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Asymmetric Copper-Catalyzed Propargylic Substitution Reaction of Propargylic Acetates with Enamines

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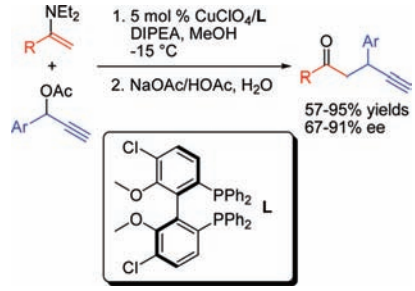
ABSTRACT



Enamines served as carbon-nucleophiles for the first time in the Cu-catalyzed asymmetric propargylic substitution reaction of propargylic acetates, providing corresponding chiral β-ethynyl-substituted ketones in high yields and in good to high enantioselectivity.

The diverse transformations of the alkyne moiety into other functional groups make the propargylic substitution reaction an attractive protocol in the construction of complex molecules.[1] Nicholas reported the reaction of electron-rich aromatic compounds with a stoichiometric amount of Co-complex in 1977.[2] Murahashi realized the propargylic substitution reaction of propargyl esters with amines by using a catalytic amount of CuCl.[3] Since then, great progress has been made. Nowadays, a variety of metal- and organo-catalysts have been used as catalysts effectively, and amines, amides, thiols, ketones, and many others have served as nucleophiles, providing corresponding propargyl derivatives.[4] However, the asymmetric version of the reaction with a catalytic amount of chiral catalyst had not been realized for a long time. The breakthrough was made by Nishibayashi, who reported the first successful example of an asymmetric propargylic substitution reaction of propargylic alcohols with acetone catalyzed by the Ru complex, up to 82% ee being realized.[5] Recently, van Maarseveen and Nishibayashi independently realized Cu-catalyzed asymmetric propargylic substitution of propargylic acetates with amines as nucleophiles, affording corresponding chiral amines in up to 88% and 89% ee, respectively.[6] Despite these great achievements, the asymmetric catalytic version of the reaction is still rare; in particular, the carbon-nucleophile has been limited in the use of acetone and aromatic compounds.[5,7] Asymmetric catalytic propargylic substitution reactions with carbon-nucleophiles are still a far

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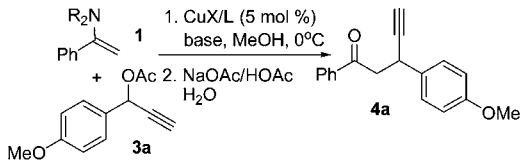
less explored field,[8,9] though the corresponding allylic substitution reaction has been investigated in detail and widely used in organic synthesis.[1,10] In the course of our research on the palladium-catalyzed asymmetric allylic alkylation reaction, we have demonstrated the use of "hard" carbon-nucleophiles in palladium-catalyzed allylic alkylation.[11] Upon the basis of these results, the propargylic substitution reaction with carbon nucleophiles was investigated. In this communication, we report our preliminary results of the copper-catalyzed asymmetric propargylic substitution reaction using enamines as carbon nucleophiles. To the best of our knowledge, this is the first report of metal-catalyzed asymmetric propargylic substitution involving enamines.

Initially, we examined the reaction of propargylic acetate **3a** with acetophenone **2** in the presence of 10 mol % of CuI as catalyst and LDA as base at 0 °C. However, no desired product was provided. Considering that the enamines have widely been used successfully as the equivalent of enolates,[12] the enamine **3a** was tested in the reaction (eq 1). It was found that the reaction of **1a** and **3a** in MeOH with 5 mol % of $CuClO_4(MeCN)_4$ as catalyst afforded the product in 10% yield, while 2,6-bis(oxazolinyl)pyridine **L1** was used as ligand and product **4a** was provided in 76% yield and in 27% ee. With these results in hand, the influence of the parameters on the reaction was investigated further (eq 1, Table 1).



1a. $R_2 = O(CH_2CH_2)_2$, **1b**. $R_2 = (CH_2CH_2)_2$, **1c**. R = Et (1)

The results revealed that the ligand with a different type of coordination atom showed its great impact on the enantioselectivity of the reaction. The enantioselectivity of the reaction was lower when the PYBOX **L1**−**L3**[13a] (Figure 1) were used, which was improved greatly if *P*,*P*-ligand BINAP was used (entry 4 vs entries 1−3). The enantioselectivity of the reaction increased from 40% to 54% further if the reaction proceeded at 0 °C (entry 5 vs entry 4). The substituent on nitrogen of enamines **1** is another important factor not only on the enantioselectivity but also on the reactivity of the reaction. The reaction provided product **4a** in 90% yield with 72% ee when diethylamino alkene **1c** was used, while both yield and ee value decreased if morpholinyl and pyrrolidinyl alkenes **1a** and **1b** were used, respectively (entry 7 vs entries 5 and 6). The investigation of the solvent effect showed that the MeOH is the only choice. Very poor yields were provided or no reaction took place if other common solvents, including THF, DME, MeCN, toluene, CH_2Cl_2, DMF, and EtOH, were used in the reaction of **1c**

Table 1. Influence of the Parameters on the Reaction[a]

entry	1	ligand	base	yield (%)[b]	ee (%)[c]
1[d]	**1a**	**L1**	DIPEA	76	27
2[d]	**1a**	**L2**	DIPEA	73	9
3[d]	**1a**	**L3**	DIPEA	72	10
4[d]	**1a**	**L4**	DIPEA	59	40
5	**1a**	**L4**	DIPEA	62	54
6	**1b**	**L4**	DIPEA	63	53
7	**1c**	**L4**	DIPEA	90	72
8	**1c**	**L4**	−	65	65
9	**1c**	**L4**	K_2CO_3	NR	−
10	**1c**	**L4**	Et_3N	86	70
11	**1c**	**L4**	pyridine	complex	−
12	**1c**	**L4**	DBU	trace	−
13	**1c**	**L5**	DIPEA	88	71
14	**1c**	**L6**	DIPEA	74	4
15	**1c**	**L7**	DIPEA	74	62
16	**1c**	**L8**	DIPEA	93	79
17	**1c**	**L9**	DIPEA	50	5
18	**1c**	**L10**	DIPEA	77	12
19	**1c**	**L11**	DIPEA	61	59
20	**1c**	**L12**	DIPEA	85	61
21[e]	**1c**	**L8**	DIPEA	88	81

[a] Molar ratio: **3a**/**1**/base/$CuClO_4$·$(MeCN)_4$/**L** = 1/2/4/0.05/0.05. [b] Isolated yield. [c] Determined by HPLC. [d] Run at rt. [e] Run at −15 °C.

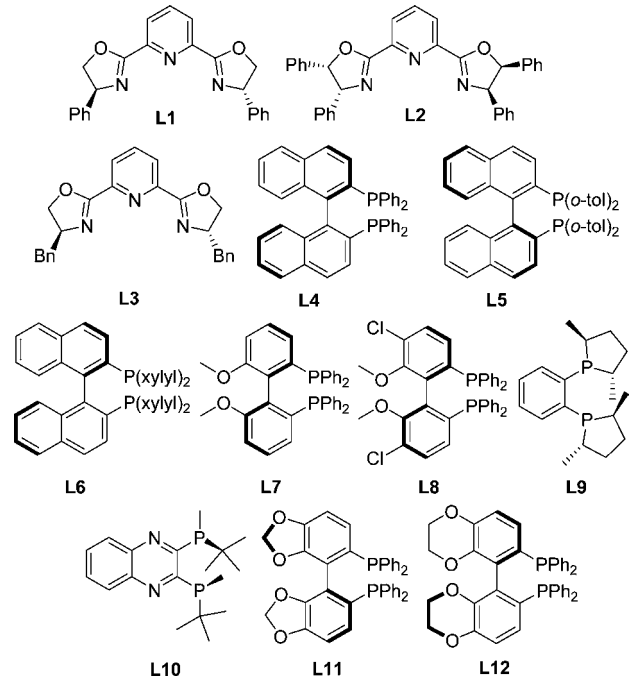


Figure 1. Structure of the ligands.

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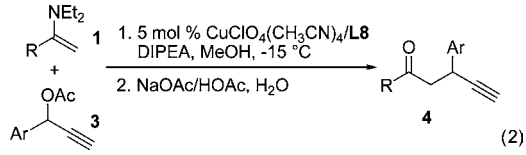
and **3a** with $CuClO_4$/BINAP as catalyst at 0 °C (not shown in Table 1). The base also showed its effect on the reaction. The reaction afforded product **4a** in 65% yield with 65% ee in the absence of base (entry 8), while the use of Et_3N provided the same results as that of DIPEA (entry 10 vs entry 7). However, worse results were given when K_2CO_3, pyridine, and DBU were used as base (entries 9, 11, and 12). The screen of *P*,*P*-ligands showed that (*S*)-tol-binap **L5** with steric hindrance on the P atom afforded the product in a little bit lower ee (entry 13). Even worse enantioselectivity was given if (*S*)-xylyl-binap **L6**, (*S*)-Duphos **L9**,[13b] and (*R*,*R*)-(−)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline **L10**[13c] were used, respectively (entries 14, 17, and 18). Product **4a** with similar ee was obtained when the ligands **L7**, **L11**, and **L12** were used (entries 15, 19, and 20), and the ee value increased to 79% if (*R*)-Cl−MeO-biphep **L8** was the ligand (entry 16). The investigation of the impact of different Cu-salts provided that $CuClO_4$ is the best choice among the Cu-salts we screened, including CuI, CuTc, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$ (not shown in Table 1). The studies on the temperature effect on the reaction showed that lower temperature was in favor of product in higher ee (entry 4 vs entry 5 and entry 16 vs entry 21). The influence of the leaving group of the propargyl compound was also studied. It was found that the alkyne was decomposed if the Ac group in **3b** was replaced by CF_3CO-, $ClCH_2CO$-, and pyridinyl-2 CO- groups (not shown in Table 1).

Using optimized reaction conditions, the scope of the reaction was examined (eq 2, Table 2).[14] Generally, a wide



(2)

range of enamines **1** and propargyl acetates **3** were suitable for the reaction, affording propargylic-substituted products in good to high yields with 67−91% ee. Either enamines **1** or electrophiles **3** having electron-withdrawing groups afforded products in higher enantioselectivity (entries 6−8 for **3**, 15−18 and 20−23 for **1**). Replacing the phenyl group by a naphthyl group in either the enamine or propargyl compound gave the product in higher yields but a little bit lower ee (entries 9 and 13 vs entry 2). Higher ee (84%) was given when heteroaromatic substrate **1l** was used, albeit the yield was lower (entry 19) while the ee value was lower if heteroaromatic propargyl acetate **3j** was the reagent (entry 10). It is worth noting that enamine **1n** derived from

Table 2. Enantioselective Cu-Catalyzed Propargylic Substitution Reaction of Propargylic Acetates **3** with Enamines **1**[a]

entry	**1**, R	**3**, Ar	**4**, yield (%)[b]	*ee* (%)[c]
1	**c**, Ph	**a**, 4-$MeOC_6H_4$	**a**, 88	81
2	**c**, Ph	**b**, Ph	**b**, 77	85
3	**c**, Ph	**c**, 3-MeC_6H_4	**c**, 83	84
4	**c**, Ph	**d**, 4-MeC_6H_4	**d**, 95	82
5	**c**, Ph	**e**, 3-$MeOC_6H_4$	**e**, 67	80
6	**c**, Ph	**f**, 4-FC_6H_4	**f**, 88	80
7[d]	**c**, Ph	**g**, 4-ClC_6H_4	**g**, 73	85
8[d]	**c**, Ph	**h**, 4-BrC_6H_4	**h**, 65	85
9	**c**, Ph	**i**, 1-naphthyl	**i**, 95	73
10	**c**, Ph	**j**, 2-furyl	**j**, 80	67
11	**d**, 4-$MeOC_6H_4$	**b**, Ph	**l**, 57	80
12	**e**, 4-MeC_6H_4	**b**, Ph	**m**, 72	80
13	**i**, 2-naphthyl	**b**, Ph	**n**, 85	78
14	**j**, 2-furyl	**b**, Ph	**o**, 55	77
15	**f**, 4-FC_6H_4	**b**, Ph	**p**, 81	87
16	**g**, 4-ClC_6H_4	**b**, Ph	**q**, 70	85
17	**h**, 4-BrC_6H_4	**b**, Ph	**r**, 67	86
18	**k**, 4-$NO_2C_6H_4$	**b**, Ph	**s**, 61	91
19	**l**, 3-pyridyl	**b**, Ph	**t**, 40	84
20	**m**, 2,4-$Cl_2C_6H_3$	**b**, Ph	**u**, 63	82
21[d]	**f**, 4-FC_6H_4	**c**, 3-MeC_6H_4	**v**, 79	85
22[d]	**f**, 4-FC_6H_4	**f**, 4-ClC_6H_4	**w**, 58	85
23[d]	**k**, 4-$NO_2C_6H_4$	**c**, 3-MeC_6H_4	**x**, 59	90

[a] Molar ratio: **3a**/**1**/base/$CuClO_4$.$(MeCN)_4$/**L** = 1/2/4/0.05/0.05. [b] Isolated yield. [c] Determined by HPLC. [d] The reaction was performed at −5 °C.

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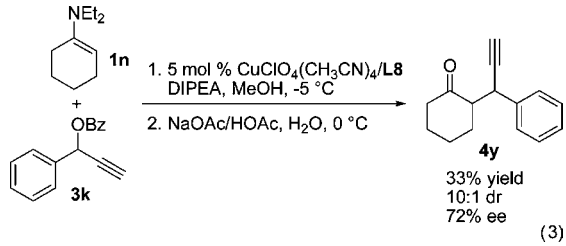
(14) **Typical procedure for the Cu-catalyzed asymmetric propargylic substitution reaction of *N*,*N*-diethyl-1-phenylethenamine 1c with propargylic acetate 3a**: To a flame-dried Schlenk tube with $CuClO_4$·$(CH_3CN)_4$ (3.3 mg, 0.01 mmol) and (*R*)-Cl-MeO-biphep (6.9 mg, 0.01 mmol) was added anhydrous methanol (1.0 mL) under argon, and the resulting mixture was stirred at rt for 30 min. The flask was kept at −15 °C, **3a** (35 mg, 0.20 mmol), and *N*,*N*-diethyl-1-phenylethenamine **1c** (70 mg, 0.40 mmol) and diisopropylethylamine (103 mg, 0.80 mmol) in anhydrous methanol (1.0 mL) were added. The mixture was stirred at −15 °C, monitored by TLC. After completion, the reaction mixture was quenched with buffer of NaOAc/HOAc (1.0 mL), and the resulting solution was stirred for 10 min at rt. Water was added (5.0 mL) and extracted with Et_2O (20 mL × 3). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by preparative TLC (hexane/ethyl acetate = 10/1) to give product **4a** (46.7 mg, 88% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.95−7.92 (m, 2H), 7.58−7.26 (m, 5H), 6.89−6.84 (m, 2H), 4.40 (dt, J = 7.1, 2.4 Hz, 1H), 3.78 (s, 3H), 3.56 (dd, J = 17.1, 7.8 Hz, 1H), 3.34 (dd, J = 17.0, 6.8 Hz, 1H), 2.26 (d, J = 3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.88, 158.62, 136.60, 133.26, 132.61, 128.59, 128.48, 128.09, 114.03, 85.63, 70.80, 55.24, 47.10, 31.81. HRMS: calcd. for $C_{18}H_{16}O_2$, 264.1150. Found: 264.1148. $[\alpha]_D^{20}$ +4.8 °(*c* 1.01, $CHCl_3$). The optical purity was determined by HPLC analysis: Chiralcel OD, hexane/^{i}PrOH = 98/2, flow rate = 0.6 mL/min, λ = 230 nm, retention time: 22.7 min (major) and 26.0 min (minor), 81% ee.

aliphatic cyclohexanone was also a suitable substrate, providing the product in 33% yield with 72% ee and 10:1 dr when using OBz as the leaving group (eq 3). However, the aliphatic



(3)

(benzyl-substituted) propargyl acetate and 1,3-diphenyl-2-propynyl acetate, a propargylic acetate bearing an internal alkyne moiety, could not react at all.

The absolute configuration of product **4a** was determined as (*S*) by reducing the acetylene group of **4a** to the ethyl group and comparing the sign of optical rotation of product with that of known compound reported in the literature.[15]

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In summary, we have described the first example of copper-catalyzed enantioselective propargylic substitution reactions of propargylic acetates with enamines to afford β-ethynyl-substituted ketones with good to high yield and enantioselectivity. Further investigations on extending the reaction scope using other types of enamines and applications of this method in organic synthesis as well as on the understanding of the reaction mechanism are in progress.

Acknowledgment. Financially supported by the Major Basic Research Development Program (2006CB806106), National Natural Science Foundation of China (20532050, 20872161 and 20821002), Chinese Academy of Sciences, Croucher Foundation of Hong Kong, and Science and Technology Commission of Shanghai Municipality. This paper is dedicated to Professor You Qi Tang on the occasion of his 90th birthday.

Supporting Information Available: Detailed experimental procedures and analytic data, ^{1}H and ^{13}C NMR and HPLC spectra for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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