Asymmetric Catalysis

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# Enyne Chlorides: Substrates for Copper-Catalyzed Asymmetric Allylic Alkylation**

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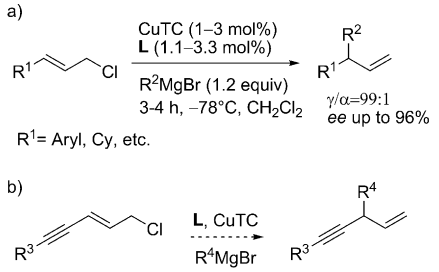
Copper-catalyzed asymmetric allylic alkylation (AAA) is one of the most useful and efficient carbon–carbon bond-forming methods that leads to optically enriched molecules.[1] Owing to the properties of copper, this transformation allows the use of nonstabilized carbon nucleophiles, namely alkyl or aryl groups in the form of organometallic species. After the pioneering work of van Koten, Bäckvall, and co-workers on copper-catalyzed AAA using Grignard reagents,[2] much attention has focused on this field. Compared to other organometallic reagents, such as organozinc or organoaluminium reagents, Grignard reagents are advantageous under several circumstances because of their diversity and availability.

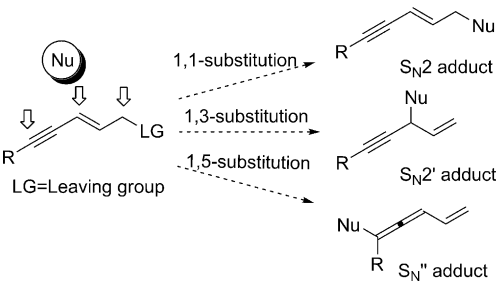
In the past few years, our group has reported highly regio- and enantioselective copper/phosphoramidite catalytic systems for AAA of allylic chlorides with organomagnesium reagents (Scheme 1a);[3] later, the range of substrates was




***Scheme 1.*** a) Previous work. b) Proposed use of enyne chlorides as new substrates for AAA.

extended to include β-disubstituted allylic chlorides, 1,4-difunctionalized allylic type substrates, etc.[4] Additionally, the dynamic kinetic asymmetric transformation process was also studied, and involved using racemic cyclic or acyclic substrates under copper-catalyzed AAA conditions with phosphoramidite ligands.[5] Subsequently, we focused on the use of the more vulnerable and synthetically interesting prochiral substrates, which generate chiral products, 1,4-enynes in this case, as a result of the AAA process (Scheme 1b)

As far as we know, the AAA on the extended multiple bond system, especially the enyne substrates, has not been studied much.[6] Trost et al. have performed an enantioselective molybdenum-catalyzed process on enyne carbonates, with malonate salts as nucleophiles; good regioselectivities were observed in favor of the 1,3-substitution together with excellent *ee* values (Scheme 2).[7] One year later, Takeuchi




***Scheme 2.*** Possible products by substitution reaction.

et al. described an iridium-catalyzed allylic substitution system; however the regioselectivity for the linear enyne acetate substrate was moderate.[8] The very first example to introduce alkyl groups, was reported by Krause et al. By performing the substitution reactions on enyne acetates and employing the readily in situ generated cuprate, they observed the exclusive 1,5-substitution, thus directly accessing vinylallenes, without the formation of products arising from substitution at the α or γ position ($S_N2$ or $S_N'$) of the allylic system.[9] Subsequent to this work a highly enantioselective process, using enantiopure enyne acetates under "remote stereocontrol" to introduce the chirality from the starting materials to the adducts, was described.[10] Although the formation of allenes was taken for granted, we were intrigued by a report from Hoveyda et al. describing a copper-catalyzed AAA on two examples of enyne phosphate substrates using diethylzinc, which lead to the formation of tertiary and quaternary stereogenic carbon centers.[11]

Herein, we report a series of enyne chloride substrates that undergo the copper-catalyzed AAA by employing Grignard reagents to provide excellent regioselectivities for the 1,3-allylic substitution products without any trace of vinylallene formation, and excellent enantiomeric excesses. To our knowledge, these results represented the first catalytic asymmetric 1,3-substitution on this type of enyne substrate by using a variety of Grignard reagents as nucleophiles without

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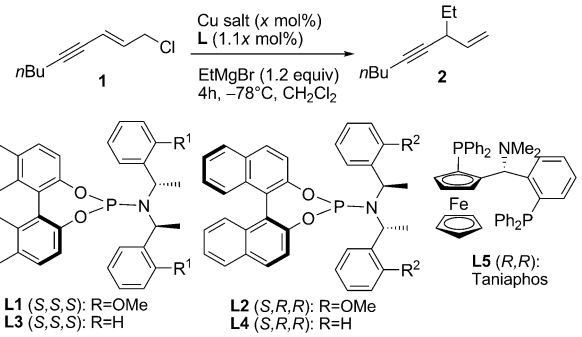
reacting with the triple bonds. As Hoveyda and co-workers recently published a reversed process of a copper-catalyzed AAA using alkynyl aluminium reagents as nucleophiles to directly introduce the triple bond in the allylic substitution to provide the 1,4-enynes,[12] our methodology can be also considered as an easily accessible alternative to achieving the 1,4-enyne products bearing tertiary chiral carbon centers.

Our preliminary investigation started from the AAA reaction of (*E*)-1-chlorononon-2-en-4-yne (**1**) with ethylmagnesium bromide in dichloromethane at −78 °C. Under the reaction conditions published by our group for the cinnamyl chloride substrate,[3] a combination of 3 mol% copper(I) thiophenecarboxylate (CuTC) and the phosphoramidite ligand **L1** served as the catalyst.[3c] After 4 hours full conversion was observed together with good regioselectivity ($S_N2'/S_N2 = 98:2$) and in 96% *ee* (Table 1, entry 1). An increase in catalyst loading to 5 mol% led to a negligible

***Table 1:*** Optimization of the methodology.[a]




| Entry | L | Cu salt | Catalyst loading [%] | Conv. [%][b] | $S_N2'/S_N2$[b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **L1** | CuTC | 3 | >99 | 98:2 | 96 |
| 2 | **L1** | CuTC | 5 | >99 | 98:2 | 97 |
| 3 | **L1** | CuTC | 1 | 99 | 94:6 | 95 |
| 4 | **L2** | CuTC | 5 | 95 | 83:17 | 63 |
| 5 | **L3** | CuTC | 5 | 99 | 88:12 | 75.5 |
| 6 | **L4** | CuTC | 5 | >99 | 95:5 | 95 |
| 7 | **L1** | $CuBr{\cdot}SMe_2$ | 5 | >99 | 97:3 | 96 |
| 8[d] | **L5** | $CuBr{\cdot}SMe_2$ | 5 | 72 | 90:10 | 94 |

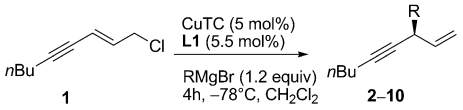
[a] Reaction conditions: the substrate (0.25 mmol) was added to a solution of CuTC and chiral ligand in dry $CH_2Cl_2$ at −78 °C. The ethereal solution of the Grignard reagent (1.2 equiv) was added dropwise over a 30 min period and the reaction mixture was stirred at −78 °C for 4 h. [b] Determined by $^1H$ NMR spectroscopy. [c] Determined by GC analysis using a chiral stationary phase. [d] Overnight (18 h).

improvement of the enantioselectivity (entry 2). Even with a 1 mol% catalyst loading, the reaction kept rendering an excellent enantioselectivity with a small decrease in the $S_N2'/S_N2$ ratio (entry 3). The use of ligand **L2** led to lowering of both the regio- and enantioselectivity, and can be reasoned to arise from the mismatch effect of the prochiral center with the copper/phosphoramidite complex (entry 4). The diastereoisomeric phosphoramidite ligands **L3** and **L4** were tested, and provided no further improvement (entries 5 and 6). Replacing the CuTC by $CuBr{\cdot}SMe_2$ showed a slight decrease in selectivity. And finally, the use of (*R,R*)-Taniaphos (**L5**) in combination with $CuBr{\cdot}SMe_2$, as reported by Feringa and co-workers,[13] provided both poorer regio- and enantioselectivity. Furthermore, full conversion was not observed after an even longer reaction time. It should be added that the substrate **13** (see Table 3 for structure) gave only the allene and the $S_N2$ adduct when reacted with $Bu_2CuLi$ under the reaction conditions described by Krause et al.[9]

These observations indicate that this methodology should be such a robust catalytic process, as it is not dependant on the copper source or the catalyst loading. We have shown that: 1) decrease of catalyst loadings (from 5 mol% to 1 mol%) has no significant results influence on regio- and enantioselectivity, and this can be useful for scale-up or industrial processes; and 2) a cheaper copper source and the more simple and available ligand **L4** provided similar results in terms of reactivity and selectivity. As a result, 5 mol% CuTC with 5.5 mol% **L2** were chosen as the optimized reaction conditions for further studies.

A range of alkylmagnesium bromide reagents were employed to target the corresponding $S_N2'$ products, and demonstrate the advantage of using Grignard reagents over alkylzinc reagents (Table 2). The employment of simple primary alkyl Grignard reagents provided (entries 1–3) excellent regio- and enantioselectivities in all the cases. Those primary alkyl nucleophiles bearing a double bond (entries 4 and 5) showed no interference with the selectivity. More-bulky groups, such as the secondary alkyl nucleophiles, led to a reasonable drop in enantioselectivity, but maintained the excellent $S_N2'/S_N2$ ratios (entries 6 and 7). However, in the case of phenyl magnesium bromide, the $S_N2$ product was obtained nearly exclusively (entry 8), thus illustrating the special character of the phenyl nucleophile in the copper-catalyzed AAA. The more challenging methyl group was

***Table 2:*** Scope of Grignard reagents.[a]



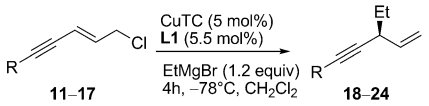

| Entry[a] | R | Prod. | Yield [%] | $S_N2'/S_N2$[b] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | Et | **2** | 72 | 98:2 | 97 |
| 2 | *n*Bu | **3** | 84 | 98:2 | 96 |
| 3[d] | $PhCH_2CH_2$ | **4** | 92 | 98:2 | >99 |
| 4 | $CH_2{=}CHCH_2CH_2$ | **5** | 92 | 95:5 | 95 |
| 5 | $CH_2{=}C(CH_3)CH_2CH_2$ | **6** | 90 | 96:4 | 95 |
| 6 | *i*Pr | **7** | 76 | 99:1 | 85 |
| 7 | Cy | **8** | 96 | 98:2 | 87 |
| 8 | Ph | **9** | – | <1:99 | – |
| 9 | Me | **10** | – | 47:53[e] | 93 |

[a] Reaction conditions: the substrate (0.25 or 0.5 mmol) was added to a solution of CuTC and chiral ligand in dry $CH_2Cl_2$ at −78 °C. The ethereal solution of Grignard reagent (1.2 equiv) was added dropwise over a 30 min period and the reaction mixture was stirred at −78 °C for 4 h. [b] Determined by $^1H$ NMR spectroscopy. [c] Determined by GC analysis using a chiral stationary phase. [d] 1.05 equiv of phenethyl Grignard reagent was used; the desired product **4** is mixed with 5.7 mol% homocoupling product of phenethyl Grignard reagent, namely, 1,4-diphenylbutane. Yield calculated from the percentage in the mixture. [e] Besides the α and γ adducts, the *Z* isomer of the $S_N2$ adduct (≈10%) was detected in the resulting mixture. Cy = cyclohexyl.

introduced with good enantioselectivity but with an $S_N2'/S_N2$ ratio of nearly 1:1, thus showing that the conventional limitation of AAA reactions can still not be overcome in this system (entry 9).[14] Finally, a control experiment with the *Z* isomer of **1** gave the opposite enantiomer, albeit with a poor *ee* value of 32% and a low $S_N2'/S_N2$ ratio (79:21).

The generality of the reaction was exploited by employing different *E*-configured enyne chloride substrates (Table 3). A longer carbon chain (R) has the same reactivity (entry 1). Replacing it by more-bulky alkyl groups such as cyclohexyl or *tert*-butyl groups, maintained the good selectivity (entries 2 and 3); this was also the case for the cyclopropyl group (entry 4), which is an important moiety present in many natural products. As shown in entry 5, the introduction of a phenyl group leads to a more conjugated and rigid structure, but this does not interfere with the selectivity. A more versatile substituent, the trimethylsilyl group, also had no significant influence on the reactivity (entry 6). Finally, a protected alcohol successfully provided a valuable $S_N2'$ product with high optical purity (entry 7). The scale-up reaction (2.5 mmol substrate **15**) lead to no change in the regio- and stereoselectivity, and the product yield was 87%.[15]

***Table 3:*** Scope of enyne chloride substrates.[a]

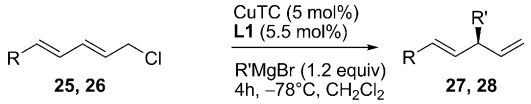



**11–17** **18–24**

| Entry[a] | R | Sub. | Prod. | Yield [%] | $S_N2'/S_N2$[b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | *n*Pent | **11** | **18** | 83 | 97:3 | 97 |
| 2 | Cy | **12** | **19** | 93 | 96:4 | 97 |
| 3[d] | *t*Bu | **13** | **20** | 80 | 99:1 | 97 |
| 4 | *c*Propyl | **14** | **21** | 77 | 96:4 | 95 |
| 5 | Ph | **15** | **22** | 94 | 94:6 | 97 |
| 6 | TMS | **16** | **23** | 74 | 96:4 | 97.5 |
| 7 | $CH_2OTBS$ | **17** | **24** | 85 | 96:4 | 94 |

[a] Reaction conditions: the substrate (0.25 mmol) was added to a solution of CuTC and chiral ligand in dry $CH_2Cl_2$ at −78 °C. The ethereal solution of Grignard reagent was added dropwise over a 30 min period and the reaction mixture was stirred at −78 °C for 4 h. [b] Determined by $^1$H NMR spectroscopy. [c] Determined by GC analysis using a chiral stationary phase. [d] For convenient GC separation, *n*BuMgBr was employed instead of EtMgBr. TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

To additionally test the generality of this method, we investigated the conjugated *E*,*E*-diene chloride substrates, which maybe a priori more challenging because there is a reduced electronic discrimination between the 1,3-substitution versus the 1,5-substitution. We studied two examples (Scheme 3), and to our delight these *E*,*E*-diene chloride substrates (**25** and **26**) behaved similarly in the catalytic reactions as their aforementioned enyne chloride counterparts, thus affording almost exclusively the 1,3-substitution adduct with good regio- and enantioselectivity; note that this outcome is not common for alkyl nucleophiles,[7,16,17] namely alkyl Grignard reagents in our case. These preliminary results are very encouraging and additional investigations on this reaction are underway in the laboratory.




**25, 26** **27, 28**

**25** (R=Me, R'=$PhCH_2CH_2$): 66% yield; $S_N2'/S_N2$=90:10; 90% *ee*

**26** (R=Ph, R'=Et): 71% yield; $S_N2'/S_N2$=97:3; 91% *ee*

***Scheme 3.*** Examples of copper-catalyzed AAA using diene chlorides as substrates.

In conclusion, we have developed a method that employs prochiral *E*-configured enyne chlorides as substrates in the copper-catalyzed AAA, wherein different alkyl magnesieum bromide reagents can be introduced as nucleophiles, thus leading to interesting chiral 1,4-enyne building blocks. In most cases excellent regio- and enantioselectivities ($S_N2'/S_N2$ ratio up to 98:2; *ee* values up to >99%) were obtained. Additionally, two examples of *E*,*E*-diene chlorides were shown to behave similarly in the catalytic process with very good selectivities to provide the chiral 1,4-diene products in high optical purity.

## Experimental Section

A dried Schlenk tube was charged with a copper salt (5 mol%) and the chiral ligand (5.5 mol%). Dichloromethane (1.5 mL) was added and the mixture was stirred at room temperature for 10 min. The allylic chloride (0.25 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for an additional 5 min before cooling the reaction mixture to −78 °C using an ethanol/dry ice cold bath. The Grignard reagent (3 M in diethyl ether, 1.2 equiv) was added manually over a 30 min period. Once the addition was complete the reaction mixture was left at −78 °C for an additional 4 h. The reaction was quenched by addition of aqueous hydrochloric acid (1 N, 2 mL). Diethyl ether (5 mL) was added and the aqueous phase was separated and extracted with diethyl ether (3 × 2 mL). The combined organic fractions were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude reaction mixture was purified by chromatography on silica gel using pentane as the eluant. The desired product was recovered as a colorless oil. For additional details, see the Supporting Information.

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**Keywords:** alkylation · asymmetric catalysis · copper · enynes · Grignard reagents

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