Synthetic Methods

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

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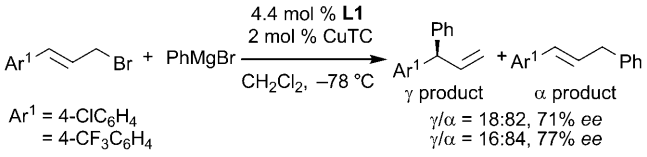
Copper-catalyzed asymmetric allylic alkylation is an efficient C–C bond-forming reaction for obtaining optically active compounds.[1] The use of hard alkyl nucleophiles such as Grignard or organozinc reagents usually produces S_N2' products (γ products) with excellent regio- and enantioselectivity.[2] 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 catalyzed by a newly designed chiral N-heterocyclic carbene (NHC)[12]–copper(I) complex **C2** (Figure 1).[13]



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

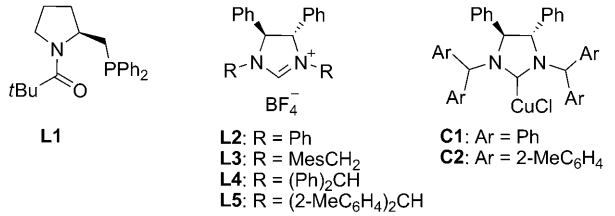
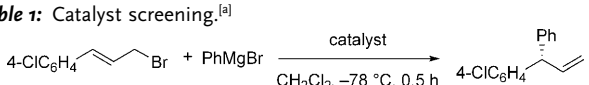


Figure 1. Chiral ligands and NHC–copper(I) complexes.

As illustrated in Table 1, a diethyl ether solution of PhMgBr (3 M; 0.20 mL, 0.6 mmol) diluted with CH_2Cl_2 (0.25 mL) was added over a 15 minute period to a solution of 4-chlorocinnamyl bromide (**1a**; 0.50 mmol) in CH_2Cl_2 (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 regioselec-

Table 1: Catalyst screening.[a]



Entry	Catalyst[b]	Yield [%]	γ/α[c]	*ee* [%][c]
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 ^{1}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 ^{1}H NMR analysis of the crude reaction mixture. [e] Yield of isolated product.

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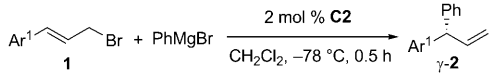
tivity (γ/α 62:38). An isolated air-stable NHC–CuCl complex **C1** derived from **L4** also gave comparable results to afford γ-**2a** with 96% *ee* and a γ/α ratio of 67:33 (Table 1, entry 4). We speculated that a ligand with bulky Ar groups might improve the regioselectivity by enhancing the rate of 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-MeC_6H_4), 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 (≥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.



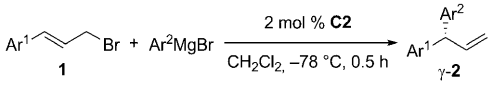
Entry	1	Ar^1	2	Yield [%][a]	γ/α[b]	*ee* [%][c]
1	**1a**	4-ClC_6H_4	**2a**	96	93:7	95
2	**1b**	3-ClC_6H_4	**2b**	99	95:5	93
3	**1c**	2-ClC_6H_4	**2c**	99	96:4	96
4	**1d**	4-$CF_3C_6H_4$	**2d**	99	93:7	93
5	**1e**	3,4-$Cl_2C_6H_3$	**2e**	99	95:5	92
6	**1f**	2-MeC_6H_4	**2f**	99	95:5	98
7[d]	**1f**	2-MeC_6H_4	**2f**	99	97:3	97
8[e]	**1f**	2-MeC_6H_4	**2f**	98	93:7	98
9[f]	**1f**	2-MeC_6H_4	**2f**	99	90:10	97
10	**1g**	2-$MeOC_6H_4$	**2g**	91	94:6	93
11[g]	**1h**	1-naphthyl	**2h**	97	75:25	93

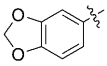
[a] Yield of isolated product. [b] Determined by GC analysis on a chiral stationary phase or by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase after conversion into the corresponding terminal alcohol by hydroboration/oxidation or by chiral 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 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 enantioselec-

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

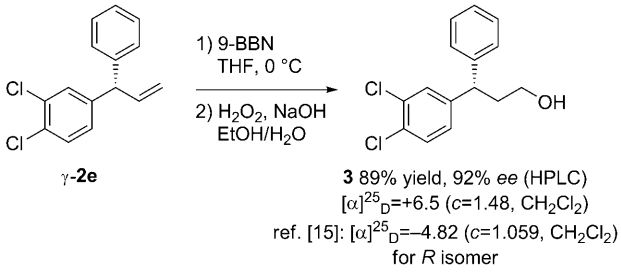


Entry	1	Ar^1	Ar^2	2	Yield [%][a]	γ/α[b]	*ee* [%][c]
1	**1f**	2-MeC_6H_4	4-FC_6H_4	**2i**	96	97:3	97
2	**1f**	2-MeC_6H_4	4-ClC_6H_4	**2j**	96	94:6	97
3	**1f**	2-MeC_6H_4	4-MeC_6H_4	**2k**	94	96:4	98
4	**1c**	2-ClC_6H_4		**2l**	68[d]	97:3	92

[a] Yield of isolated product. [b] Determined by GC or ^{1}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 (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 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_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: $[\alpha]_D^{21} = -9.5$ ($c = 0.52$, $CHCl_3$). Enantio- and regioselectivity were determined by GC analysis on a chiral stationary phase: Chiraldex B-DM (25 m × 0.25 mm × 0.25 μm), initial temp. 60 °C, 0.5 °C min^{-1}, intermediate temp. 120 °C, 30 min, 0.5 °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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