

Synthetic Methods

Efficient Chiral N-Heterocyclic Carbene/Copper(I)-Catalyzed Asymmetric Allylic Arylation with Aryl Grignard Reagents**

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Copper-catalyzed asymmetric allylic alkylation is an efficient C–C bond-forming reaction for obtaining optically active compounds.^[1] The use of hard alkyl nucleophiles such as Grignard or organozinc reagents usually produces S_N2' products (γ products) with excellent regio- and enantioselectivity.^[2] In contrast, substitution with aryl metal nucleophiles produces insufficient regio- and enantioselectivity as well as low yield.^[3,4] In 2007, Hoveyda and co-workers reported highly regio- and enantioselective arylation with organozinc reagents on very specific vinylsilane substrates.^[5] To date, however, there have been no reports of successful copper-catalyzed asymmetric allylic arylation (AAAr) of cinnamyl-type substrates with aryl metal reagents,^[6] even though the resulting trisubstituted carbon atom having two aryl groups is an important structural motif which is often found in pharmaceuticals (e.g., sertraline^[7] and tolterodine^[8]), biologically active compounds (e.g., indatraline^[9]), and natural products (e.g., podophyllotoxin^[10]).

Recently, we reported a catalytic AAAr of arylmagnesium bromide to aliphatic allylic bromides, using a chiral amidophosphane **L1**–copper(I) catalyst, to afford high regio- and enantioselectivity (up to exclusive γ selectivity, 81 % *ee*). The reactions of cinnamyl-type substrates, however, had poor γ selectivity (γ/α 16:84) (Scheme 1).^[11] Herein, we report a powerful method for enantioselective synthesis of a range of diarylvinylmethanes by unprecedented AAAr of arylmagnesium bromides to cinnamyl-type substrates efficiently cata-

lyzed by a newly designed chiral N-heterocyclic carbene (NHC)^[12]–copper(I) complex **C2** (Figure 1).^[13]

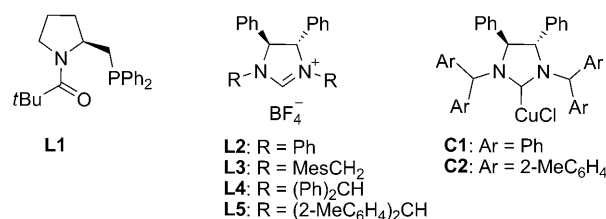
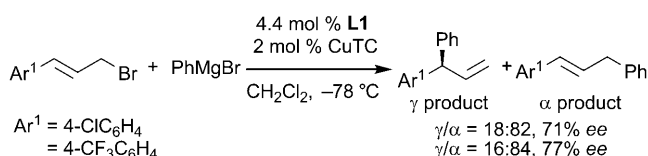


Figure 1. Chiral ligands and NHC–copper(I) complexes.

As illustrated in Table 1, a diethyl ether solution of PhMgBr (3 M; 0.20 mL, 0.6 mmol) diluted with CH₂Cl₂ (0.25 mL) was added over a 15 minute period to a solution of 4-chlorocinnamyl bromide (**1a**; 0.50 mmol) in CH₂Cl₂ (1 mL) at –78 °C. NHC–Cu catalysts (2 mol %) were prepared in situ by deprotonating the corresponding imidazolidinium salts **L2–4** with *n*BuLi (6.6 mol %) in the presence of copper thiophenecarboxylate (CuTC). The catalyst derived from **L2**,^[12] having a phenyl group on the nitrogen atom, afforded γ -**2a** with poor enantioselectivity (29 % *ee*) and low γ selectivity (γ/α 27:73). The catalyst derived from **L3**, having a mesitylmethyl substituent,^[12] gave mostly α product α -**2a** with a slight amount of γ -**2a** having a 31 % *ee* (γ/α 4:96). Fortunately, the in situ prepared **L4**–Cu catalyst exhibited high enantioselectivity (95 % *ee*) with moderate regioselectivity.



Scheme 1. Amidophosphane **L1**–Cu-catalyzed AAAr with PhMgBr.

Table 1: Catalyst screening.^[a]

Entry	Catalyst ^[b]	Yield [%]	γ/α ^[c]	<i>ee</i> [%] ^[d]
1	L2 –Cu	> 99 ^[d]	27:73	ent-29
2	L3 –Cu	> 99 ^[d]	4:96	31
3	L4 –Cu	> 99 ^[d]	62:38	95
4	C1	98 ^[e]	67:33	96
5	C2	96 ^[e]	93:7	95

[a] PhMgBr (1.2 equiv) was added to the reaction mixture over a period of 15 minutes. Cinnamyl bromide **1a** was not detected by ¹H NMR analysis of the crude reaction mixtures. [b] Copper complexes derived from **L2–4** were prepared in situ using 2.2 mol % of ligand (**L2–4**), 2 mol % of CuTC, and 6.6 mol % of *n*BuLi. **C1** and **C2** (2 mol %) were used as isolated complexes. [c] Determined by GC analysis on a chiral stationary phase (Chiraldex B-DM). [d] Yield determined from ¹H NMR analysis of the crude reaction mixture. [e] Yield of isolated product.

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tivity (γ/α 62:38). An isolated air-stable NHC–CuCl complex **C1** derived from **L4** also gave comparable results to afford γ -**2a** with 96% *ee* and a γ/α ratio of 67:33 (Table 1, entry 4). We speculated that a ligand with bulky Ar groups might improve the regioselectivity by enhancing the rate of the reductive elimination step of the initially formed γ - σ -allyl–Cu^{III} intermediate.^[14] As expected, an isolated air-stable NHC–CuCl **C2** derived from **L5**, having an *ortho*-methyl group on the phenyl moieties (Ar = 2-MeC₆H₄), dramatically increased the γ selectivity to 93:7 without affecting the high enantioselectivity (95% *ee*; Table 1, entry 5).

Having established the optimal catalyst for cinnamyl-type substrates (Table 1, entry 5), we evaluated the arylation of other substrates. The reaction of substrates with electron-deficient aryl moieties, for example, a chloro substituent at the *ortho*, *meta*, or *para* position or a *para*-trifluoromethyl group, gave the γ products γ -**2a–e** with 92–96% *ee* and high regioselectivity (\geq 93:7) in high yield (Table 2, entries 1–5). Moreover, sterically demanding *o*-tolyl substrate **1f** gave an

Table 2: Copper-catalyzed asymmetric allylic arylation of cinnamyl-type substrates using PhMgBr.

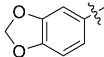
$\text{Ar}^1\text{---CH=CH---CH}_2\text{Br} + \text{PhMgBr} \xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 0.5\text{ h}]{2\text{ mol \% C2}} \text{Ar}^1\text{---CH(Ph)---CH=CH}_2$						
Entry	1	Ar ¹	2	Yield [%] ^[a]	γ/α ^[b]	<i>ee</i> [%] ^[c]
1	1a	4-ClC ₆ H ₄	2a	96	93:7	95
2	1b	3-ClC ₆ H ₄	2b	99	95:5	93
3	1c	2-ClC ₆ H ₄	2c	99	96:4	96
4	1d	4-CF ₃ C ₆ H ₄	2d	99	93:7	93
5	1e	3,4-Cl ₂ C ₆ H ₃	2e	99	95:5	92
6	1f	2-MeC ₆ H ₄	2f	99	95:5	98
7 ^[d]	1f	2-MeC ₆ H ₄	2f	99	97:3	97
8 ^[e]	1f	2-MeC ₆ H ₄	2f	98	93:7	98
9 ^[f]	1f	2-MeC ₆ H ₄	2f	99	90:10	97
10	1g	2-MeOC ₆ H ₄	2g	91	94:6	93
11 ^[g]	1h	1-naphthyl	2h	97	75:25	93

[a] Yield of isolated product. [b] Determined by GC analysis on a chiral stationary phase or by ¹H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase after conversion into the corresponding terminal alcohol by hydroboration/oxidation or by chiral GC analysis. [d] Used 4 mol% of **C2**. [e] Used 1 mol% of **C2**. [f] Used 0.5 mol% of **C2**. [g] Reaction run for 1 h.

unprecedented high enantioselectivity (98% *ee*) and a high γ/α ratio (95:5; Table 2, entry 6). The catalyst amount affected the selectivity of the reaction;^[11] gradually decreasing the catalyst loading from 4 to 0.5 mol% did not affect the enantioselectivity, whereas the γ/α ratio decreased from 97:3 to 90:10 (Table 2, entries 7–9). These results indicate that the high catalyst loading accelerated the reaction, thereby preventing the formation of the undesirable diphenylcuprate intermediate, which might lead to an α product through π -allyl equilibration.^[15] The optimum amount of **C2** was determined to be 2 mol%. Allylic bromide **1g** with an *o*-methoxy group afforded γ -**2g** with 93% *ee* and 94:6 γ/α selectivity (Table 2, entry 10). The more sterically hindered naphthyl substrate **1h** gave γ -**2h** with 93% *ee* in 75:25 regioselectivity (Table 2, entry 11).^[16]

The enantioselective arylation of *o*-methylcinnamyl bromide (**1f**) with *p*-fluoro-, *p*-chloro-, and *p*-methylphenyl Grignard reagents proceeded in high yield with excellent regio- and enantioselectivity (up to 96% yield, γ/α 97:3, 98% *ee*; Table 3, entries 1–3). High regio- and enantioselectivity

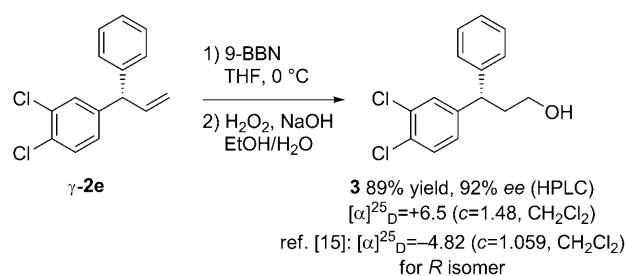
Table 3: Copper-catalyzed asymmetric allylic arylation of **1c** and **1f** using various aryl Grignard reagents.

$\text{Ar}^1\text{---CH=CH---CH}_2\text{Br} + \text{Ar}^2\text{MgBr} \xrightarrow[\text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 0.5\text{ h}]{2\text{ mol \% C2}} \text{Ar}^1\text{---CH(Ar}^2\text{)---CH=CH}_2$						
Entry	1	Ar ¹	Ar ²	2	Yield [%] ^[a]	γ/α ^[b] <i>ee</i> [%] ^[c]
1	1f	2-MeC ₆ H ₄	4-FC ₆ H ₄	2i	96	97:3 97
2	1f	2-MeC ₆ H ₄	4-ClC ₆ H ₄	2j	96	94:6 97
3	1f	2-MeC ₆ H ₄	4-MeC ₆ H ₄	2k	94	96:4 98
4	1c	2-ClC ₆ H ₄		2l	68 ^[d]	97:3 92

[a] Yield of isolated product. [b] Determined by GC or ¹H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase after conversion into the corresponding terminal alcohol by hydroboration/oxidation or GC analysis on a chiral stationary phase. [d] Reaction run for 1 h. **1c** was recovered in 22% yield.

tivity (γ/α 97:3, 92% *ee*) were also observed with the methylenedioxyphenyl Grignard reagent leading to γ -**2l** in acceptable yield (68%) along with 22% recovery of the starting material (Table 2, entry 4).

The *ee* value of γ -**2e** was determined after transformation into alcohol **3**, the enantiomer of an alcohol with established stereochemistry,^[17] using a hydroboration/oxidation protocol (Scheme 2). Product **3** is an intermediate in the synthesis of sertraline, a major pharmaceutical for the treatment of depression.



Scheme 2. Conversion of γ -**2e** into **3**, a synthetic intermediate of sertraline. 9-BBN = 9-borabicyclo[3.3.1]nonane, THF = tetrahydrofuran.

In conclusion, we developed an air-tolerant monodentate chiral NHC–CuCl catalyst for highly enantio- and γ -selective copper-catalyzed allylic arylation of cinnamyl bromides using aryl Grignard reagents, which affords the versatile chiral building blocks diarylvinylnmethanes.

Experimental Section

Typical procedure for the AAAr reaction (Table 2, entry 1): A dry 10 mL tube was charged with NHC–CuCl catalyst **C2** (7.1 mg,

0.02 mmol) and allylic substrate **1a** (0.50 mmol). Distilled CH_2Cl_2 (1 mL) was then added to the mixture which was then cooled to -78°C and stirred for 10 min. A solution of PhMgBr (3 M in Et_2O ; 0.20 mL, 0.6 mmol) diluted with CH_2Cl_2 (0.25 mL) was added over 15 min using a syringe pump. Once the addition of PhMgBr was complete, the reaction mixture was stirred for 30 min at -78°C . The mixture was diluted with Et_2O (6 mL) and quenched with aqueous 10 % HCl (0.5 mL). The aqueous phase was separated and extracted with Et_2O (3×3 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated in vacuo. The products were purified by silica gel column chromatography (n -pentane/ Et_2O 20:1) to give a 93:7 mixture of γ -**2a** with 95 % *ee* and α -**2a** (110 mg, 96 %) as colorless oil: $[\alpha]_{\text{D}}^{21} = -9.5$ ($c = 0.52$, CHCl_3). Enantio- and regioselectivity were determined by GC analysis on a chiral stationary phase: Chiraldex B-DM ($25 \text{ m} \times 0.25 \text{ mm} \times 0.25 \mu\text{m}$), initial temp. 60°C , $0.5^\circ\text{C min}^{-1}$, intermediate temp. 120°C , 30 min, $0.5^\circ\text{C min}^{-1}$, final temp. 160°C , retention times (min): 163.6 (minor γ -**2a**), 164.6 (major γ -**2a**), and 200.5 (α -**2a**).

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