Asymmetric Amination

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Copper-Catalyzed Asymmetric Propargylic Substitution Reactions of Propargylic Acetates with Amines**

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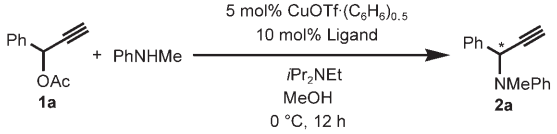
Recently, we have reported the ruthenium-catalyzed asymmetric propargylic alkylation of propargylic alcohols with acetone to give the corresponding propargylic alkylated products in good yields with a high enantioselectivity (up to 82% *ee*).[1] This was the first successful example of enantioselective and catalytic propargylic substitution reactions catalyzed by chiral thiolate-bridged diruthenium complexes.[1] More recently, as an extension of our study, we found the asymmetric propargylation of aromatic compounds with propargylic alcohols catalyzed by the same diruthenium complexes to give the corresponding propargylated aromatic compounds with a high enantioselectivity (up to 94% *ee*).[2] This method provided a novel approach for the catalytic asymmetric Friedel–Crafts alkylation of aromatic compounds by using propargylic alcohols as a new type of electrophile. However, propargylic substitution reactions with heteroatom-centered nucleophiles, such as alcohols, amines, thiols, and diphenylphosphine oxide, did not proceed enantioselectively in the presence of a catalytic amount of the same chiral diruthenium complexes. These results prompted us to investigate other transition-metal-catalyzed asymmetric propargylic substitution reactions with heteroatom-centered nucleophiles.[3]

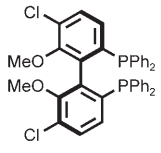
Optically active propargylic amines are synthetically versatile intermediates for the construction of various biologically active compounds and polyfunctional amino derivatives.[4] Recently, the transition-metal-catalyzed enantioselective addition of terminal alkynes to imines has been developed to produce the corresponding chiral propargylic amines with a high enantioselectivity,[5] with copper-catalysis being most reliable.[6] As another synthetic approach to chiral propargylic amines, we have now envisaged developing an enantioselective version of the copper-catalyzed propargylic substitution reactions of propargylic esters with amines that was originally reported by Murahashi and co-workers.[7] The first example of the copper-catalyzed asymmetric propargylic substitution reactions with amines has quite recently been reported by using optically active 2,6-bis(oxazolinyl)pyridines (pybox)[8] as chiral ligands, where the corresponding amines were obtained with up to 88% *ee*.[9] Herein, we describe a preliminary result of the copper-catalyzed enantioselective propargylic substitution reactions of propargylic acetates with amines by using optically active diphosphines, such as binap[10] and biphep,[11] as chiral ligands to afford the corresponding propargylic amines with a high enantioselectivity (up to 89% *ee*).

Treatment of 1-phenyl-2-propynyl acetate (**1a**) with *N*-methylaniline and *N*,*N*-diisopropylethylamine[12] in the presence of a catalytic amount of copper trifluoromethanesulfonate benzene complex, CuOTf·(benzene)$_{0.5}$, (5 mol%) and (*R*)-Cl-MeO-biphep[13,14] (10 mol%) in methanol[15] at 0°C for 12 h gave *N*-methyl-*N*-(1-phenyl-2-propynyl)aniline (**2a**) quantitatively with 85% *ee* (Scheme 1). The use of an equal amount of (*R*)-Cl-MeO-biphep (5 mol%) to the copper complex slightly decreased the enantioselectivity of **2a**. When (*R*)-binap was used in place of (*R*)-Cl-MeO-biphep as the chiral diphosphine, the reaction proceeded sluggishly with a similar enantioselectivity.[16]

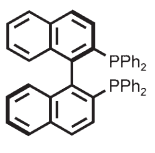


Ligand	Yield of **2a**	*ee* of **2a**
(*R*)-Cl-MeO-biphep	96%	85% *ee*
(*R*)-Cl-MeO-biphep[a]	93%	81% *ee*
(*R*)-binap	82%	85% *ee*

[a] 5 mol% of (*R*)-Cl-MeO-biphep was used.



(*R*)-Cl-MeO-biphep



(*R*)-binap

Scheme 1. Reactions of 1-phenyl-2-propynyl acetate (**1a**) with *N*-methylaniline in the presence of a catalytic amount of copper trifluoromethanesulfonate benzene complex and (*R*)-Cl-MeO-biphep or (*R*)-binap.

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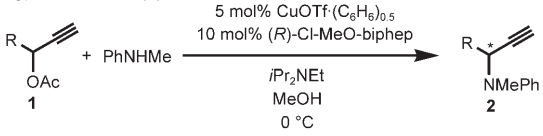
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Next, the catalytic propargylic amination of other propargylic acetates (**1**) was investigated by using (*R*)-Cl-MeO-biphep as a chiral ligand. Typical results are shown in Table 1.

Table 1: Copper-catalyzed enantioselective propargylic amination of propargylic acetates (**1**) with *N*-methylaniline.[a]



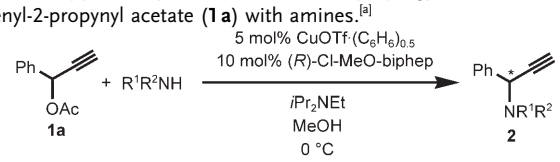
Entry	R	*t* [h]	Yield of **2** [%][b]	*ee* of **2** [%][c]
1	**1a**, Ph	12	**2a**, 96	85
2	**1b**, *p*-MeC_6H_4	12	**2b**, 98	81
3	**1c**, *p*-$MeOC_6H_4$	12	**2c**, 99	82
4	**1d**, *p*-ClC_6H_4	24	**2d**, 94	85
5	**1e**, *p*-BrC_6H_4	36	**2e**, 91	85
6	**1f**, *p*-PhC_6H_4	12	**2f**, 99	84
7	**1g**, 1-naphthyl	12	**2g**, 99	85
8	**1h**, 2-naphthyl	12	**2h**, 99	83
9	**1i**, cyclohexyl	48	**2i**, 0	–

[a] All the reactions of **1** (0.20 mmol) with *N*-methylaniline (0.40 mmol) and *N*,*N*-diisopropylethylamine (0.80 mmol) were carried out in the presence of copper trifluoromethanesulfonate benzene complex (0.010 mmol) and (*R*)-Cl-MeO-biphep (0.020 mmol) in MeOH (2.0 mL) at 0°C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details).

The introduction of substituents such as methyl, methoxy, chloro, bromo, and phenyl, at the *para*-position in the benzene ring of the propargylic acetate **1a** did not appreciably effect the yield and enantioselectivity of the products (**2**; Table 1, entries 1–6). Enantioselectivity of the same level was also observed in the reactions of 1-naphthyl-2-propynyl acetates (**1g** and **1h**) with *N*-methylaniline under the same reaction conditions (Table 1, entries 7 and 8). After recrystallization, optically pure propargylic amines were obtained in some cases. The presence of an aryl group at the propargylic position of the propargylic acetate was necessary to achieve a high enantioselectivity, and the reaction of 1-cyclohexyl-2-propynyl acetate (**1i**) with *N*-methylaniline did not proceed at all under the same reaction conditions (Table 1, entry 9). Further, the also reaction did not proceed when propargylic acetate bearing an internal alkyne moiety, such as 1,3-diphenyl-2-propynyl acetate, was used as a substrate, indicating that only the propargylic acetates bearing a terminal alkyne moiety can be employed successfully for this reaction.

A variety of amines are available as nitrogen-centered nucleophiles. Typical results are shown in Table 2. The introduction of substituents in the benzene ring of *N*-methylaniline slightly affected the enantioselectivity of the product. In fact, the presence of a chloro moiety at *para*-position of the benzene ring slightly increased the enantioselectivity, but that of a methyl group at *para*-position slightly decreased it (Table 2, entries 1–4). The use of cyclic amines such as piperidine and 1,2,3,4-tetrahydroquinoline as nucleophiles slightly decreased the enantioselectivity (Table 2, entries 5 and 6). A similar enantioselectivity was achieved when *N*-ethylaniline was used (Table 2, entry 7). In sharp contrast to the copper–pybox system[9] with which the reactions with aniline afforded the highest enantioselectivity of the products, only a low enantioselectivity was observed in our case (Table 2, entry 8).

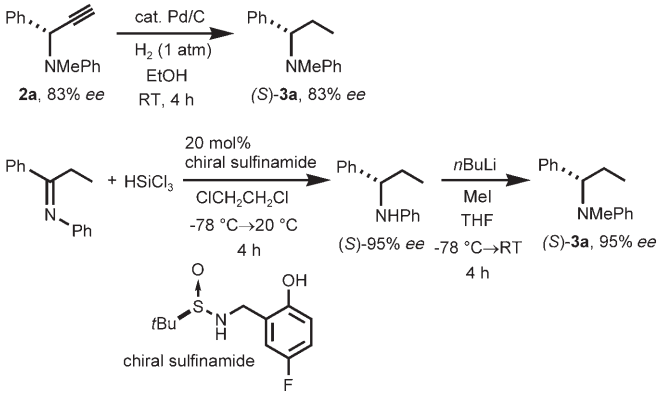
Table 2: Copper-catalyzed enantioselective propargylic amination of 1-phenyl-2-propynyl acetate (**1a**) with amines.[a]



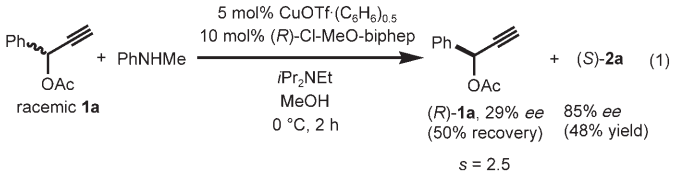
Entry	R^1, R^2	*t* [h]	Yield of **2** [%][b]	*ee* of **2** [%][c]
1	Ph, Me	12	**2a**, 96	85
2	*p*-ClC_6H_4, Me	12	**2j**, 96	89
3[d]	*p*-ClC_6H_4, Me	12	**2k**, 92	89
4	*p*-MeC_6H_4, Me	12	**2l**, 97	82
5	-$(CH_2)_5$-	12	**2m**, 64	80
6	-$C_6H_4(CH_2)_3$-[e]	12	**2n**, 97	81
7	Ph, Et	12	**2o**, 95	83
8	Ph, H	12	**2p**, 90	53

[a] All the reactions of **1a** (0.20 mmol) with amines (0.40 mmol) and *N*,*N*-diisopropylethylamine (0.80 mmol) were carried out in the presence of copper trifluoromethanesulfonate benzene complex (0.010 mmol) and (*R*)-Cl-MeO-biphep (0.020 mmol) in MeOH (2.0 mL) at 0°C. [b] Yield of isolated product. [c] Determined by HPLC (see Supporting Information for experimental details). [d] **1d** was used in place of **1a**. [e] 1,2,3,4-Tetrahydroquinoline was used as an amine.

To obtain more information on the enantioselective propargylic amination, the stereochemistry of the product **2a** was determined. Hydrogenation of **2a** in the presence of a catalytic amount of Pd/C under 1 atm of H_2 at room temperature for 4 h gave *N*-methyl-*N*-(1-phenylpropyl)aniline (**3a**; Scheme 2). The absolute configuration was in accord with (*S*)-**3a** obtained by the reported method,[17,18] showing that the original propargylic amine **2a** has an *S* absolute configuration. In a separate experiment, a low enantioselectivity was observed in **1a** after recovered a short reaction time as shown in Equation (1). This result means that there is a small difference in the reactivity between (*R*)-**1a** and (*S*)-**1a**, the latter being slightly more reactive. Although the detailed reaction pathway is not yet clear, we consider that *N*-methylaniline might attack the copper acetylide complex, which has a cationic γ-carbon atom, from the *re* face. The



Scheme 2. Determination of the absolute configuration of propargylic amine (**2a**).



(1)

copper acetylide complex is formed in situ from **1a** and the copper complex bearing (*R*)-Cl-MeO-biphep.

In summary, we have found the copper-catalyzed enantioselective propargylic substitution reactions of propargylic acetates with amines to give the corresponding propargylic amines in excellent yields with a high enantioselectivity (up to 89% *ee*). Optically active diphosphines such as Cl-MeO-biphep and binap have been found to function as suitable chiral ligands. The reaction described may provide a novel synthetic method for the preparation of chiral propargylic amines. Further investigation of the reaction mechanism[19] and for broadening the synthetic application of this asymmetric propargylic amination is in progress.

Experimental Section

A typical experimental procedure for the reaction of 1-phenyl-2-propynyl acetate (**1a**) with *N*-methylaniline: CuOTf·(benzene)$_{0.5}$ (2.5 mg, 0.010 mmol) and (*R*)-Cl-MeO-biphep (13.0 mg, 0.020 mmol) were placed in a 20 mL round-bottomed flask under N_2. Anhydrous methanol (1.0 mL) was added, and then the mixture was stirred at 60 °C for 1 h with a magnetic stirrer. Then, **1a** (34,8 mg, 0.20 mmol), *N*-methylaniline (42.8 mg, 0.40 mmol), and diisopropylethylamine (103.3 mg, 0.80 mmol) in anhydrous methanol (1.0 mL) were added under N_2, and the reaction flask was kept at 0 °C for 12 h. The solvent was concentrated under reduced pressure by an aspirator, and the residue was purified by the column chromatography (SiO_2) with hexane and ethyl acetate (97:3) as eluent to give *N*-methyl-*N*-(1-phenyl-2-propynyl)aniline (**2a**)[20] as a pale yellow solid (42.5 mg, 0.19 mmol; 96% isolated yield). $[\alpha]_D^{22} = +10.7$ (*c* 1.42, $CHCl_3$). The optical purity of **2a** was determined by HPLC analysis; DAICEL Chiralpak AD, hexane/*i*PrOH = 97/3, flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time; 5.64 min (minor) and 7.04 min (major), 85% *ee*.

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[10] Binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

[11] Biphep = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl.

[12] No reaction occurred in the absence of *N*,*N*-diisopropylethylamine. When triethylamine was used in place of *N*,*N*-diisopropylethylamine as a base, a similar enantioselectivity was observed.

[13] (*R*)-Cl-MeO-biphep = (*R*)-5,5′-dichloro-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl, is a commercially available reagent from Strem Chemicals.

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[15] The reaction did not proceed smoothly in other solvents such as EtOH, CH_2Cl_2, toluene, THF, MeCN, DMF, and 1,4-dioxane.

[16] Although a variety of optically active diphosphines and monophosphines, such as Duphos, chiraphos, diop, and mop, were investigated as chiral ligands for the propargylic amination, these did not work effectively. As a result, (*R*)-Cl-MeO-biphep was found to be the ligand of choice for the present propargylic amination. The detailed experimental results will be reported in due course.

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