Asymmetric Catalysis

DOI: 10.1002/anie.200705264

Enantioselective Copper-Catalyzed Propargylic Amination**

*Remko J. Detz, Mariëlle M. E. Delville, Henk Hiemstra, and Jan H. van Maarseveen**

Propargylic amines are versatile building blocks and intermediates for organic synthesis. 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.[1] 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. Propargylic substitution with transition metals is a poorly developed reaction type, in contrast to allylic substitution. A fundamental substitution reaction of propargylic alcohol derivatives is the Nicholas reaction, which occurs via a stoichiometric cobalt–alkyne complex.[2] 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.[3]

Although successful with alcohols and satisfactory with amides, a $TiCl_4$-mediated substitution of propargylic esters did not proceed with primary and secondary amines.[4] Murahashi and co-workers demonstrated the highly efficient preparation of several propargylic amines by a copper-catalyzed substitution reaction.[5] Rhenium, gold, rhodium, and iron complexes were also reported recently to be effective catalysts for propargylic amination.[6] Remarkably, enantioselective examples of propargylic substitution reactions are rare,[7] and to our knowledge no asymmetric amination reaction has been reported to date. Inspired by the results of Murahashi and co-workers, we describe herein an enantioselective version of the copper-catalyzed propargylic amination of propargylic acetates.

In a first attempt to induce enantioselectivity in the amination of racemic 1-phenylprop-2-ynyl acetate (**9a**), we screened a selection of copper–pyridine-2,6-bisoxazoline (pybox) complexes. Metal complexes of chiral pybox ligands are well established in asymmetric catalysis.[8] We decided to use *o*-anisidine in this study because of its function as a capped primary amine.[9] Initial experiments with the commercially available pybox ligands **2**–**5** were encouraging (Table 1). In all cases, the propargylic amine **10a** was obtained in high yield, and asymmetric induction was observed, although to a low extent.

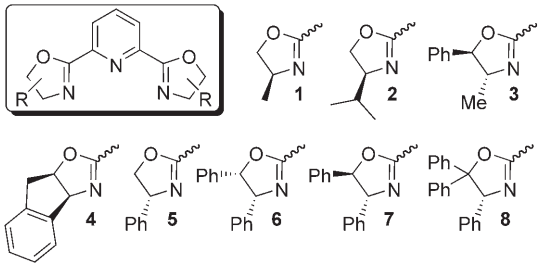
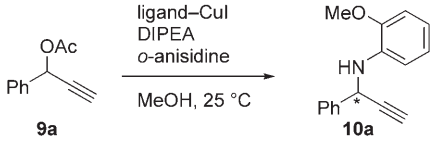


Table 1: Survey of ligands for the propargylic amination.[a]



9a **10a**

Entry	Ligand	Yield [%]	Config.[b]	*ee* [%]
1	**1**	94	*R*	25
2	**2**	93	*R*	17
3	**3**	97	*R*	12
4	**4**	74	*R*	28
5	**5**	99	*S*	42
6	**6**	97	*S*	76
7	**7**	97	*S*	19
8	**8**	97	*S*	61

[a] Reaction conditions: **9a** (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] The absolute configuration was determined by comparison of the optical rotation with a literature value.[9]

We envisaged that modification of the ligand would be necessary to improve the enantioselectivity. Gratifyingly, the use of ligand **6**, which has aromatic substituents in a *cis* relationship at the 4- and 5-positions of the two oxazoline rings, led to higher enantioselectivity. The use of ligand **1**, **7**, or **8** did not lead to an improvement in this result. The synthesis of ligands **1** and **6**–**8** is well documented, and **6**, in particular, was obtained readily in only two steps from commercially available compounds.[10]

An optimization study with ligand **6** revealed that other copper salts, such as $[Cu(CH_3CN)_4]PF_6$, CuOTf·benzene, and $Cu(OAc)_2$, gave similar results, although CuI was slightly superior with respect to the selectivity (Table 2, entries 1–3). High enantioselectivity and a high reaction rate were only observed with polar protic solvents, the best results with

[*] R. J. Detz, M. M. E. Delville, Prof. Dr. H. Hiemstra, Dr. J. H. van Maarseveen
Van't Hoff Institute for Molecular Sciences
Biomolecular Synthesis
University of Amsterdam
Nieuwe Achtergracht 129, 1018 WS Amsterdam (The Netherlands)
Fax: (+31) 20-525-5670
E-mail: jvm@science.uva.nl
Homepage: http://www.science.uva.nl/hims-bms

[**] The National Research School Combination—Catalysis (NRSC-C) is gratefully acknowledged for financial support of this project.

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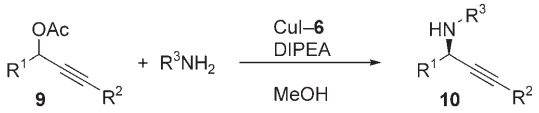
Table 2: Effect of the reaction conditions on the propargylic amination of **9a** with the pybox ligand **6**.[a]

Entry	Catalyst	Base	Solvent	*t* [h]	Yield [%]	*ee* [%]
1	$[Cu(CH_3CN)_4]PF_6$	DIPEA	MeOH	1	76	74
2	CuOTf·benzene	DIPEA	MeOH	1.5	99	73
3	$Cu(OAc)_2$	DIPEA	MeOH	1.5	99	73
4	CuI	DIPEA	toluene	25	99	21
5	CuI	DIPEA	CH_2Cl_2	25	97	34
6	CuI	DIPEA	THF	29	99	36
7	CuI	DIPEA	EtOH	1.5	99	60
8	CuI	–	MeOH	4	93	56
9	CuI	DBU	MeOH	0.5	2	7
10	CuI	Cs_2CO_3	MeOH	0.5	8	33
11[b]	CuI	DIPEA	MeOH	3	99	82
12[c]	CuI	DIPEA	MeOH	24	97	85
13[d]	CuI	DIPEA	MeOH	48	99	86

[a] Reaction conditions: **9a** (0.20 mmol), *o*-anisidine (0.40 mmol), the base (0.80 mmol), the Cu salt (0.02 mmol), and **6** (0.024 mmol) were stirred in the indicated solvent (2 mL) at 25 °C. [b] The reaction was performed at 0 °C. [c] The reaction was performed at −20 °C. [d] The reaction was performed at −40 °C. Tf = trifluoromethanesulfonyl.

Table 3: Propargylic amination with various propargylic acetates.[a]



Entry	R^1, R^2	R^3	Product	Yield [%]	*ee*[b] [%]
1	Ph, H	2-$MeOC_6H_4$	**10a**	97	85 (99)
2	4-$MeOC_6H_4$, H	2-$MeOC_6H_4$	**10b**	97	83
3	4-$CF_3C_6H_4$, H	2-$MeOC_6H_4$	**10c**	84	80
4	2,4-$Me_2C_6H_3$, H	2-$MeOC_6H_4$	**10d**	91	88
5	2,4-$Cl_2C_6H_3$, H	2-$MeOC_6H_4$	**10e**	88	79
6	2-pyridyl, H	2-$MeOC_6H_4$	**10f**	80	74
7	1-naphthyl, H	2-$MeOC_6H_4$	**10g**	91	85 (99)
8	2-naphthyl, H	2-$MeOC_6H_4$	**10h**	96	86 (99)
9	cinnamyl, H	2-$MeOC_6H_4$	**10i**[c]	62	57
10[d]	*i*Pr, H	2-$MeOC_6H_4$	**10j**	27	40
11[d]	pentyl, H	2-$MeOC_6H_4$	**10k**	76	13
12	Ph, H	4-$MeOC_6H_4$	**10l**	93	78
13	Ph, H	Ph	**10m**	94	87
14	Ph, H	4-$CF_3C_6H_4$	**10n**	87	86
15	Ph, Ph	2-$MeOC_6H_4$	**10o**	n.r.	–

[a] The propargylic acetate (0.20 mmol), the amine (0.40 mmol), DIPEA (0.80 mmol), CuI (0.02 mmol), and **6** (0.024 mmol) were stirred in methanol (2 mL) at −20 °C. [b] The *ee* value after recrystallization is given in brackets. [c] Product **10i** was accompanied by (*E*)-2-methoxy-*N*-(1-phenylpent-2-en-4-ynyl)aniline (24%, 16% *ee*). [d] The reaction was performed at 40 °C. n.r. = no reaction.

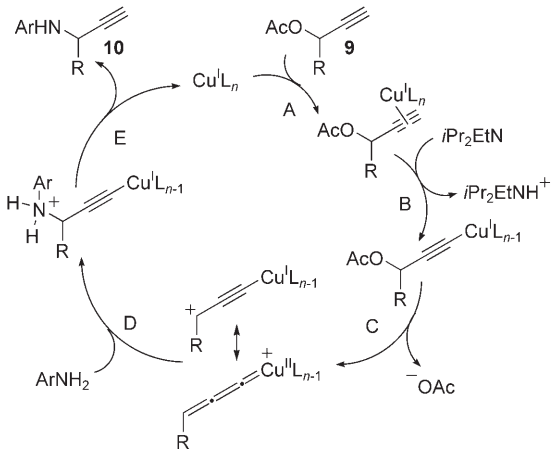
methanol.[11] The addition of a base seemed to be crucial in terms of both the yield and the selectivity (Table 2, entry 8). At a first glance, the base appeared to be only a rate-accelerating component; however, in its absence the enantioselectivity dropped by 20%. Stronger bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or cesium carbonate, had a detrimental effect on both the yield and the selectivity of the reaction (Table 2, entries 9 and 10). The best results were obtained with tertiary amines, such as diisopropylethylamine (DIPEA). At lower temperatures the enantioselectivity was improved further at the expense of an increase in reaction time (Table 2, entries 11–13).

Having established an optimal reaction protocol, we explored the scope and the generality of the method. 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*; Table 3). Slightly higher *ee* values were observed with more-electron-rich aromatic substrates (Table 3, compare entries 2 and 3, and entries 4 and 5). The reaction became more complex when the cinnamyl derivative **9i** was used (Table 3, entry 9). In this case, two major products were isolated: **10i**, with the amino group at the propargylic position as expected (62%, 57% *ee*), and an analogue in which the amino substituent is located at the alternative allylic position next to the phenyl moiety (24%, 16% *ee*).

Aliphatic substrates were less reactive, and a higher temperature (40 °C) was necessary for sufficient conversion. The catalytic process seems to be unsatisfactory with aliphatic substrates: Only low enantioselectivity was observed (Table 3, entries 10 and 11). Similar results to those with *o*-anisidine were obtained when electron-rich or electron-poor anilines were used as the nucleophile. As reported by Murahashi and co-workers,[5] no reaction occurred with an internal acetylene (Table 3, entry 15). This result serves as evidence for the necessity of the terminal acetylenic hydrogen atom.[5] Highly enantiomerically pure compounds were obtained by the recrystallization of some of the crude products (Table 3, entries 1, 7, and 8).

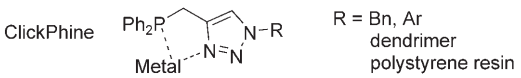
On a larger scale (with 5 mmol of the substrate; see the Experimental Section), the reaction proceeded in a similar manner, even with a lower catalyst loading (0.05 equiv). The optical purity of the product was increased through two recrystallization steps. The colorless crystals that formed were identified as the racemate; the propargylic amine **10a** was obtained in almost enantiomerically pure form (99% *ee*) from the mother liquor. Solidification of the mother liquor and recrystallization provided the optically pure enantiomer in 46% yield.

The mechanism of this reaction is still unclear. Nevertheless, we propose a catalytic cycle based upon our own experimental results and other data (Scheme 1). In the first step, the copper complex probably forms 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.[12] Deprotonation with a base gives the copper acetylide (step B); hence the necessity of the terminal acetylenic hydrogen atom. This intermediate loses the acetate group through an S_N1-type mechanism (step C), as also proposed by Murahashi and co-workers.[5] The resulting electrophilic intermediate is stabilized by resonance involving the Cu complex and attacked by the amine nucleophile (step D). The regio- and enantioselectivity of the reaction is most probably determined at this stage through the blocking of one side of the cationic intermediate by the copper–pybox complex. After proteolysis, the product is released to complete the catalytic cycle (step E).



Scheme 1. Proposed catalytic cycle for the copper-catalyzed propargylic amination of propargylic acetates.

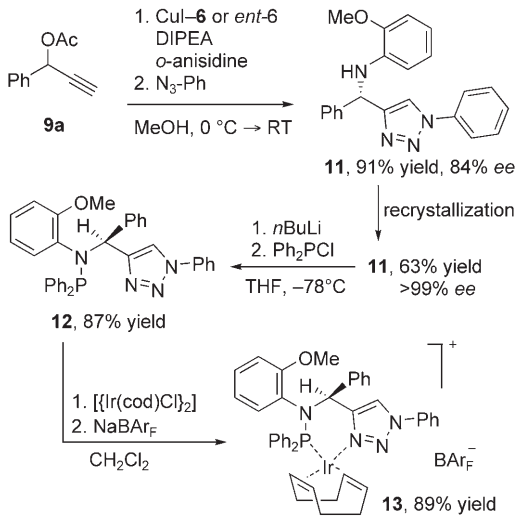
This research project originated from the search for a building block for the synthesis of a chiral ClickPhine ligand (Scheme 2). ClickPhines are P,N ligands described recently by our research group.[13] The key concept of this ligand class is the use of a triazole ring, which can be prepared readily by the



Scheme 2. Structure of ClickPhine ligands. Bn = benzyl.

copper-catalyzed 1,3-dipolar cycloaddition of alkynes with azides, as a nitrogen donor to a metal. By this approach, ligands can be synthesized and functionalized readily. To retain the simplicity of the synthesis and modification of these ligands, the route to a chiral building block should be straightforward and short. We envisaged that a chiral propargylic amine would be a suitable source of chirality. Having established a practical protocol for the synthesis of chiral propargylic amines, we investigated the synthesis of a chiral ClickPhine ligand. The chiral propargylic amine **10a** was converted readily into the corresponding triazole **11** through Cu^{I}-catalyzed 1,3-dipolar cycloaddition. Indeed, the transformation of the acetate **9a** into **11** via the amine **10a** could even be carried out in one pot (Scheme 3). A single enantiomer of **11** was obtained through a single recrystallization step. The amine **11** was deprotonated with *n*-butyllithium and coupled with chlorodiphenylphosphane to give the ClickPhine ligand **12** in good yield. The formation of the Ir^{I} complex **13** with ligand **12** gave some initial insight into the coordination behavior of this class of ligands. Enantioselective catalysis with the newly developed chiral ClickPhine ligand is currently under investigation.

In conclusion, 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 acetates. The procedure is practical and does not require the exclusion of air and moisture. Enantiomerically



Scheme 3. Synthesis of the chiral ClickPhine ligand **12** and the Ir^{I} complex **13**. cod = 1,5-cyclooctadiene, BAr$_F$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

pure propargylic amines (> 99 % *ee*) could be obtained by recrystallization of the products. Furthermore, we demonstrated the application of these amines as useful chiral building blocks through the synthesis of an optically active ClickPhine ligand.

Experimental Section

Typical procedure: CuI (48 mg, 0.25 mmol) and the pybox ligand **6** (156 mg, 0.30 mmol) were stirred in MeOH (40 mL) for 30 min. The acetate **9a** (0.87 g, 5.0 mmol) was added as a solution in MeOH (4 mL) to the resulting red mixture, which contained small white particles, probably of excess ligand. The mixture was cooled to −18 °C, and a cooled solution of *o*-anisidine (1.1 mL, 10 mmol) and diisopropylethylamine (3.5 mL, 20 mmol) in MeOH (6 mL) was added. The reaction mixture was stirred for 21 h at −18 °C, and then the volatile components were removed by evaporation. Column chromatography of the residue on silica gel (CH_2Cl_2/petroleum ether 1:2) gave **10a** (1.15 g, 97 %, 85 % *ee*) as a yellow oil. After two recrystallization steps (EtOAc/petroleum ether, heptane), **10a** (0.55 g, 46 %) was obtained as a single enantiomer (> 99.5 % *ee*).

Received: November 15, 2007
Published online: February 18, 2008

Keywords: amination · asymmetric catalysis · P,N ligands · propargylic amines · pybox ligands

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[11] More details of the optimization study can be found in Table 1 of the Supporting Information.

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