

# Enantioselective Copper-Catalyzed Allylic Alkylation with Dialkylzincs Using Phosphoramidite Ligands

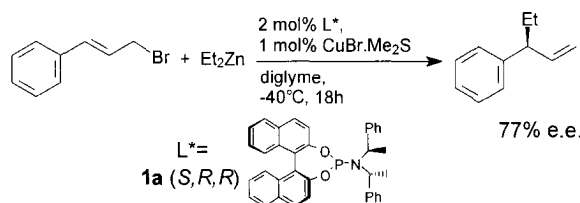
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## ABSTRACT



In the presence of a catalytic amount of copper salts, cinnamyl halides undergo a regio- and enantioselective  $\text{S}_{\text{N}}2'$  alkylation with dialkylzincs using chiral phosphoramidites as ligands. An  $\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$  ratio of 85:15 and enantiomeric excesses up to 77% for the chiral  $\text{S}_{\text{N}}2'$  products are found. Variation of solvent and reaction temperature revealed that the highest regio- and enantioselectivities are found using coordinating solvents of  $-40^\circ\text{C}$ .

Transition metal mediated carbon-carbon bond formations are among the most versatile synthetic methodologies in contemporary organic chemistry.<sup>1</sup> In recent years, the alkylation of allylic substrates has attracted much attention in approaches toward branched, chiral products.<sup>2</sup> Several highly selective palladium-catalyzed allylic substitutions using malonates as carbon nucleophiles have been described.<sup>1,3,4</sup> Van Koten and Bäckvall reported the first asymmetric copper-catalyzed allylic alkylation using Grignard reagents albeit

with moderate enantioselectivities.<sup>5</sup> Recently, Dübner and Knochel<sup>6</sup> introduced a highly regioselective copper-catalyzed alkylation method with dineopentylzinc employing chiral ferrocenylamines as ligands resulting in  $\text{S}_{\text{N}}2'$  products with up to 98% ee.

However, highly enantioselective allylic alkylation with nonsterically demanding (linear) alkylzinc reagents remains a major challenge. In this Letter, we report an asymmetric copper(I)-catalyzed allylic alkylation with dialkylzincs and cinnamyl bromide resulting in ee's up to 77%. This selectivity is achieved using 1 mol % of catalyst, prepared in situ from  $\text{CuBr} \cdot \text{Me}_2\text{S}$  and a chiral phosphoramidite ligand (**1a**, Figure 1). These ligands are known to give excellent

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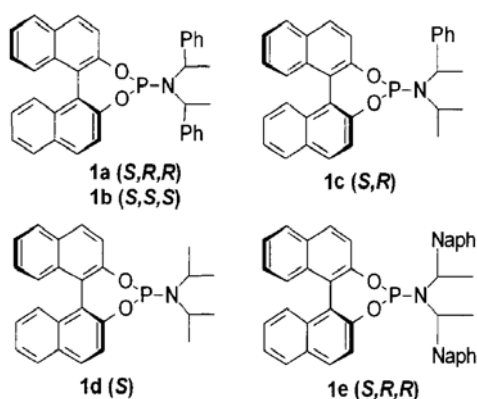
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**Figure 1.** Phosphoramidite ligands.

selectivities in the copper-catalyzed 1,4-addition of diorganozinc compounds to cyclic and acyclic enones,<sup>7</sup> cyclohexadienones,<sup>8</sup>  $\alpha,\beta$ -unsaturated nitro-esters,<sup>9</sup> nitro-olefins,<sup>10</sup> and cyclic 1,3-diene-epoxides<sup>11</sup> as well as in the asymmetric rhodium-catalyzed hydrogenation.<sup>12</sup>

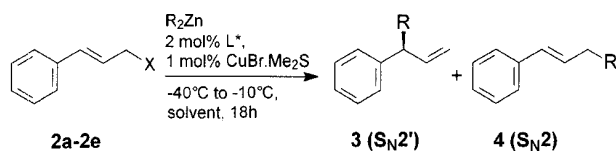
The preliminary reactions were carried out with cinnamyl chloride (**2a**), diethylzinc, 1 mol % of CuBr·Me<sub>2</sub>S, and 2 mol % of ligand **1a** in THF. The initial temperature of the alkylation was -40 °C, and upon warming to room tem-

perature 70% conversion was reached after 2 d. A 75:25 mixture of regioisomers was found with an enantiomeric excess of 17% for the S<sub>N</sub>2' product. These observations initiated a more detailed investigation of the optimal solvent, reaction conditions, and chiral ligands.

Diglyme gave the highest ee for the allylic alkylation with **2a** (Table 1, entry 8), for the various solvents examined, although the highest regioselectivity was observed using THF (Table 1, entry 4). Noncoordinating solvents such as toluene and CH<sub>2</sub>Cl<sub>2</sub> showed low regioselectivity and almost no asymmetric induction for the S<sub>N</sub>2' product (Table 1, entries 2 and 3). Among the different cinnamyl halides tested, cinnamyl bromide turned out to be the most reactive and selective starting material (Table 1, entry 12).

The allylic acetate and phosphate were not reactive under these reaction conditions even after 2 days at room temperature (Table 1, entries 9 and 10). Furthermore, a number of phosphoramidite ligands were tested in the allylic alkylation (Table 1, entries 12–16). Using ligand **1a**, carrying a chiral bis[(*R*)-1-phenylethyl]amine moiety, and CuBr·Me<sub>2</sub>S in the reaction of cinnamyl bromide with diethylzinc, the corresponding S<sub>N</sub>2' product was obtained with an enantioselectivity of 64% (Table 1, entry 12).<sup>13</sup> The other phosphoramidites, with different stereochemistries or different chiral amines (**1b–1e**), resulted in lower enantioselectivities. When the reaction was carried out at a constant low reaction

**Table 1.** Enantioselective Copper-Catalyzed Allylic Alkylation with Dialkylzincs Using Phosphoramidites **1a–1e** as Ligands: Effect of the Solvent, Leaving Group, Ligand, and Temperature



entry	substrate	X	R	solvent	L*	3:4	convn <sup>a</sup> (%)	yield <sup>a</sup> of 3 (%)	ee of 3 (%)
1	<b>2a</b>	Cl	Et	Et <sub>2</sub> O	<b>1a</b>	47:53	100 <sup>b</sup>	nd	nd
2	<b>2a</b>	Cl	Et	toluene	<b>1a</b>	59:41	100	27	<5
3	<b>2a</b>	Cl	Et	CH <sub>2</sub> Cl <sub>2</sub>	<b>1a</b>	62:38	100	84	<5
4	<b>2a</b>	Cl	Et	THF	<b>1a</b>	75:25	70 <sup>b</sup>	nd	17
5	<b>2a</b>	Cl	Et	1,4-dioxane	<b>1a</b>	52:48	100	63	17
7	<b>2a</b>	Cl	Et	DME	<b>1a</b>	57:43	85 <sup>b</sup>	nd	22
8	<b>2a</b>	Cl	Et	diglyrne	<b>1a</b>	57:43	90 <sup>b</sup>	57	28
9	<b>2b</b>	OAc	Et	diglyrne	<b>1a</b>		0 <sup>c</sup>		
10	<b>2c</b>	OP(O)(OEt) <sub>2</sub>	Et	diglyrne	<b>1a</b>		0 <sup>c</sup>		
11	<b>2d</b>	I	Et	diglyrne	<b>1a</b>	66:34	90	24	63
12	<b>2e</b>	Br	Et	diglyrne	<b>1a</b>	84:16	100	90	64
13	<b>2e</b>	Br	Et	diglyrne	<b>1b</b>	68:32	79	70	25
14	<b>2e</b>	Br	Et	diglyrne	<b>1c</b>	78:22	96	23	31
15	<b>2e</b>	Br	Et	diglyrne	<b>1d</b>	73:27	98	63	12
16	<b>2e</b>	Br	Et	diglyrne	<b>1e</b>	72:28	73	62	13
17	<b>2e</b>	Br	Et	diglyrne	<b>1a</b>	85:15	35 <sup>d</sup>	32	77
18	<b>2e</b>	Br	Et	diglyrne	<b>1a</b>	84:16	70 <sup>d,e</sup>	54	77
19	<b>2e</b>	Br	Me	diglyrne	<b>1a</b>	nd	40	nd	11
20	<b>2e</b>	Br	Me	diglyrne	<b>1a</b>	49:51	44 <sup>d,e</sup>	nd	24
21	<b>2e</b>	Br	Bu	diglyrne	<b>1a</b>	84:16	65	nd	71

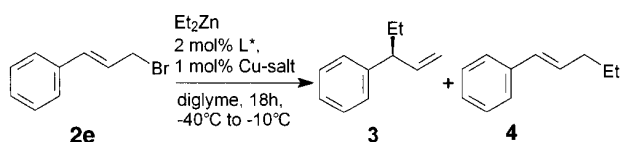
<sup>a</sup> Determined by GC. <sup>b</sup> Conversion after 2 d. <sup>c</sup> After 18 h at -10 °C, the reaction was stirred at rt for 2 d. <sup>d</sup> Reaction performed at a constant temperature of -40 °C. <sup>e</sup> 5 mol % of catalyst was used.

temperature of  $-40\text{ }^{\circ}\text{C}$ , an enantioselectivity of 77% was found. Using 5 mol % instead of 1 mol % of catalyst, the conversion of the starting material can be increased from 35% to 70% (Table 1, entry 18).

In addition to diethylzinc, different dialkylzincs were also used in the allylic alkylation with cinnamyl bromide. With dimethylzinc, 40% conversion was found after 18 h with no regioselectivity and 11 % ee (24% ee at constant  $-40\text{ }^{\circ}\text{C}$ ) for the ( $\text{S}_{\text{N}}2'$ ) product (Table 1, entries 19 and 20). Dibutylzinc gives a regioselectivity similar to that of diethylzinc in this reaction with 71 % ee for the ( $\text{S}_{\text{N}}2'$ ) product but with a lower conversion rate (Table 1, entry 21).

Besides  $\text{CuBr}\cdot\text{Me}_2\text{S}$  for the in situ preparation of the catalyst, different copper(I) and copper(II) salts were also used in the allylic alkylation (Table 2). Copper(I) cyanide

**Table 2.** Enantioselective Copper-Catalyzed Allylic Alkylation with Cinnamyl Bromide and Diethylzinc Using Phosphoramidite **1a** as a Ligand. The Effect of the Copper(I) and Copper(II) Salts



entry	Cu salt	$\text{S}_{\text{N}}2':\text{S}_{\text{N}}2$	convn (%)	yield of <b>3</b> (%)	ee of <b>3</b> (%)
1	CuI	76: 24	41	36	62
2	CuCN	94: 6	69	nd	3
3	CuBr	79: 21	80	nd	63
4	$\text{Cu}(\text{F-acac})^b$	81: 19	54	50	62
5	$\text{CuBr}\cdot\text{Me}_2\text{S}$	84: 16	100	nd	64
6	$\text{Cu}(\text{OTf})_2$	81: 19	51	48	64
7	$\text{CuBr}_2$	79: 21	79	75	12
8	$\text{Cu}(\text{OAc})_2$	79: 21	63	nd	60
9	CuOTf	85: 15	69	60	69
10 <sup>a</sup>			1		

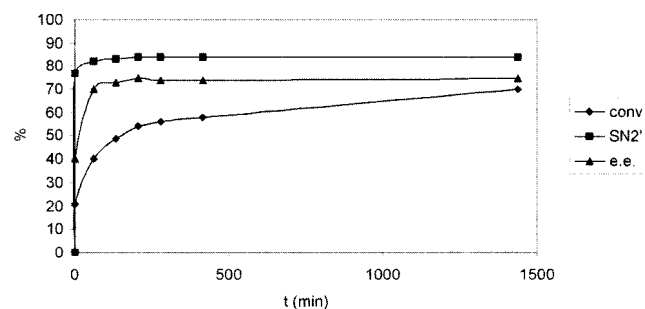
<sup>a</sup> No ligand was used in this reaction. <sup>b</sup> (F-acac) is trifluoroacetylacetate.

gives a remarkable high ratio of regioisomers, but very little enantioselectivity for the major ( $\text{S}_{\text{N}}2'$ ) product (Table 2, entry 2). The highest enantiomeric excess (69%) was observed using copper(I) triflate with a conversion of 69% within 18 h (Table 2, entry 9). Notable is the finding that  $\text{CuBr}\cdot\text{Me}_2\text{S}$  complex gives a higher conversion than the pure  $\text{Cu}^{\text{I}}\text{Br}$  salt (Table 2, entries 5 and 3). Furthermore, a few experiments employing different organometallic reagents were carried out. In contrast to Grignard reagents ( $\text{EtMgBr}$ ), which show no selectivity at all under these reaction conditions,  $\text{EtZnCl}$  results in a regioselectivity of 79% for the  $\text{S}_{\text{N}}2'$  product with an enantiomeric excess of 49%.

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To establish the regio- and enantioselectivity during the progress of the allylic alkylation, the reaction of **2e** with  $\text{Et}_2\text{Zn}$ , catalyzed by  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (5 mol %)/**1a** (15 mol %), at constant temperature ( $-40\text{ }^{\circ}\text{C}$ ), was followed in time. The conversion, the relative amount of  $\text{S}_{\text{N}}2'$  product, and the enantiomeric excess were monitored, and the results are presented in Figure 2. The time profile of the reaction reveals



**Figure 2.** Time profile of the conversion, the regioselectivity, and the enantiomeric excess of the allylic alkylation.

that the reaction is fast at the beginning and slows down after 3 h. The relative amount of  $\text{S}_{\text{N}}2'$  product is almost constant during the reaction. A striking feature is the fact that the enantiomeric excess increased in time. Because no blank reaction occurs (Table 2, entry 10), this feature indicates that different catalytic species are present at the early stage of the reaction. The nature of the catalytic species involved is subject to a current detailed investigation.

In conclusion, we found a new enantioselective copper-catalyzed alkylation of cinnamyl bromides with dialkylzincs by applying phosphoramidites as chiral ligands. The product **3** was obtained in a good yield with enantiomeric excesses up to 77%. This is, to the best of our knowledge, the highest ee obtained in a copper-catalyzed catalytic allylic alkylation using unbranched organometallic reagents.

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(13) **Typical procedure for enantioselective allylic alkylation** (Table 2, entry 5): Under an argon atmosphere the phosphoramidite ligand **1a** (5.4 mg, 0.01 mmol) and  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (1 mg, 0.005 mmol) were dissolved in diglyme (5 mL) and stirred for 10 min at room temperature. To the cooled solution ( $-40\text{ }^{\circ}\text{C}$ ) was added  $\text{Et}_2\text{Zn}$  (1 M in hexane, 0.6 mL, 74 mg, 0.6 mmol). After 5 min **2e** (99 mg, 0.5 mmol) was added and the reaction was allowed to warm to  $-10\text{ }^{\circ}\text{C}$  over 18 h. The mixture was quenched with 1 M aqueous  $\text{H}_2\text{SO}_4$ , and the separated aqueous layer was extracted 2 times with diethyl ether. The combined organic layers were treated with brine, dried over  $\text{MgSO}_4$ , and concentrated in vacuo. After purification by column chromatography ( $\text{SiO}_2$ , diethyl ether:pentane, 1:50), the products **3** and **4** were obtained in 81 % yield. The enantiomeric excess of **3** was determined by gas chromatography (chiral column Betadex 120, 30m, 0.25 mm, oven temperature =  $75\text{ }^{\circ}\text{C}$ ,  $t_r(\text{3})$  = 39.8 and 40.5 min) to be 64%.