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Furanoside phosphite–phosphoroamidite and diphosphoroamidite ligands applied to asymmetric Cu-catalyzed allylic substitution reactions

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ABSTRACT

A phosphite–phosphoroamidite and diphosphoroamidite ligand library was applied in the Cu-catalyzed allylic substitution of a range of cinnamyl-type substrates using several organometallic nucleophiles. Results indicated that selectivity depended strongly on the ligand parameters (position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, as well as the configuration of C-3, the introduction of a second phosphoroamidite moiety, the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties), the nature of the leaving group of the substrate and the alkylating reagent. Good enantioselectivities (up to 76%) and activity combined with high regioselectivities were obtained.

1. Introduction

Developing methods for enantioselective carbon–carbon bond formation is one of the key issues in organic synthesis. A versatile method for doing this is transition metal-catalyzed asymmetric allylic substitution with carbon nucleophiles.[1] Great effort has been put into controlling the chemo-, regio-, and enantioselectivities of the reaction. Most asymmetric allylic substitutions have been reported with soft nucleophiles (i.e., malonates and related stabilized anions) and Pd as the metal source, although Mo, W, Ru, Rh, and Ir catalysts have also proved to be effective for these nucleophiles.[1] In contrast, copper allows the use of hard, nonstabilized nucleophiles, such as small alkyl groups in the form of organometallic species.[2] Among the broad range of reagents available, the use of Grignard reagents in the catalyzed asymmetric allylic substitution reaction was first reported by Bäckvall and van Koten, with chiral copper thiolate **1** (Fig. 1), yielding moderate enantiomeric excesses.[3] This pioneering work was soon followed by that of Dübner and Knochel, who reported a highly enantioselective version using a different system based on diorganozinc reagents with ligand **2** (Fig. 1).[4] Since then, most efforts have been directed toward developing new efficient Cu catalysts for these organozinc reagents.[5] An important breakthrough in the use of Grignard reagents was made by Alexakis et al. They reported highly regio- and enantioselective Cu-phosphoroamidite catalyzed allylic substitution of di- and tri-substituted cinnamyl chloride substrates (Fig. 1, ligands type **3**).[6] Other successful ligands have been introduced for stereoselective allylic addition of organomagnesium reagents, such as chiral diaminocarbenes (Fig. 1, ligands type **4**) by Okamoto et al.[7] and more recently ferrocenic bidentate phosphines (Fig. 1, ligand type **5**) by Feringa et al.[8]

Apart from these latter bidentate phosphines, the most successful ligands developed for this transformation are monodentate. However, Alexakis et al. found that the successfully MeO-substituted phosphoroamidite monodentate phosphorus ligands **3** can act as bidentate P,O-ligands.[6b] On the basis of this finding we decided to study a library of bidentate furanoside phosphite–phosphoroamidite and diphosphoroamidite ligands **L1**–**L5a**–**f** in the Cu-catalyzed allylic substitution reaction. These ligands have the same advantages as carbohydrate and phosphite/phosphoroamidite ligands: that is, they are available at low cost, they have high resistance to oxidation, and they have simple modular constructions.[9] Therefore, with this library we fully investigated the effects of systematically varying the position of the phosphoroamidite group at both C-5 (ligands **L1** and **L2**) and C-3 (ligands **L3** and **L4**) of the furanoside backbone, as well as the effects of the configuration at C-3 of the furanoside backbone, the introduction of a second phosphoroamidite moiety (ligands **L5**), and the substituents/configurations in the biaryl phosphite/phosphoroamidite moieties (**a**–**f**). By carefully selecting the best of these elements and using a range of Grignard reagents, we achieved good regio- and enantioselectivities, and activities in different substrate types.

2. Results and discussion

Initially, we evaluated the phosphite–phosphoroamidite and diphosphoroamidite ligand library **L1**–**L5a**–**f** (Fig. 2) in the copper-catalyzed asymmetric allylic alkylation of cinnamyl chloride

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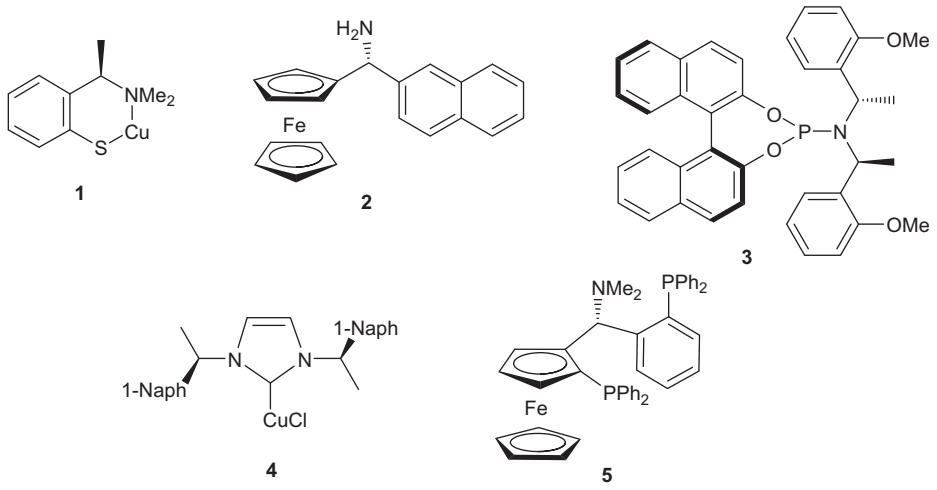
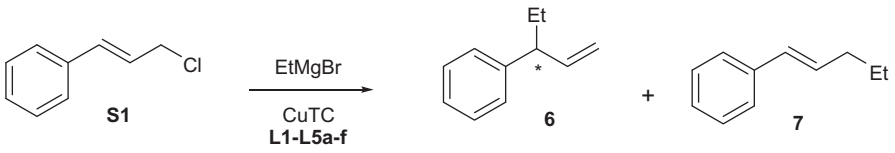


Figure 1. Ligands previously applied in asymmetric Cu-catalyzed allylic substitution reactions.

S1 using EtMgBr as the nucleophile (Eq. 1). The catalytic system was generated in situ by adding the corresponding ligand to a suspension of the catalyst precursor copper thiophene 2-carboxylate (CuTC).



(1)

The results are shown in Table 1. They indicate that regio- and enantioselectivities are affected by the position of the phosphoroamidite group at either C-5 or C-3 of the furanoside backbone, and by the configuration of C-3, the introduction of a second phosphoroamidite moiety, and the substituents and configurations in the biaryl phosphite/phosphoroamidite moieties (**a**–**f**).

We first studied the effect of the position of the phosphoroamidite group at either C-5, ligands **L1** and **L2**, or C-3, ligands **L3** and **L4**, of the furanoside backbone and the configuration of C-3. We observed a cooperative effect between the position of the phosphoroamidite group and the configuration of carbon atom C-3 of the furanoside backbone. The results indicate that the best combination of these ligand parameters is achieved with ligands **L2**, whose phosphoroamidite moiety is attached to C-5 and which have an (*R*)-configuration of carbon atom C-3 on the tetrahydrofuran ring (Table 1, entries 1–4).

We then used ligands **L5** to study how catalytic performance was affected by replacing the phosphite moiety with a phosphoroamidite group in preferred ligands **L2**. The results indicated that the presence of a second phosphoroamidite moiety in the ligands had a negative effect on enantioselectivity (Table 1, entries 5 vs 2).

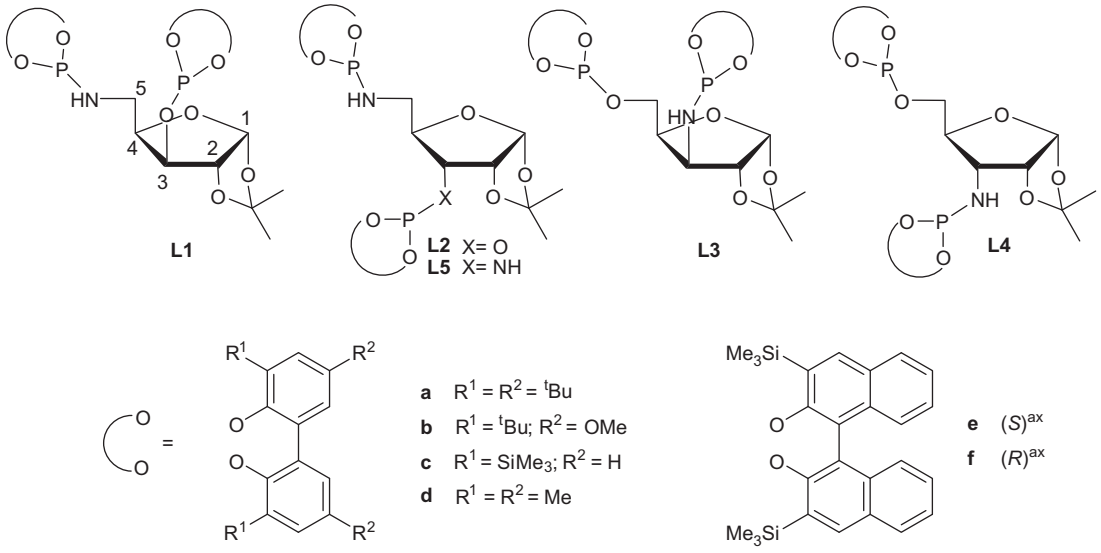


Figure 2. Furanoside-based phosphite–phosphoroamidite and diphosphoroamidite ligand library **L1**–**L5a**–**f**.

Table 1
Selected results for the Cu-allylic substitution of cinnamyl chloride with EtMgBr using ligands **L1**–**L5a**–**f**[a]

Entry	L	% Conv[b]	**6**/**7**[c]	% ee[d]
1	**L1a**	100	94/6	39 (*S*)
2	**L2a**	99	97/3	60 (*S*)
3	**L3a**	100	88/12	3 (*S*)
4	**L4a**	100	92/8	38 (*S*)
5	**L5a**	100	96/4	12 (*S*)
6	**L2b**	100	95/5	48 (*S*)
7	**L2c**	100	96/4	32 (*S*)
8	**L2d**	100	97/3	6 (*S*)
9	**L2e**	90	95/5	43 (*S*)
10	**L2f**	96	96/4	16 (*R*)
11[e]	**L2a**	99	98/2	70 (*S*)

[a] Reaction conditions: CuTC (1 mol %), ligand (1 mol %), EtMgBr (1.2 equiv, 1.2 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), $T = -50$ °C.
[b] Conversion determined by GC after 1 h.
[c] Regioselectivity determined by GC.
[d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column.
[e] Reaction carried out at −78 °C.

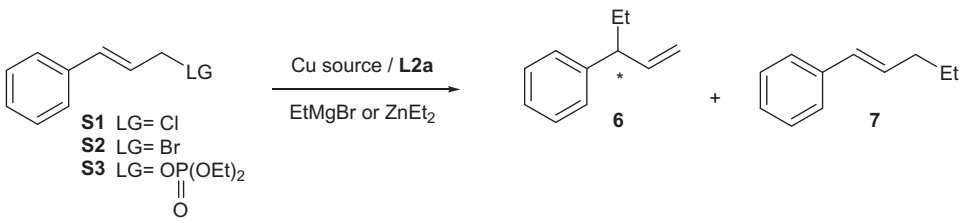
We next studied the effects of the biaryl phosphite/phosphoroamidite moieties using ligands **L2a**–**f** (Table 1). We found that these moieties mainly affected enantioselectivity, while their effect on regioselectivity was less important. Results indicated that bulky substituents at both *ortho* and *para* positions of the biphenyl phosphite/phosphoroamidite moieties need to be present if enantioselectivities are to be high (Table 1, entries 2 vs 6–8). This indicates that bulky substituents are necessary to control the tropoisomerization of the biaryl phosphite/phosphoroamidite moieties in the catalytic active species. Similar behavior has been observed for other phosphite/phosphoroamidite based ligands in other metal-catalyzed asymmetric transformations.[10] Moreover, the presence of bulky enantiopure binaphthyl moieties (**e**–**f**) did not further improve enantioselectivity (Table 1, entries 2 vs 9–10). This suggests that in ligand **L2a**, the biphenyl moiety attached to the phosphoroamidite adopts a configuration that is different from that of the configuration of the biphenyl phosphite moiety.

To sum up, the best result was obtained with ligand **L2a**, which contains the optimal combination of ligand parameters. These results clearly show the efficiency of highly modular scaffolds in ligand design. Regio- and enantioselectivities can be improved by controlling not only the structural but also the reaction parameters. In this case, both regio- and enantioselectivities were further improved (98% regioselectivity with 70% ee) with ligand **L2a** by lowering the reaction temperature to −78 °C (Table 1, entry 11).

It has been shown that the catalytic performance for this transformation is highly dependent on a subtle balance between the nature of the leaving group, the type of organometallic reagent, and the copper source among other reaction parameters.[2] So we next investigated whether the performance of our CuTC/**L2a** catalytic system can be improved by using other leaving groups in the substrate and by using dialkylzincs instead of Grignard reagents. The results are summarized in Table 2. Using EtMgBr, we found that the replacement of the chloride leaving group by a bromide **S2** or phosphonate group **S3** leads to lower regio- and enantioselectivities (Table 2, entries 2 and 3 vs 1). On the other hand, the use of dialkylzincs instead of Grignard reagents for the allylic substitution of cinnamyl halides **S1** and **S2** leads to significantly lower regio- and enantioselectivities (Table 2, entries 4 and 5 vs 1 and 2, respectively). However, for phosphonate **S3,** enantioselectivity and to a lesser extent regioselectivity increased when $ZnEt_2$ was used, but at the cost of activity (Table 2, entry 6 vs 3). Finally, and on the basis of our previous results on Cu-catalyzed conjugate addition which show that for some substrates the combination of dialkylzincs with $CuOTf_2$ leads to higher enantioselectivities, we decided to assess the use of $CuOTf_2$ as a source of copper. Unfortunately, no improvement in the catalytic performance was observed (Table 2, entries 7 and 8 vs 4 and 5, respectively).

Finally, we investigated the allylic substitution of a range of cinnamyl type chlorides with various Grignard reagents. Cinnamyl chloride **S1** reacts with methyl and *n*-propyl Grignard reagents as EtMgBr does (Table 3, entries 2 and 3 vs 1). However, the use of a secondary Grignard reagent, ^{i}PrMgBr, decreases both regio- and enantioselectivities (Table 3, entry 4 vs 1). Regarding the substrate scope, Table 3 shows that electron-donating groups at the *para* position of the phenyl group, substrate **S4**, slightly decrease both regio- and enantioselectivities (Table 3, entries 5 and 6 vs 1 and 4, respectively), while electron-withdrawing groups, substrate **S5**, slightly increase enantioselectivities (Table 3, entries 7 and 8 vs 1 and 4, respectively). Interestingly, the allylic substitution of 2-(3-chloro-propenyl)-naphthalene **S6** provided the highest

Table 2
Selected results for Cu-catalyzed allylic alkylation of several cinnamyl halides **S1**–**S2** and phosphonate **S3** using EtMgBr and $ZnEt_2$[a]



Entry	Cu salt	Substrate	Organometallic reagent	% Conv[b]	**6**/**7**[c]	% ee[d]
1	CuTC	**S1**	EtMgBr	99	97/3	60 (S)
2	CuTC	**S2**	EtMgBr	100	92/8	53 (S)
3	CuTC	**S3**	EtMgBr	85	70/30	42 (*S*)
4	CuTC	**S1**	$ZnEt_2$	100	84/16	39 (*S*)
5	CuTC	**S2**	$ZnEt_2$	100	78/22	44 (*S*)
6	CuTC	**S3**	$ZnEt_2$	40	75/25	55 (*S*)
7	$CuOTf_2$	**S1**	$ZnEt_2$	92	82/18	36 (*S*)
8	$CuOTf_2$	**S2**	$ZnEt_2$	85	70/30	46 (*S*)

[a] Reaction conditions: CuTC (1 mol %), ligand (1 mol %), EtMgBr (1.2 equiv, 1.2 mmol), **S1** (1 mmol), CH_2Cl_2 (2 mL), $T = -50$ °C.
[b] Conversion determined by GC after 1 h.
[c] Regioselectivity determined by GC.
[d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column.

Table 3
Selected results for the Cu-catalyzed asymmetric allylic substitution of a range of cinnamyl-type chlorides with various Grignard reagents[a]

S1 Ar= Ph
S4 Ar= 4-Me-C_6H_4
S5 Ar= 4-MeO-C_6H_4
S6 Ar= 2-Naph

Entry	Substrate	R	% Conv[b]	γ/α[c]	% ee[d]
1	**S1**	Et	99 (95)	97/3	60 (*S*)
2	**S1**	Me	98 (94)	98/2	59 (*S*)
3	**S1**	^{n}Pr	99 (96)	97/3	59 (*S*)
4	**S1**	^{i}Pr	98 (92)	92/8	35 (*S*)
5	**S4**	Et	100 (93)	93/7	54 (*S*)
6	**S4**	^{i}Pr	100 (91)	88/12	32 (*S*)
7	**S5**	Et	99 (94)	97/3	62 (*S*)
8	**S5**	^{i}Pr	100 (90)	92/8	40 (*S*)
9	**S6**	Et	100 (92)	96/4	68 (*S*)
10	**S6**	Me	100 (94)	96/4	67 (*S*)
11	**S6**	^{n}Pr	100 (96)	95/5	67 (*S*)
12	**S6**	^{i}Pr	100 (92)	90/10	41 (*S*)
13[e]	**S6**	Et	100 (91)	96/4	76 (*S*)
14[e]	**S6**	Me	100 (95)	97/3	73 (*S*)

[a] Reaction conditions: CuTC (1 mol %), **L2a** (1 mol %), RMgBr (1.2 equiv, 1.2 mmol), substrate (1 mmol), CH_2Cl_2 (2 mL), $T = -50$ °C.
[b] Conversion determined by GC after 1 h. In parentheses the isolated yield of the mixture of regioisomers.
[c] Regioselectivity determined by GC.
[d] Enantiomeric excess determined by GC on a Supelco β-DEX 120 column.
[e] Reaction performed at −78 °C.

enantioselectivities (ee's up to 76%, Table 3, entries 9–14) while maintaining excellent regioselectivity.

3. Conclusion

A library of furanoside phosphite–phosphoroamidite and diphosphoroamidite was applied in the Cu-catalyzed allylic substitution of a range of cinnamyl-type substrates using several organometallic nucleophiles. Good enantioselectivities (up to 76%) and activity combined with high regioselectivities were obtained. Systematically varying the position of the phosphoroamidite group, at either C-5 or C-3 of the furanoside backbone, as well as the configuration of C-3 and several substituents and configurations in the biaryl phosphite/phosphoroamidite moieties had a strong effect on the rate and selectivity. Enantioselectivity was the best with the catalyst precursor containing ligand **L2a**, which has the optimal combination of ligand parameters.

Our results also showed that the nature of the leaving group of the substrate and the alkylating reagent also plays an important role in determining activity and regio- and enantioselectivities.

4. Experimental

4.1. General considerations

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Ligands **L1**–**L5a**–**f**[11] and substrates **S3**–**S6**[12] were prepared by previously described methods. All other reagents were used as commercially available.

4.2. General procedure for the Cu-catalyzed enantioselective allylic substitution

A dried Schlenk tube was charged with the copper salt (1 mol %) and the chiral ligand (1 mol %). Dichloromethane (2 mL) was added and the mixture was stirred at room temperature for 30 min. The allylic chloride (1 mmol) was introduced dropwise and the reaction mixture was stirred at room temperature for a further 5 min before being cooled to −50 °C. Grignard reagent (2–3 M in diethyl ether, 1.2 equiv) in dichloromethane (0.5 mL) was added for 40 min via syringe pump. Once the addition was complete the reaction mixture was left at −50 °C for one hour. The reaction was then quenched by the addition of aqueous hydrochloric acid (1 N, 2 mL). Diethyl ether (10 mL) was added and the aqueous phase was separated and extracted further with diethyl ether (3 × 3 mL). The combined organic fractions were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and reduced in vacuo. Conversion and regioselectivity were determined by ^{1}H NMR, and enantiomeric excess was determined by GC.[6a] The absolute configuration of the alkylation products has been assigned by comparing the retention times with those obtained with enantioenriched samples prepared according to the literature.[6a] The oily residue was purified by flash column chromatography (eluent = pentane) to yield the product as a mixture of S_N2' and S_N2 regioisomers.[6a]

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