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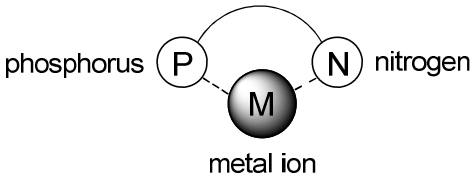
SUMMARY

TRIAZOLE-BASED P,N LIGANDS

DISCOVERY OF AN ENANTIOSELECTIVE COPPER-CATALYZED PROPARGYLIC AMINATION REACTION

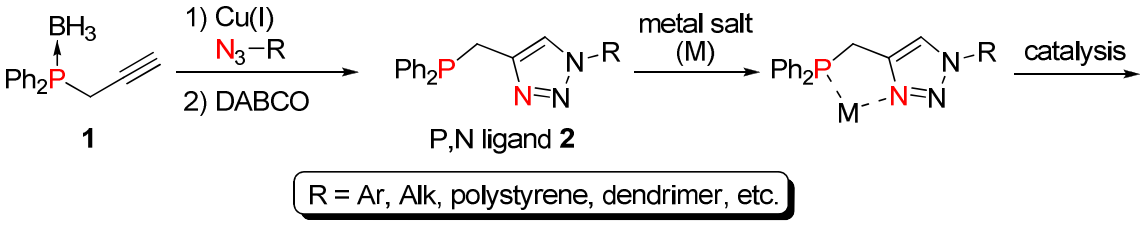
Molecular chirality plays a key role in everyday life. In the human body chiral host molecules recognize two enantiomeric guest molecules differently. Therefore, the access to enantiomerically pure compounds in the development of pharmaceuticals, but also agrochemicals, flavors, and fragrances is a very significant endeavor. Asymmetric transition metal catalysis has emerged as an efficient tool to synthesize enantiomerically enriched molecules. To influence the catalytic reactivity of the transition metal, ligands play an important role. The first chapter starts with a short overview of the history of asymmetric transition metal catalysis, and the accompanying chiral ligands. A widely used class of chiral ligands are the heterobidentate P,N ligands in which a phosphorus and a nitrogen atom coordinate to the metal ion. The development of this type of ligands is an important theme of the thesis.



The recently discovered copper(I)-catalyzed “click” reaction between azides and terminal alkynes provides 1,4-disubstituted 1,2,3-triazoles in a regioselective way. We envisaged that the use of this reaction would allow a facile, modular synthesis of novel P,N ligands with the

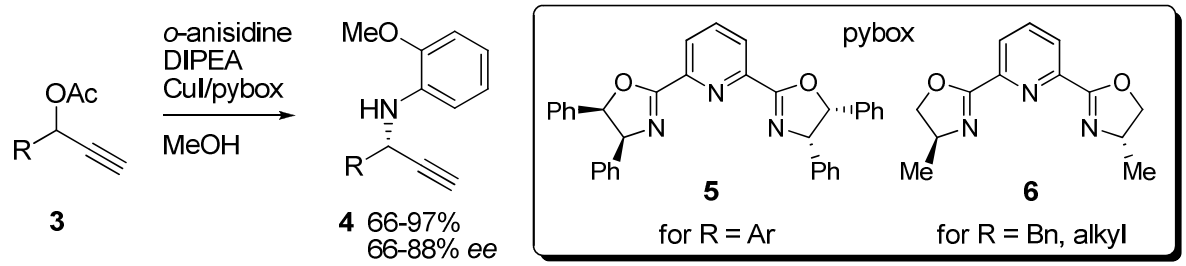
triazole moiety as the coordinating nitrogen component. To arrive at chiral, enantiopure P,N ligands for asymmetric catalysis an enantioselective propargylic substitution reaction seems well qualified to provide the required chiral building block. Besides being a versatile entity for further chemical transformations, the propargylic subunit is also part of various natural products, fine chemicals, and synthetic pharmaceuticals. However, propargylic substitutions are rather unexplored and only one metal complex, a diruthenium complex, is able to perform asymmetric propargylic substitutions catalytically. Obviously, the exploration of new enantioselective propargylic substitution reactions is of importance.

In chapter 2 the synthesis of the first, achiral, triazole-based P,N ligands is described. Propargylation of borane-protected diphenylphosphine with propargyl bromide gives the propargylic phosphine **1**. Via the copper-catalyzed azide-alkyne cycloaddition the triazole group is introduced. Interestingly, also polystyrene-bound azides or dendritic azides are allowed in this reaction leading to catalysts, which can also be recycled. Borane exchange with DABCO affords the liberated P,N ligands (**2**). As name for this class of ligands we have chosen for ClickPhine, to point out that these phos*phine*s can be prepared in a very *fine* manner with *click* chemistry. The palladium complexes of the novel ligands are highly active and selective in the Pd-catalyzed allylic alkylation of cinnamyl acetate applying the sodium salt of diethyl methylmalonate as nucleophile.

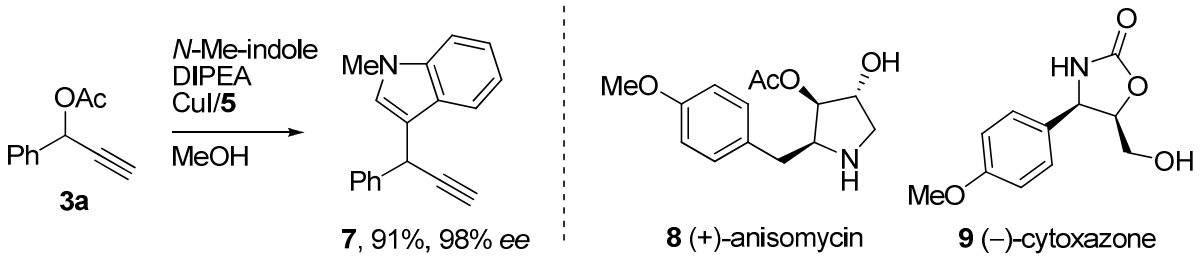


In the next chapter the first example of an enantioselective copper-catalyzed propargylic amination is described. From a variety of readily available propargylic acetates (**3**), propargylic amines (**4**) are prepared in high yields and optical purities using chiral pyridine-2,6-bisoxazoline (pybox, **5** or **6**) ligands and copper iodide as catalyst. The best results are obtained in methanol and with diisopropylethylamine (DIPEA) as the base. The investigation shows that propargylic amines with an aromatic side chain (R = Ar) are obtained with the highest *ee* values using pybox ligand **5**. With a benzyl or alkyl side chain, pybox ligand **6** affords the products with the highest enantioselectivity. As nucleophile for these aminations,

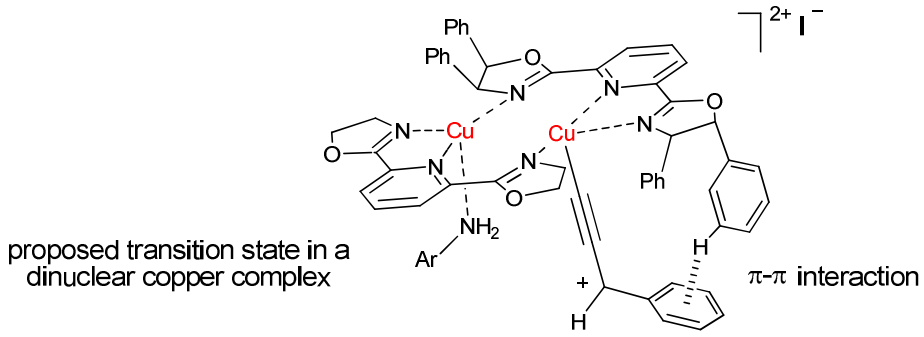
o-anisidine is chosen; the anisidyl ring can be cleaved and consequently produce the primary amine.



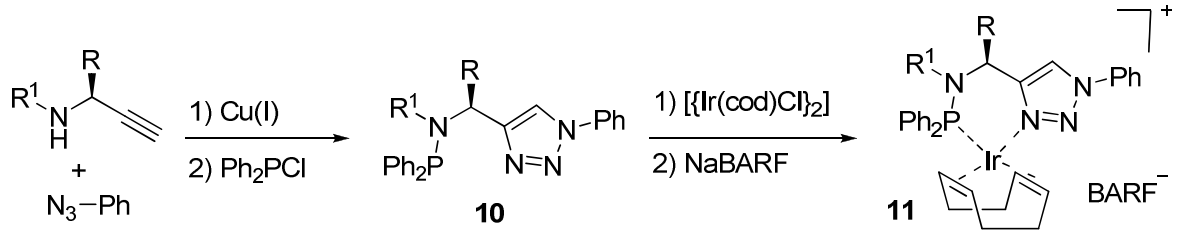
In chapter 4, different nitrogen and carbon nucleophiles are tested in the enantioselective copper-catalyzed propargylic substitution reaction. Although carbamides, and sulfonamides are ineffective, amine nucleophiles give the desired products in high yields (66-97%). The enantioselectivity obtained is highest for aniline, and its derivatives (up to 87% *ee*). Interestingly, some carbon nucleophiles can also be used, and with indoles excellent *ee* values are obtained (98% *ee* for **7**). To illustrate the versatility of the obtained propargylic amines formal total syntheses of two biologically active compounds, (+)-anisomycin **8** and (−)-cytoxazone **9**, are accomplished.



The mechanism of the enantioselective copper-catalyzed propargylic amination is discussed in chapter 5. By following the reaction with chiral HPLC, NMR and ESI-MS, new data are acquired with the purpose to elucidate the mechanism. Although initial rate kinetics and ESI-MS experiments suggest the formation of multinuclear copper clusters, no direct prove for the presence of either an active mononuclear or multinuclear copper species is obtained. Studying the substrate and solvent dependency of the reaction reveals that π-π interactions may influence the enantiodiscriminating step. Based on own results and those of other research groups, a catalytic cycle is proposed together with possible transition states.



The final chapter deals with the synthesis of enantiopure ClickPhine P,N ligands starting from chiral propargylic amines. The propargylic amines are provided by the enantioselective copper-catalyzed propargylic amination or derived from the α-amino acid (*S*)-proline. The enantiopure P,N ligands **10** are obtained by coupling of the triazolyl amines, acquired by the copper-catalyzed azide-alkyne "click" reaction, with a chlorophosphine. The Ir-BARF complexes of these ligands (**11**) are effectively used in the asymmetric hydrogenation of challenging olefins affording the saturated products with promising enantioselectivity (up to 77% *ee*).



cod = 1,5-cyclooctadiene, BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.