## 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.<sup>[1]</sup> The use of hard alkyl nucleophiles such as Grignard or organozinc reagents usually produces S<sub>N</sub>2' products (y products) with excellent regio- and enantioselectivity.<sup>[2]</sup> In contrast, substitution with any metal nucleophiles produces insufficient regio- and enantioselectivity as well as low yield.<sup>[3,4]</sup> In 2007, Hoveyda and co-workers reported highly regio- and enantioselective arylation with organozinc reagents on very specific vinylsilane substrates.<sup>[5]</sup> To date, however, there have been no reports of successful coppercatalyzed asymmetric allylic arylation (AAAr) of cinnamyltype substrates with aryl metal reagents,<sup>[6]</sup> 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<sup>[7]</sup> and tolterodine<sup>[8]</sup>), biologically active compounds (e.g., indatraline<sup>[9]</sup>), and natural products (e.g., podophyllotoxin<sup>[10]</sup>).

Recently, we reported a catalytic AAAr of arylmagnesium bromide to aliphatic allylic bromides, using a chiral amidophosphane **L1**–copper(I) catalyst, to afford high regioand enantioselectivity (up to exclusive  $\gamma$  selectivity, 81 % *ee*). The reactions of cinnamyl-type substrates, however, had poor  $\gamma$  selectivity ( $\gamma/\alpha$  16:84) (Scheme 1).<sup>[11]</sup> 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-



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

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lyzed by a newly designed chiral N-heterocyclic carbene  $(NHC)^{[12]}$ -copper(I) complex **C2** (Figure 1).<sup>[13]</sup>



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

As illustrated in Table 1, a diethyl ether solution of PhMgBr (3M; 0.20 mL, 0.6 mmol) diluted with CH<sub>2</sub>Cl<sub>2</sub> (0.25 mL) was added over a 15 minute period to a solution of 4-chlorocinnamyl bromide (**1a**; 0.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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**,<sup>[12]</sup> having a phenyl group on the nitrogen atom, afforded  $\gamma$ -**2a** with poor enantioselectivity (29% *ee*) and low  $\gamma$  selectivity ( $\gamma/\alpha$  27:73). The catalyst derived from **L3**, having a mesitylmethyl substituent,<sup>[12]</sup> gave mostly  $\alpha$  product  $\alpha$ -**2a** with a slight amount of  $\gamma$ -**2a** having a 31% *ee* ( $\gamma/\alpha$  4:96). Fortunately, the in situ prepared **L4**-Cu catalyst exhibited high enantioselectivity (95% *ee*) with moderate regioselec-

## Table 1: Catalyst screening.[a]

4-CIC <sub>6</sub> H <sub>4</sub>	Br + PhMgE	Cataly Br	vst	Ph	
	1a	CH <sub>2</sub> Cl <sub>2</sub> , –78	°C, U.5 h	γ- <b>2a</b>	
Entry	Catalyst <sup>[b]</sup>	Yield [%]	$\gamma/\alpha^{[c]}$	ee [%] <sup>[c]</sup>	
1	<b>L2</b> –Cu	>99 <sup>[d]</sup>	27:73	ent-29	
2	<b>L3</b> –Cu	>99 <sup>[d]</sup>	4:96	31	
3	<b>L4</b> –Cu	> <b>99</b> <sup>[d]</sup>	62:38	95	
4	C1	98 <sup>[e]</sup>	67:33	96	
5	C2	96 <sup>[e]</sup>	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 <sup>1</sup>H 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 <sup>1</sup>H NMR analysis of the crude reaction mixture. [e] Yield of isolated product.

## Communications

tivity ( $\gamma/\alpha$  62:38). An isolated air-stable NHC–CuCl complex **C1** derived from **L4** also gave comparable results to afford  $\gamma$ -**2a** with 96% *ee* and a  $\gamma/\alpha$  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  $\gamma$ - $\sigma$ -allyl–Cu<sup>III</sup> intermediate.<sup>[14]</sup> As expected, an isolated air-stable NHC–CuCl **C2** derived from **L5**, having an *ortho*-methyl group on the phenyl moieties (Ar = 2-MeC<sub>6</sub>H<sub>4</sub>), dramatically increased the  $\gamma$  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  $\gamma$  products  $\gamma$ -**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.

			<b>)</b> -	2 mol % C2	Pn	
	Ar	✓ Br + Philige 1	CH <sub>2</sub>	Cl <sub>2</sub> , –78 °C, 0.5 h	Αr <sup>1</sup> γ-2	
Entry	1	Ar <sup>1</sup>	2	Yield $[\%]^{[a]}$	$\gamma/\alpha^{[b]}$	ee [%] <sup>[c]</sup>
1	la	4-CIC <sub>6</sub> H <sub>4</sub>	2a	96	93:7	95
2	1 b	3-ClC <sub>6</sub> H₄	2 b	99	95:5	93
3	1c	2-ClC <sub>6</sub> H₄	2 c	99	96:4	96
4	٦d	$4-CF_3C_6H_4$	2 d	99	93:7	93
5	le	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2e	99	95:5	92
6	1 f	2-MeC <sub>6</sub> H₄	2 f	99	95:5	98
7 <sup>[d]</sup>	1 f	2-MeC <sub>6</sub> H <sub>4</sub>	2 f	99	97:3	97
8 <sup>[e]</sup>	1 f	$2 - MeC_6H_4$	2 f	98	93:7	98
<b>9</b> <sup>[f]</sup>	1 f	2-MeC <sub>6</sub> H <sub>4</sub>	2 f	99	90:10	97
10	1g	$2 - MeOC_6H_4$	2g	91	94:6	93
11 <sup>[g]</sup>	1ĥ	1-naphthyl	2 h	97	75:25	93

[a] Yield of isolated product. [b] Determined by GC analysis on a chiral stationary phase or by <sup>1</sup>H 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  $\gamma/\alpha$  ratio (95:5; Table 2, entry 6). The catalyst amount affected the selectivity of the reaction;<sup>[11]</sup> gradually decreasing the catalyst loading from 4 to 0.5 mol% did not affect the enantioselectivity, whereas the  $\gamma/\alpha$  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  $\alpha$  product through  $\pi$ -allyl equilibration.<sup>[15]</sup> The optimum amount of **C2** was determined to be 2 mol%. Allylic bromide **1g** with an *o*-methoxy group afforded  $\gamma$ -**2g** with 93% *ee* and 94:6  $\gamma/\alpha$  selectivity (Table 2, entry 10). The more sterically hindered naphthyl substrate **1h** gave  $\gamma$ -**2h** with 93% *ee* in 75:25 regioselectivity (Table 2, entry 11).<sup>[16]</sup>

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

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

	Ar <sup>1</sup>	Br +	Ar <sup>2</sup> MgBr — CH <sub>2</sub>	2 mol	% <b>C2</b> 8 °C, 0.5 h	Ar <sup>2</sup>	
Entry	1	Ar <sup>1</sup>	Ar <sup>2</sup>	2	Yield [%] <sup>[a]</sup>	γ- <b>2</b> γ/α <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	1f	2-MeC <sub>6</sub> H <sub>4</sub>	4-FC <sub>6</sub> H <sub>4</sub>	2i	96	97:3	97
2 3	1† 1f	2-MeC <sub>6</sub> H₄ 2-MeC <sub>6</sub> H₄	4-CIC <sub>6</sub> H <sub>4</sub> 4-MeC <sub>6</sub> H <sub>4</sub>	2j 2k	96 94	94:6 96:4	97 98
4	1c	2-CIC <sub>6</sub> H <sub>4</sub>		21	68 <sup>[d]</sup>	97:3	92

[a] Yield of isolated product. [b] Determined by GC or <sup>1</sup>H 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 ( $\gamma/\alpha$  97:3, 92% *ee*) were also observed with the methylenedioxyphenyl Grignard reagent leading to  $\gamma$ -**21** in acceptable yield (68%) along with 22% recovery of the starting material (Table 2, entry 4).

The *ee* value of  $\gamma$ -**2e** was determined after transformation into alcohol **3**, the enantiomer of an alcohol with established stereochemistry,<sup>[17]</sup> 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  $\gamma$ -**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  $\gamma$ -selective copper-catalyzed allylic arylation of cinnamyl bromides using aryl Grignard reagents, which affords the versatile chiral building blocks diarylvinylmethanes.

## **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<sub>2</sub>Cl<sub>2</sub> (1 mL) was then added to the mixture which was then cooled to -78°C and stirred for 10 min. A solution of PhMgBr (3м in Et<sub>2</sub>O; 0.20 mL, 0.6 mmol) diluted with CH2Cl2 (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<sub>2</sub>O (6 mL) and quenched with aqueous 10% HCl (0.5 mL). The aqueous phase was separated and extracted with Et<sub>2</sub>O ( $3 \times 3$  mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The products were purified by silica gel column chromatography (n-pentane/Et<sub>2</sub>O 20:1) to give a 93:7 mixture of  $\gamma$ -2a with 95% ee and  $\alpha$ -2a (110 mg, 96%) as colorless oil:  $[\alpha]_{D}^{21} = -9.5$  (c = 0.52, CHCl<sub>3</sub>). Enantio- and regioselectivity were determined by GC analysis on a chiral stationary phase: Chiraldex B-DM ( $25 \text{ m} \times 0.25 \text{ mm} \times 0.25 \text{ µm}$ ), initial temp.  $60 \degree \text{C}$ , 0.5°Cmin<sup>-1</sup>, intermediate temp. 120°C, 30 min, 0.5°Cmin<sup>-1</sup>, final temp. 160°C, retention times (min): 163.6 (minor γ-2a), 164.6 (major  $\gamma$ -2a), and 200.5 ( $\alpha$ -2a).

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