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Copper-Catalyzed Enantioselective Synthesis of Axially Chiral Allenes

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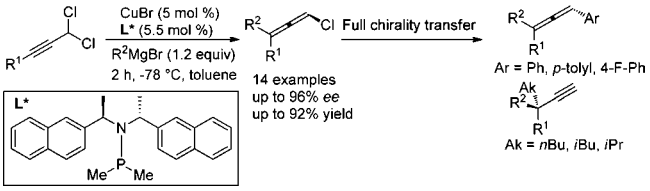
ABSTRACT



A simple copper-catalyzed enantioselective synthesis of axially chiral chloroallenes from the propargylic dichlorides is reported, employing a catalytic amount of easily prepared SimplePhos ligand. Exclusive formation of the desired allenes was observed with good enantioselectivities (ee's 62−96%). Further transformations to trisubstituted allenes or terminal alkynes with a propargylic quaternary carbon center keep a high level of enantiopurity.

Allene compounds have drawn more and more attention as a frequent building block and a versatile intermediate for organic synthesis.[1] Among the existing methodologies for their preparation, the copper-mediated 1,3-substitution of carbon nucleophiles on propargylic electrophiles is one of the most direct and efficient ways.[2] Toward this approach, asymmetric synthesis of chiral allenes has emerged more than 20 years ago, starting from propargylic alcohol derivatives, in most of the cases.[3] Although stoichiometric organocopper reagents were mainly used, catalytic versions appeared recently.[4−7] However, all these processes require enantioenriched starting propargylic substrates; upon full chirality transfer, the corresponding chiral allenes can be formed with high enantiomeric excesses (Scheme 1, eq 1).

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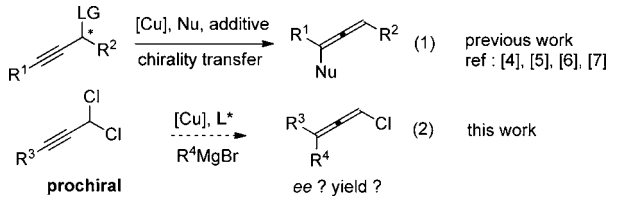
Referring to the copper-catalyzed asymmetric allylic alkylation (AAA) for the prochiral allylic compounds,[8,9] a similar process on prochiral propargylic compounds is highly desirable, which could provide the chiral allenes from nonchiral substrates in one single substitution step, employing catalytic amount of copper salt and chiral ligand.

Scheme 1. Prochiral Substrate for Allene Synthesis

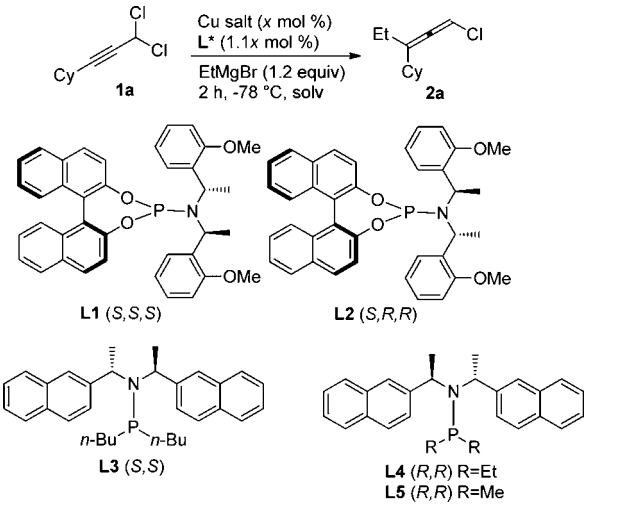


Inspired by the recent work of Knochel et al.,[10] the prochiral 1,1-dichloro propargylic molecules drew our attention by their facile preparation from the corresponding propargylic aldehyde and are considered promising substrates for the following catalytic process (Scheme 1, eq 2). The desired product bearing a chlorine atom will attract more interest for further functionalization compared to allenes bearing only alkyl or aryl groups. Finally, it should be mentioned that Woodward has recently attempted a similar approach with diacetates instead of dichlorides; however, no enantioselective version was reported.[11]

Herein, we report the first examples of copper-catalyzed highly enantioselective 1,3-substitution on the aforementioned prochiral propargylic substrates, leading to the exclusive formation of desired chloroallenes with high enantiomeric excesses. By the selection of several easily prepared chiral ligands, we managed to reach high level of *ee* and obtained the desired products without other regioisomers. In addition, the family of alkyl Grignard reagent was employed as nucleophile, which is advantageous over other alkyl organometallic reagents such as organozinc or organoaluminum due to its easy preparation and large availability.

We started our investigation on 1,1-dichloro-3-cyclohexyl-2-propyne as substrate (its synthesis is described in the Supporting Information), under the reported optimized conditions for copper-catalyzed asymmetric allylic alkylation reactions,[9b] using copper(I) thiophenecarboxylate (CuTC) as copper source, phosphoramidite **L1** as chiral ligand, and ethylmagnesium bromide as nucleophile in CH_2Cl_2 (Table 1, entry 1). The reaction showed excellent regioselectivity, affording exclusively the desired allene without formation of 1,1-substitution regioisomer. However, the ee was not ideal. Another diastereoisomer **L2** was equally tested under the same conditions (entry 2) to exclude the possible "match−mismatch effect" in the catalytic process.

Table 1. Optimization of the Methodology[a]



entry[a]	ligand **L***	Cu salt	solvent	catalyst loading (%)	ee[b] (%)
1	**L1**	CuTC	CH_2Cl_2	10	39
2	**L2**	CuTC	CH_2Cl_2	10	40
3	**L3**	CuTC	CH_2Cl_2	10	50
4	**L3**	CuTC	toluene	10	4
5	**L4**	CuTC	CH_2Cl_2	10	58
6	**L4**	CuTC	toluene	10	82
7	**L5**	CuTC	CH_2Cl_2	10	58
8	**L5**	CuTC	toluene	10	89
9	**L5**	CuI	toluene	10	91
10	**L5**	CuBr	toluene	10	92
11	**L5**	CuBr	toluene	5	92

[a] Reaction conditions: the substrate (0.25 mmol) was added to a solution of copper salt and chiral ligand in dry solvent at −78 °C. The ethereal solution of Grignard reagent (1.2 equiv) was added dropwise during 20 min, and the reaction mixture was stirred at −78 °C for 2 h. The desired product was confirmed by ^{1}H NMR. [b] Determined by GC analysis using a chiral stationary phase. Cy = cyclohexyl.

Without having much success in terms of enantiomeric excess on the trials with phosphoramidite ligands, we switched to another family of chiral phosphorus ligand: SimplePhos.[12] The ligand screening started with the readily prepared **L3**, which showed good performances in some asymmetric conjugated addition reactions.[13] A promising value of 50% ee was achieved (entry 3). Switching the solvent to toluene while keeping the same ligand led to a dramatic drop of enantioselectivity (entry 4). In order to emphasize the chiral information carried by the amine moiety of the ligand, we envisaged that smaller substituents on phosphorus atom should enable more facile binding of the complex to substrate and then increase the enantioselective discrimination. For this reason, the diethyl

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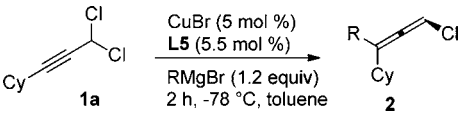
analogue **L4** was also prepared and studied under the similar conditions using two different solvents respectively (entries 5 and 6). Surprisingly, at this time the choice of toluene as solvent seemed to be essential and provided a great improvement of ee. Finally, replacing the substituent on P-atom of ligand by two tinier methyl groups (**L5**), keeping toluene as solvent (entry 8), brought us a nice breakthrough on selectivity: a very good ee of 89% was obtained retaining the perfect regioselectivity. An optimization of the copper source showed that CuBr can still gain 3% of ee (entry 10). Because of its low price and large availability, CuBr was chosen for the further investigation. Lowering the catalyst loading from 10 to 5 mol % had no influence on the outcome (entry 11). In addition, many other classes of chiral ligands were equally investigated, but no further improvement could be achieved (see the Supporting Information).

With these optimized conditions in hand, a range of alkyl Grignard reagents were introduced to form the corresponding axially chiral allenes. The employment of simple primary alkylmagnesium bromide afforded, in all the studied cases, chiral chloroallenes with very good enantioselectivities (Table 2, entries 1−3). A bulkier primary alkyl group, such as isobutyl, could also promote the nucleophilic attack and keep high level of ee (entry 4). A more vulnerable alkyl group bearing a remote double bond had no interference to the selectivity and the yield (entry 5). Interestingly, the introduction of a sterically demanding secondary alkyl group behaved even better, providing excellent enantioselectivity (entry 6). Similar results were observed in the case of the cyclopentyl group (entry 7). We theorized that the secondary alkyl groups might have the most suitable size when approaching the metal−ligand complex. Finally, we intended to study the challenging methyl nucleophile, which cannot be easily introduced to allylic substrates under copper-catalyzed AAA conditions with good selectivity. Fortunately, to our delight, in this case, the methyl group attacked the substrate successfully and formed the corresponding chloroallene as the only regioisomer with very nice enantioselectivity (entry 8). Considering the steric requirements of an sp carbon, as compared to an sp2 carbon on allylic substrates, it is remarkable to attain such high level of enantiocontrol on propargylic substrate. As shown in the last entry, the use of *t*-BuMgBr only led to racemic product (entry 9), which is also conventional in copper-catalyzed asymmetric allylic alkylation.[8]

The generality of this methodology was exploited by employing different 1,1-dichloro propargylic substrates (Table 3). These substrates can be easily prepared from the corresponding alkynes in only two single steps,[10] which facilitated our study on the scope of substrates (see the Supporting Information). The acyclic aliphatic carbon chain at the R position keeps the same reactivity with very good enantioselectivity (entry 1). Introducing a terminal chlorine atom on the carbon chain did not interfere with the enantioselectivity (entry 2), while the obtained allene, bearing two halogens, would be potentially useful for synthetic purposes. Replacing the R group with a bulkier alkyl group such as *tert*-butyl maintained the good

Table 2. Scope of Grignard Reagents[a]

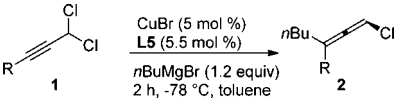


entry[a]	R	product	yield (%)	ee[b] (%)
1	Et	**2a**	84	92
2	*n*-Bu	**2b**	92	94
3	$PhCH_2CH_2$	**2c**	84	90
4	*i*-Bu	**2d**	84	93
5	$CH_2{=}C(CH_3)CH_2CH_2$	**2e**	92	94
6	*i*-Pr	**2f**	88	96
7	cyclopentyl	**2g**	84	96
8	Me	**2h**	82	91
9	*t*-Bu		nd	0

[a] Reaction conditions: the substrate (0.25 mmol) was added to a solution of CuBr and chiral ligand in dry toluene at −78 °C. The ethereal solution of Grignard reagent (1.2 equiv) was added dropwise during 20 min and the reaction mixture was stirred under −78 °C for 2 h. Full conversion and the desired products were confirmed by ^{1}H NMR. [b] Determined by GC analysis using a chiral stationary phase.

selectivity (entry 3). With a more versatile R group such as trimethylsilyl, the reaction still yielded a practical ee of 85% (entry 4). The resulting chiral allenylsilane moiety can be widely used in organic transformations.[14] Utilizing a phenyl group on the substrate showed some limitations for this methodology. The regioselectivity was never an issue; however, the enantioselectivity decreased to 64% ee. Finally, a protected alcohol functionality on the R group successfully provided a valuable 2-allenic alcohol moiety albeit with a moderate optical purity. The scaled-up reaction (2.0 mmol substrate **1a**) was carried out employing methyl Grignard reagent leading to no change of enantioselectivity (90% ee) and a good yield of 95% (see Supporting Information).

Table 3. Scope of 1,1-Dichloropropargylic Substrates[a]



entry[a]	R	subst	product	yield (%)	ee[c] (%)
1	*n*-pent	**1b**	**2i**	82	92
2	$ClCH_2CH_2CH_2CH_2$	**1c**	**2j**	77	89
3	*t*Bu	**1d**	**2k**	71	84
4[b]	TMS	**1e**	**2l**	72	85
5[b]	Ph	**1f**	**2m**	82	64
6	CH_2O-*t*-Bu	**1g**	**2n**	85	62

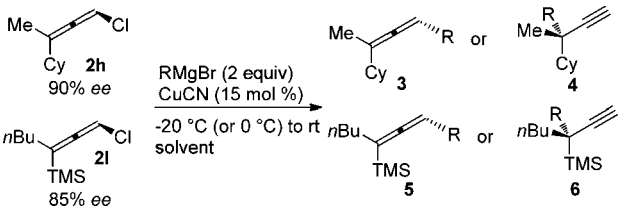
[a] Reaction conditions: the substrate (0.25 mmol) was added to a solution of CuBr and chiral ligand in dry toluene at −78 °C. The ethereal solution of Grignard reagent (1.2 equiv) was added dropwise during 20 min, and the reaction mixture was stirred under −78 °C for 2 h. The desired products were confirmed by ^{1}H NMR. [b] 1.05 equiv of Grignard reagent was used in order to avoid the double alkylation as a side reaction. [c] Determined by GC analysis using a chiral stationary phase.

To demonstrate the synthetic potential of the above enantioenriched chloroallenes, we performed some further transformations (Table 4). A simple and quickly accessible application followed a typical procedure reported by Knochel and co-workers on racemic chloroallene.[10] To our delight, during this process, no loss of enantiomeric excesses was observed, and the chirality was fully transferred to the products (entries 1–3) whether the aryl group was introduced with electron-donating ($-CH_3$, entry 2) or electron-withdrawing (−F, entry 3) groups at the para position.

An attempt to introduce the alkyl group under the same conditions failed to afford the desired alkylated allene compounds as successfully as in previous arylation cases. Instead, the dechlorinated nonchiral allene was observed as a major product when the reaction was preformed using *n*-butyl Grignard reagent as the nucleophile. However, when we simply changed the solvent from THF to dichloromethane, under similar conditions, the reaction led to almost exclusive formation of 1,3-substitution product on the chloroallene, namely the terminal alkyne bearing a stereogenic quaternary carbon center (entries 4–6). What is exciting in this derivatization is that the reactions always proceeded with full chirality transfer. In addition, compared to the well-established method which suffered from synthesizing the starting materials of high enantiomeric purity, our methodology provides a more direct way for the formation of all-carbon propargylic stereogenic center through enantioselective propargylic substitution.[15] This nice approach to obtain the chiral terminal alkyne compounds further increases the value of the chiral chloroallene synthesis reported herein. From a synthetic point of view, two more trials were focused on the silyl compound **2l**; under the two different conditions, respectively, the corresponding trisubstituted allenylsilane and propargylsilane were obtained in optically enriched form, which represents the highly useful reagents in organic synthesis (entries 7 and 8).[16]

In order to have more insight to these products, alkyne **4a** was subjected to "click" reaction conditions with *p*-bromophenyl azide. X-ray diffraction on the resulting crystalline product allowed the determination of the absolute configuration (see the Supporting Information).

Table 4. Copper-Catalyzed Transformations of Chloroallene[a]



entry[a]	subst	R	solvent	product	yield (%)	ee[b] (%)
1	**2h**	Ph	THF	**3a**	85	90
2	**2h**	*p*-tolyl	THF	**3b**	85	90
3	**2h**	4-F-Ph	THF	**3c**	84	90
4	**2h**	*n*-Bu	CH_2Cl_2	**4a**	89	90
5	**2h**	*i*-Bu	CH_2Cl_2	**4b**	97	90
6	**2h**	*i*-Pr	CH_2Cl_2	**4c**	79	90
7	**2l**	Ph	THF	**5**	75	83
8	**2l**	*i*-Bu	CH_2Cl_2	**6**	87	83

[a] Reaction conditions: the substrate (0.20 mmol) was added to a mixture of CuCN and dry solvent at −20 °C (or 0 °C). The ethereal solution of Grignard reagent (2 equiv in order to ensure the full conversion) was added dropwise, the reaction mixture was warmed back to room temperature and stirred during 2 h. The desired products were confirmed by ^{1}H NMR. [b] Determined by GC analysis using a chiral stationary phase.

In conclusion, we have discovered a highly enantioselective synthesis of axially chiral chloroallenes, using a catalytic amount of easily prepared SimplePhos ligand, as chiral source, and readily available Grignard reagents as nucleophile. These versatile compounds can be easily further transformed to trisubstituted allenes or terminal alkynes with a propargylic quaternary carbon center, keeping a high level of enantiopurity. We believe this methodology makes a useful contribution to asymmetric organic synthesis.

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Supporting Information Available. Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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