ynyl acetate (35 mg, 0.20 mmol) in MeOH (0.3 mL) was added. The mixture was stirred for 15 minutes, followed by addition of a solution of *o*-anisidine (45 µL, 0.40 mmol), DIPEA (140 µL, 0.80 mmol) and ethylbenzene (24.8 µL, 0.20 mmol, internal standard) in MeOH (0.3 mL). The reaction was followed in time by taking at intervals small aliquots from the reaction mixture and filtrate these over a short pad of silica followed by injection into the chiral HPLC apparatus. HPLC conditions: Chiralcel AD-H, Heptane/IPA 99:1, 1.0 mL/min, λ = 254 nm: ethylbenzene (3.3 min), 1-phenylprop-2-ynyl acetate (7.0 and 7.6 min), *o*-anisidine (11.6 min), 2-methoxy-*N*-(1-phenylprop-2-ynyl)aniline (9.1 and 12.4 min).

Initial-rate kinetics with NMR. The substrate was dissolved in CD_3OD and added to a solution of the copper-pybox complex in CD_3OD in a NMR tube. With the addition of a solution of *o*-anisidine and DIPEA in CD_3OD to the NMR tube, the reaction was started. After quick mixing, the NMR tube was placed in the NMR apparatus. The first datapoint was collected after 1 or 2 minutes after *o*-anisidine addition. Every minute a spectrum was measured (1 scan). The integrals of the α-H signal of the substrate (6.42 ppm) and product (5.33 ppm) were used for the determination of the conversion.

ESI-MS Measurements. An alkaloid tube was filled with stock solutions of the appropriate substances in methanol, followed by addition of methanol to afford a total amount of 500 µL and a copper concentration of 0.8 mM. Amounts of stock solution added of respectively CuI-pybox (100 µL, ratio 1:1.2, 4 mM in [Cu]), 1-phenylprop-2-ynyl acetate (40 µL, 100 mM), *o*-anisidine (40 µL, 200 mM), and DIPEA (40 µL, 400 mM). The stock solutions of *o*-anisidine and DIPEA were mixed before addition. The solution in the alkaloid tube was thoroughly mixed and subsequently injected in the ESI-MS at a typical flow rate of 20 µL/min. The scan range was *m*/*z* 100–2000.

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