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Copper-Catalyzed Enantioselective Propargylic Substitution of Propargylic Acetates with Enamines

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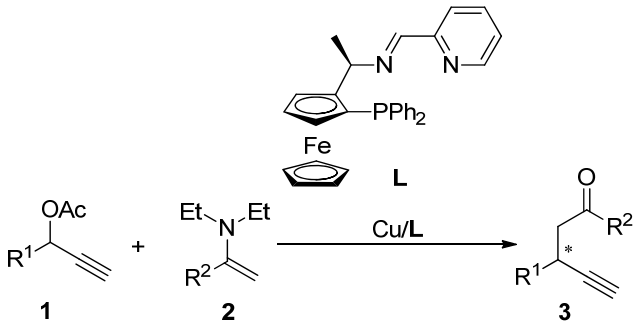
With the use of chiral tridentate P,N,N ligand, Copper-catalyzed enantioselective propargylic substitution of propargylic acetates with enamines has been achieved, giving the corresponding propargylic ketones in high yields and with excellent enantioselectivities.

The propargylic substitution reaction of propargylic alcohol as well as its derivatives with nucleophiles is one of the most useful tools for synthesis of various alkyne moiety-containing molecules,[1] which could easily be further transformed into useful complex compounds.[2] Since Nicholas and coworkers reported Co-mediated propargylic substitution reaction of propargylic alcohol in 1977,[3] many metal catalytic systems such as Ti, Fe, Ni, Cu, Ru, Pd, Re, Bi, Sc, Ir, Pt, and Au, have successfully been developed.[1] A wide range of nucleophiles such as carbon, oxygen, sulfur, and nitrogen can be used in the reaction. Owing to very significant value of chiral propargylic-substituted products in organic synthesis, asymmetric catalytic propargylic substitution reaction of propargylic alcohol derivatives with nucleophiles has attracted much attention in recent years.[4] In 2003, using thiolate-bridged diruthenium complexes as chiral catalyst, Hidai, Uemura, and co-workers achieved the first catalytic asymmetric propargylic substitution reaction of propargylic alcohol with acetone.[5] Although only up to 35%ee was obtained in the reaction, the work triggered the researcher's intense interest to asymmetric catalytic propargylic substitution reaction. In the past decade, a few metal catalysts such as Ru[6] and Cu[7] for asymmetric propargylic substitution reaction have been discovered. In the presence of these catalysts, a variety of nucleophiles such as ketone, aromatic compounds, alkene, aldehyde, amine, enamine and β-keto acid could undergo asymmetric propargylic substitution reaction to give chiral propargylic-substituted products. Among various nucleophiles, enamine is a quite attractive one. It can be used as a variation of the α-carbanions of ketones, avoiding using a strong base in the reaction process.[8] In 2009, Hou and coworkers first used enamines as carbon nucleophiles in asymmetric propargylic substitution reactions.[7d] Using $CuClO_4$/(*R*)-Cl-MeOBIPHEP as the catalyst, the reaction of propargylic alcohol acetate with enamines worked efficiently under mild conditions to give the corresponding chiral*β*-ethynyl-substituted ketones in high yields and in good to high enantioselectivities. However, the enantioselectivities of the reactions were not very satisfactory. The ees of the chiral products except for two cases were below 90%. Therefore novel chiral catalyst with better enantioselectivity for this reaction is highly desirable. Recently, chiral tridentate P,N,N ligands have been used in the propargylic substitution and cycloaddition reactions of propargylic alcohol derivatives, giving the corresponding products in high yields and excellent enantioselectivities.[9] In this context, we explored the application of chiral tridentate P,N,N ligand in propargylic substitution of propargylic acetates with enamines (Scheme 1). Herein, we reported in the presence of chiral tridentate P,N,N ligand, copper-catalyzed highly enantioselective propargylic substitution of propargylic acetates with enamines for synthesis of chiral propargylic ketones.

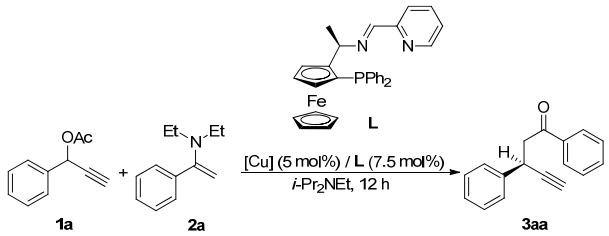


Scheme 1 Cu-catalyzed propargylic substitution of propargylic acetates with enamines.

In the initial experiments, using the tridentate P,N,N ligand (**L**) as chiral ligand,[9e,10] we studied propargylic substitution of propargylic acetate (**1a**) with enamine (**2a**) (Table 1). Since copper catalyst has been demonstrated to be a good catalyst for propargylic substitution

of propargylic acetate (**1a**) with enamine (**2a**),[7d] several copper salts were examined with methanol as the solvent. To our delight, in the presence of 5 mol% of $Cu(OAc)_2$ and 7.5 mol% of chiral ligand (**L**), propargylic acetate (**1a**) was treated with enamine (**2a**) in methanol for 12 h to give the corresponding product **3aa** in 52%yield and 76%ee (entry 1). Using $Cu(OTf)_2$ as the catalyst, the product could be obtained in 70%yield and 73%ee (entry 2). The yield was markedly increased, at the same time, the enantioselectivity nearly did not degraded. But the copper salts such as CuCl and CuI were sluggish, resulting in the propargylic substitution product in poor yield with poor or moderate ee (entries 3, 4). In particular, using 5 mol% of $Cu(CH_3CN)_4ClO_4$, the product **3aa** was obtained in 75%yield and 93%ee (entry 5). The solvent screening revealed that other solvents such as THF, toluene, CH_2Cl_2, acetone and acetonitrile are not compatible with this reaction. Using these solvents, no product or trace of product was observed on the TLC (entries 6–10). Through lowering the reaction temperature to 0 °C, the yield and ee were increased to 90% and 97%, respectively (entry 11). According to these screening results, the following propargylic substitution reactions were carried out in MeOH at 0 °C in the presence of $Cu(CH_3CN)_4ClO_4$ (5 mol%), tridentate P,N,N ligand (**L**) (7.5 mol%) and the base *i*-Pr_2NEt.

Table 1 Screening of the reaction conditions[a]

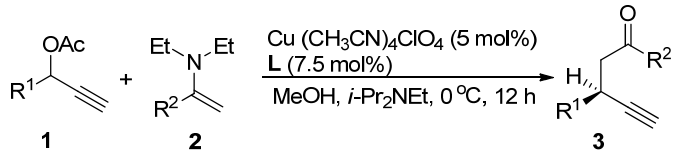


Entry	[Cu]	Solvent	T	Yield (%)[b]	Ee (%)[c]
1	$Cu(OAc)_2$	MeOH	rt	52	76
2	$Cu(OTf)_2$	MeOH	rt	70	73
3	CuCl	MeOH	rt	25	8
4	CuI	MeOH	rt	30	55
5	$CuClO_4$	MeOH	rt	75	93
6	$CuClO_4$	THF	rt	n.r.[d]	n.d.[e]
7	$CuClO_4$	toluene	rt	n.r.	n.d.
8	$CuClO_4$	CH_2Cl_2	rt	trace	n.d.
9	$CuClO_4$	acetone	rt	trace	n.d.
10	$CuClO_4$	CH_3CN	rt	n.r.	n.d.
11	$CuClO_4$	MeOH	0 °C	90	97

[a] Reactions of **1a** (0.5 mmol), **2a** (1.0 mmol), copper salt (0.025 mmol), **L** (0.038 mmol) and *i*-Pr_2NEt (1.2 mmol) were carried out in 4.0 mL of solvent for 12 h. $CuClO_4$ = $Cu(CH_3CN)_4ClO_4$. [b] Isolated yields. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparing the optical rotation with the data in ref. 9e. [d] n.r. = no reaction. [e] n.d. = not determined.

Under the optimized conditions, we examined the scope of propargylic acetate and enamine. As indicated in Table 2, propargylic substitution of various propargylic acetate (**1**) with *N*,*N*-diethyl-1-phenylethenamine (**2a**) worked very well to give the propargylic substitution ketones in high yield (75–95%) and excellent enantioselectivities (95–98%ee) (entries 1–11). Both electron-donating and electron-withdrawing substituents on the benzene ring of propargylic acetates were well tolerated in the propargylic substitution reactions, and the substitution pattern had no significant influence on the activity and stereoselectivity (entries 1–9). In addition, 2-naphthyl and 2-thienyl propargylic acetates (**1j** and **1k**) were also compatible substrates (entries 10–11). 2-Naphthyl substituted propargylic acetate (**1j**) carried out propargylic substitution with enamine (**2a**), providing the corresponding product in 85%yield and 96%ee (entry 10). 2-Thienyl substituted propargylic acetate (**1k**) underwent the reaction to give the substitution product in 76%yield and 96%ee (entry 11). After investigation of the scope of propargylic acetates, different enamines were evaluated in asymmetric propargylic substitution reaction with 1-phenylprop-2-yn-1-yl acetate (**1a**). A broad range of aromatic enamines with electron-donating and electron-withdrawing substituents were employed under the optimal reaction conditions, affording the corresponding products in 80–88% yields with uniformly excellent enantioselectivities (96–97%ee) (entries 12–17).

Table 2 Cu-catalyzed enantioselective propargylic substitution of propargylic acetates (**1**) with enamines (**2**)[a]



Entry	R^1	R^2	**3**	Yield (%)[b]	Ee (%)[c]
1	Ph (**1a**)	Ph (**2a**)	**3aa**	90	97
2	4-MeC_6H_4 (**1b**)	Ph (**2a**)	**3ba**	92	97
3	4-$OMeC_6H_4$ (**1c**)	Ph (**2a**)	**3ca**	95	95
4	4-FC_6H_4 (**1d**)	Ph (**2a**)	**3da**	86	96
5	2-ClC_6H_4 (**1e**)	Ph (**2a**)	**3ea**	75	97
6	3-ClC_6H_4 (**1f**)	Ph (**2a**)	**3fa**	88	98
7	4-ClC_6H_4 (**1g**)	Ph (**2a**)	**3ga**	95	97
8	4-BrC_6H_4 (**1h**)	Ph (**2a**)	**3ha**	83	96
9	4-$CF_3C_6H_4$ (**1i**)	Ph (**2a**)	**3ia**	80	96
10	2-naphthyl (**1j**)	Ph (**2a**)	**3ja**	85	96
11	2-thienyl (**1k**)	Ph (**2a**)	**3ka**	76	96
12	Ph (**1a**)	4-MeC_6H_4 (**2b**)	**3ab**	81	96
13	Ph (**1a**)	4-$OMeC_6H_4$ (**2c**)	**3ac**	88	96
14	Ph (**1a**)	4-FC_6H_4 (**2d**)	**3ad**	83	96
15	Ph (**1a**)	3-ClC_6H_4 (**2e**)	**3ae**	87	96
16	Ph (**1a**)	4-ClC_6H_4 (**2f**)	**3af**	86	97
17	Ph (**1a**)	4-BrC_6H_4 (**2g**)	**3ag**	80	96

[a] Reactions of **1** (0.5 mmol), **2** (1.0 mmol), $Cu(CH_3CN)_4ClO_4$ (0.025 mmol), **L** (0.038 mmol) and *i*-Pr_2NEt (1.2 mmol) were carried out in 4.0 mL of MeOH at 0 °C for 12 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparing the optical rotation with the data in ref. 9e.

Conclusions

In summary, using a chiral tridentate P,N,N ligand, we have developed Cu-catalyzed enantioselective propargylic substitution of propargylic acetates with enamines to give the propargylic ketones in high yields with excellent enantioselectivities. The reaction proceeds smoothly under mild conditions and provides an expedient access to highly valuable chiral propargylic ketone compounds.

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† Electronic Supplementary Information (ESI) available: characterization data spectra of all products. See DOI: 10.1039/b000000x/

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