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Highly Enantioselective Copper-Catalyzed Allylic Alkylation with Phosphoramidite Ligands

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Abstract: New phosphoramidites were applied as chiral ligands in the Cu-catalyzed allylic alkylation with dialkylzinc reagents. A variety of substrates, reagents and chiral ligands were screened, resulting in improved catalytic methodology for allylic bromides in which enantioselectivities up to 88% were reached.

Keywords: allylic alkylation; asymmetric catalysis; copper; diorganozinc compounds; phosphoramidite ligands; S_N2'-substitution

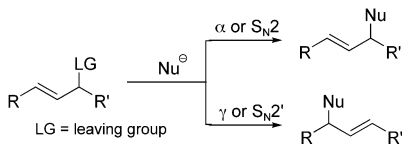
Introduction

Among the most important tools of the synthetic organic chemist are transition metal-catalyzed C–C bond forming reactions.[1] The allylic alkylation[2] holds a prominent position due to its high versatility as the products can easily be further transformed and functionalized in a variety of ways. Moreover, it is possible to alkylate the substrate by two distinct pathways (Scheme 1). Direct displacement leads to α (S_N2) substitution whereas the alternative pathway leads to substitution at the γ position (S_N2'). When the substrate has different substituents at the α and γ positions of the allylic moiety, the two pathways lead to different products.

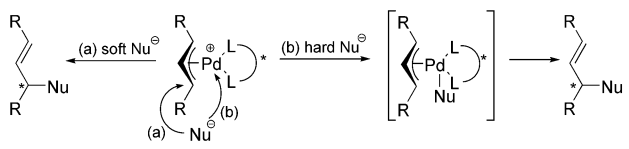
Control of the regio- and stereochemistry has been the focal point in research on the transition metal-catalyzed allylic alkylation and, in particular, the development of a highly enantioselective version has enjoyed widespread attention in recent years.[3] A variety of chiral Pd catalysts has shown excellent enantioselectivities with acyclic[3b] and cyclic[3d] substrates substituted identically at both α and γ positions. The formation of optically active branched products from monosubstituted allylic substrates, where the two regioisomeric products are distinct, proved to be more challenging, although very good results have been attained recently.[4] A number of catalysts, including chiral W,[5] Ir,[6] Mo,[7] Pt[8] and Rh[9] complexes, have been used for the enantioselective alkylation of monosubstituted allylic substrates, in some cases with excellent results. In all these reactions, including those catalyzed by palladium, a soft stabilized carbon nucleophile such as a malonate anion is used. Hard organometallic-based nucleophiles, in order to directly introduce simple alkyl groups, have been used only to a limited extent in asymmetric allylic alkylation reactions with palladium.[3,10]

Distinct mechanisms are proposed for nucleophilic substitution with hard or soft nucleophiles.[3,11] In a palladium-catalyzed reaction the soft nucleophile will approach the allyl moiety from the opposite side of the coordinated metal ion (path a), whereas in allylic alkylations with hard nucleophiles initial addition to the transition metal is followed by reductive elimination (path b) (Scheme 2).[11]

Nickel complexes have been used as catalyst in an enantioselective allylic alkylation with hard nucleophiles and although in some cases good selectivities have been achieved with cyclic[12] and acyclic[13] substrates, in general the results have been disappointing.



Scheme 1.



Scheme 2.

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Cu-catalysts have shown to be good candidates for highly selective allylic substitution reactions with hard nucleophiles,[14] but surprisingly, the enantioselective copper-catalyzed allylic alkylation has not been studied extensively.[15] Bäckvall and van Koten et al. reported the first asymmetric copper-catalyzed allylic alkylation,[16a] with Grignard reagents, using chiral thiolate ligands, reaching enantioselectivities up to 64%.[16] More recently the enantioselectivities could be improved using phosphites[17] and phosphoramidites[17b] as chiral ligands.

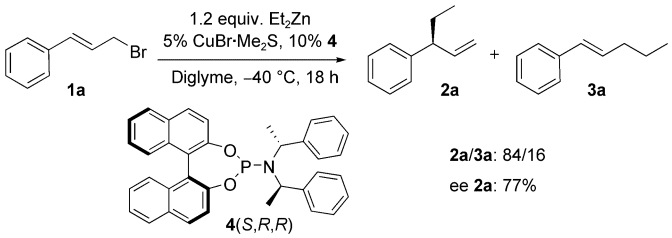
Asymmetric copper-catalyzed allylic alkylations using dialkylzinc reagents[18] and chiral amine ligands resulted in very high selectivities,[19] but only if the very bulky dineopentylzinc was used, as with diethylzinc only 44% ee was reached.

Hoveyda and co-workers developed peptide-derived Schiff base ligands and achieved up to 75% ee in the copper-catalyzed allylic alkylation of cinnamyl phosphates with diorganozinc reagents.[20a] The allylic alkylation of unsaturated esters with a phosphate leaving group at the γ position led to ees as high as 97%.[20b]

Employing a ligand library, based on chiral sulfonamides,[21] enantioselectivities up to 88% were reached in desymmetrization reactions of cyclic *meso* compounds with two phosphate leaving groups in the allylic positions.[21b]

Our group reported the copper-catalyzed asymmetric allylic alkylation with dialkylzinc reagents and phosphoramidite ligands.[22] Using $CuBr \cdot Me_2S$ in the presence of ligand **4**, cinnamyl bromide **1a** could be alkylated with high regioselectivity (84:16) and good enantioselectivity (77%) (Scheme 3).

We now report improved conditions for this allylic alkylation, which result in higher reactivity, regioselectivity and enantioselectivity. Furthermore the scope with respect to substrates and dialkylzinc reagents was extended using this new procedure.



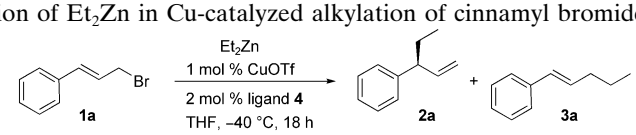
Scheme 3.

Results and Discussion

The relatively high enantiomeric excess obtained with simple dialkylzinc reagents was a major incentive to further improve our system for the allylic alkylation. To achieve maximum selectivity it was, however, necessary to perform the reaction at a constant temperature of −40 °C, because the enantioselectivity of the reaction turned out to be temperature dependent.[22] At that temperature the reaction proceeds rather slowly, even with 5 mol % of catalyst, and in addition the melting point of diglyme prevented further cooling to improve selectivity.[23]

Preliminary experiments exploring the use of different copper salts for the allylic alkylation of cinnamyl bromide **1a** with diethylzinc showed that the use of CuOTf[24] resulted in a higher asymmetric induction than $CuBr \cdot Me_2S$.[22] At −40 to −10 °C in diglyme, $CuBr \cdot Me_2S$ provides **2a** with 64% ee and the use of CuOTf resulted in 69% ee and a similar product ratio. Furthermore, it was found that THF as solvent improved the S_N2':S_N2 ratio to 75:25 compared to a ratio of 57:43 in diglyme. Therefore, further investigations with THF as solvent and CuOTf as copper salt were carried out. The reactions were performed at −40 °C in the presence of the catalyst prepared *in situ* from 1 mol % of CuOTf and 2 mol % of ligand **4**. First a few variations in the addition of diethylzinc were examined (Table 1).

Table 1. Variations in the addition of Et_2Zn in Cu-catalyzed alkylation of cinnamyl bromide.



Entry	Reagent (solvent)	Yield [%][a, b]	S_N2':S_N2[a] (**2**:**3**)	ee [%][a]
1	Et_2Zn (in hexanes)	96	85:15	67
2	Et_2Zn (in toluene)	96	85:15	64
3	Et_2Zn (neat)	92	85:15	55
4	Et_2Zn (in hexanes)[c]	96	85:15	69
5	Et_2Zn (in hexanes)[c, d]	86	85:15	77

[a] Determined by GC.
[b] Product, remainder is starting material.
[c] Reverse addition of starting materials.
[d] Reaction performed at −60 °C.

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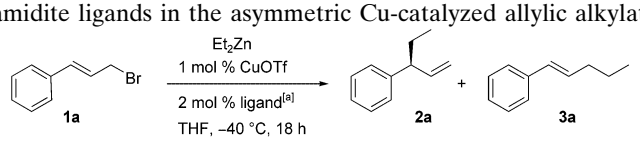
Table 2. Screening of phosphoramidite ligands in the asymmetric Cu-catalyzed allylic alkylation.



Entry	Ligand (config.)[a]	Ref.[b]	Yield [%][c, d]	S_N2':S_N2[c] (**2**:**3**)	ee **2a** [%][c]	Config. **2a**
1	**4** (S_a,*R*,*R*)	[26]	96	85:15	69	(*S*)
2	**5** (S_a,*S*,*S*)	[26]	97	79:21	30	(*S*)
3	**6** (S_a,*R*,*R*)	[26]	70	92:8	60	(*S*)
4	**7** (S_a,*S*,*S*)	e	74	94:6	75	(*S*)
5	**8** (S_a,*R*)	[27]	87	89:11	48	(*S*)
6	**9** (S_a,*S*)	[27]	96	78:22	0	–
7	**10** (S_a,*S*)	[26]	67	90:10	58	(*S*)
8	**11** (S_a,*R*)	[27]	49	90:10	30	(*S*)
9	**12** (S_a,*S*)	[e]	92	83:17	24	(*S*)
10	**13** (S_a,*S*)	[e]	92	82:18	39	(*S*)
11	**14** (*S*,*S*)	[e]	93	91:9	7	(*R*)
12	**15** (*S*,*S*)	[28]	37	84:16	43	(*R*)
13	**16** (S_a,*R*,*R*)	[27]	95	91:9	82	(*S*)
14	**17** (R_a,*S*,*S*)	[27]	66	91:9	45	(*R*)
15	**18** (S_a,*R*,*R*)	[27]	76	83:17	65	(*S*)
16	**19** (*R*,*R*)	[29]	94	89:11	20	(*S*)
17	**20** (*R*,*R*)	[29]	87	92:8	3	(*R*)
18	**21** (*R*,*R*)	[29]	96	91:9	8	(*R*)
19	**22** (*R*,*R*)	[29]	95	90:10	14	(*S*)
20	**23** (*R*,*R*)	[29]	94	91:9	23	(*S*)
21	**24** (R_a,R_a)	[30]	88	91:9	14	(*S*)
22	**25** (R_a,R_a)	[30]	95	89:11	12	(*R*)
23	**26** (R_a,R_a)	[30]	7	92:8	33	(*S*)
24	**27** (S_a,S_a,*S*,*S*)	[30]	98	90:10	8	(*R*)
25	**28** (R_a,R_a,*S*,*S*)	[30]	94	91:9	5	(*S*)

[a] Bidentate ligands **24**–**28** added in 1 mol %.
[b] Reference to ligand preparation.
[c] Determined by GC.
[d] Product, remainder is starting material.
[e] Ligand not reported before (see Supporting Information).

The reaction of cinnamyl bromide in THF at −40 °C with diethylzinc as a hexane solution proceeded faster than in the original procedure, providing **2a/3a** in 96% yield after 18 h (Table 1, entry 1). Et_2Zn as a toluene solution or neat Et_2Zn did not improve the results (Table 1, entries 2 and 3), but on reverse addition[25] of the starting materials a small enhancement of ee was observed. Decreasing the temperature to −60 °C resulted in an ee of 77%.

The finding that at −60 °C and in the presence of only 1 mol % catalyst 77% enantioselectivity is reached and still the reaction proceeds much faster than in our original procedure, shows that a significant improvement has been reached and that allylic alkylation in THF using CuOTf as the copper source is superior to the one in diglyme with $CuBr \cdot Me_2S$.

Using the improved reaction conditions, a screening for more selective phosphoramidite ligands was executed. All reactions were performed at −40 °C and the ligands used are depicted in Scheme 4. The results are summarized in Table 2.

Monodentate phosphoramidites **4**–**13**[26,27] with a BINOL backbone (Table 2, entries 1–10) afforded **2a**/**3a** in yields that were generally, although not always, good. The C–C bond formation was always in favor of the S_N2' product, with regioselectivities up to 94:6; although the enantioselectivities obtained by applying these ligands were highly varying. A ligand backbone with (*S*) configuration leads to the (*S*) configuration in the product, but the type and configuration of the amine group can have a large influence on the enantioselectivity.

A few other monodentate ligands **14**–**18**[27,28] with *N*,*N*-bis(1-phenylethyl)amine attached to different backbones were subsequently screened (Table 2, entries 11–15). The three ligands with a BINOL-type backbone gave similar results to the former ligands. The ligands with a catechol (**14**, entry 11) and biphenyl (**15**, entry 12) backbone are the only ligands in which the configuration

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of the amine dictates the configuration of the product, but the low enantioselectivities actually show the necessity of a more bulky chiral backbone.

TADDOL-based phosphoramidites **19**–**23**[29] as ligands afforded **2a**/**3a** in excellent yields and high regioselectivities (around 90:10) (Table 2, entries 16–20). Unfortunately, low asymmetric induction was observed with all these ligands.

Bidentate BINOL-derived phosphoramidite ligands **24**–**28**[30] were also used as ligands in the allylic alkylation of cinnamyl bromide with diethylzinc (Table 2, entries 21–25). Again, high yields and very good **2a**/**3a** ratios (around 90:10) were obtained except for ligand **26** (Table 2, entry 23), which gave an unexpected low yield. The enantioselectivities found for the bidentate phosphoramidite ligands are remarkably low.

In general monodentate phosphoramidites with a BINOL-type backbone are the most effective ligands for this reaction. The best results were obtained with ligand **4** and the new ligands **7** and **16** (Scheme 4). Using ligand **7**, 74% yield, an excellent ratio of 94:6 and an ee for **2a** of 75% was found (Table 2, entry 4). It is interesting to note that **7**, which has an (S_a,*S*,*S*) configuration, gives better selectivities than its diastereomer, which points to an opposite matched-mismatched effect to the other ligands, where the (S_a,*R*,*R*) or (S_a,*R*) is the matched diastereomer.[31] The reaction with bromide **1a** and diethylzinc in the presence of CuOTf and **16** affords **2a**/**3a** in 95% yield and a ratio of 91:9 (Table 2, entry 13). The asymmetric induction improved to 82% and because this is the highest enantioselectivity yet observed, further experiments were conducted using this ligand.

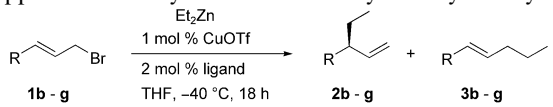
A number of different allylic bromides were used as substrates in the copper-catalyzed allylic alkylation. Cinnamyl bromide derivatives with different electron-withdrawing substituents **1b**–**e** and naphthyl- and cyclohexyl-substituted allylic bromides **1f** and **1g** were applied. The results are summarized in Table 3.

Good yields were obtained for the different *para*-substituted cinnamyl bromides after 18 h (Table 3, entries 1–4). Due to volatility of the products, only moderate isolated yields (54%) were obtained for **2b/3b** and **2c/3c** (Table 3, entries 1 and 2). The less volatile compounds **2d/3d** and **2e/3e**, in contrast, were obtained in 71% and 83% yield, respectively (Table 3, entries 3 and 4). The regio- and enantioselectivities obtained for *para*-substituted cinnamyl bromides were similar. Using Pd[4a,32] and Ir[6a] catalysts, the regioselectivity was strongly dependent on the electronic properties of the *para*-substituents. In contrast, when using chiral Cu catalysts on distinct substituted cinnamyl substrates, the regioselectivity was found to be fairly constant, but then the enantioselectivity varied considerably.[17b,20a] It is therefore quite striking that both regio- and enantioselectivity are constant in the present system.

Surprisingly, in case of naphthyl substituted allylic bromide **1f** only 26% ee was observed using ligand **16**. Ligand **4** resulted in a lower regioselectivity but a higher enantioselectivity of 67% was found (Table 3, entry 6). In the allylic alkylation with cyclohexyl substituted allylic bromide **1g**, using ligand **16**, the ee found for **2g** was only 53%, pointing to a considerable effect of the nature of the R substituent in the allylic substrate.

Subsequently, different diorganozinc reagents, including Et_2Zn, *i*-Pr_2Zn and *n*-Bu_2Zn, were used to alkylate cinnamyl bromide **1a** at −60 °C (Table 4). In the case of diethyl- and dibutylzinc the yield was somewhat lower due to a slower reaction (entries 1 and 3), but the alkylation with diisopropylzinc reached full conversion within 18 h (entry 2). The S_N2':S_N2 ratio was excellent in all cases and similar high ees (86–88%) for all three products were found.

Table 3. Different allylic bromides applied in the asymmetric Cu-catalyzed allylic alkylation.



Entry	R		Ligand	Yield [%][a, b,c]	S_N2':S_N2[a] (**2**:**3**)	ee **2b**–**g** [%][a, d]
1	*p*-Cl-C_6H_4	**1b**	**16**	81 (54)	91:9	78
2	*p*-CF_3-C_6H_4	**1c**	**16**	89 (54)	91:9	77
3	*p*-NO_2-C_6H_4	**1d**	**16**	98 (71)	93:7	77
4	*p*-MeO_2C-C_6H_4	**1e**	**16**	91 (83)	91:9	81
5	1-Naphthyl	**1f**	**16**	98 (77)	96:4	26
6	1-Naphthyl	**1f**	**4**	96 (n.d.)	88:12	67
7	Cyclohexyl	**1g**	**16**	89 (57)	90:10	53

[a] Determined by GC.
[b] Product, remainder is starting material.
[c] Isolated yield in parentheses.
[d] Branched products likely to have (*S*) configuration based on GC.

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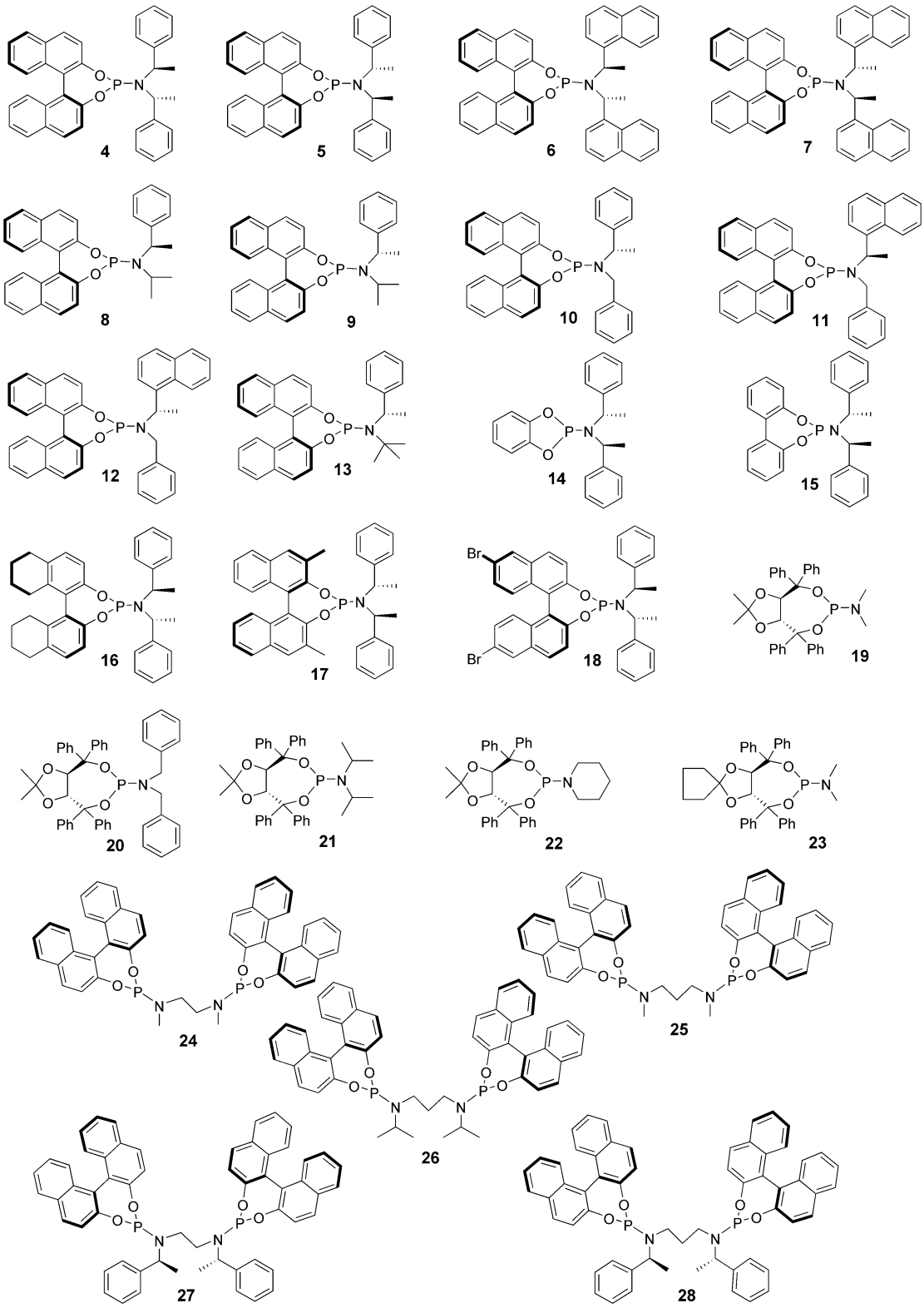

Scheme 4. Chiral phosphoramidite ligands applied in Cu-catalyzed allylic alkylation.

As expected, lowering the temperature to $-60\,^{\circ}C$ raised the enantioselectivity as was observed with ligand **4** (entry 5, Table 1), but with ligand **16** the regioselectivity was also enhanced. Quite striking is the enantioselectivity, being independent of the nature of the Zn reagent, which holds promise for the applicability of a

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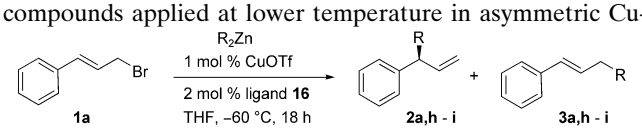
Table 4. Different diorganozinc compounds applied at lower temperature in asymmetric Cu-catalyzed allylic alkylation.



Entry	R_2Zn	Yield [%][a, b]	$S_N2':S_N2$[a] (**2**:**3**)	ee [%][a]
1	Et_2Zn	74	93 : 7	86
2	*i*-Pr_2Zn	94	97 : 3	88
3	*n*-Bu_2Zn	58	91 : 9	87[c]

[a] Determined by GC.
[b] Product, remainder is starting material.
[c] Branched product likely to have (*S*) configuration based on GC.

large range of dialkylzinc reagents. Also interesting to note is the fact that the higher reactivity of diisopropylzinc does not hamper the selectivity, in fact, the reaction is even slightly more selective than in the other cases, giving **2h** with high regioselectivity (97 : 3) and excellent enantioselectivity (88% ee).

Conclusion

We have considerably improved the catalytic system for the enantioselective copper-catalyzed allylic alkylation with dialkylzinc reagents by changing the solvent and Cu salt to THF and CuOTf, respectively, and employing the new ligand **16**.

We also showed that this system allows electronically different substituted cinnamyl substrates to be alkylated with equal selectivities, but that sterically distinct substrates are likely to need a different ligand. Several diorganozinc reagents can also be used with constant high regio- and enantioselectivities, although the reactivities differ somewhat.

The enantioselectivities are the highest achieved so far in the copper-catalyzed allylic isopropylation and *n*-butylation and especially for the *n*-butylation of allyl halides the new catalytic system represents a substantial improvement.

Detailed mechanistic studies on the enantioselective copper-catalyzed allylic alkylation are currently in progress.

Experimental Section

General Remarks

All solvents were reagent grade and were dried and distilled before use. All solvents were stored under nitrogen. All reactions were carried out under an argon atmosphere using dried glassware (standard Schlenk procedures). Chromatography: silica gel Merck Type 9385 230 – 400 mesh, TLC: silica gel 60, Merck, 0.25 mm. Optical rotations were measured on a Perkin-Elmer 241 MC (at room temperature). Mass spectra (HRMS) were recorded on an AEI MS-902. HPLC analyses were performed on a Waters 480 with an LC spectrophotometer or a Waters 600E system controller with a Waters 991 photodiode array detector using different chiral columns that are specified where necessary. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Varian Gemini-200 (50.32 MHz), Varian 300 (75.48 MHz) or Varian 500 (125.80 MHz) spectrometer in $CDCl_3$. Chemical shift values are denoted in δ units (ppm) relative to residual solvent peaks ($CHCl_3$, δ = 7.24 ppm for protons, δ = 77 ppm for carbon atoms and external H_3PO_4, δ = 0.0 ppm for phosphorus atoms). GC measurements were performed either on an HP 5890 A, an HP 5890 series II or an HP6890 gas chromatograph with flame ionization detector using different columns that are specified where necessary.

General Procedure for the Enantioselective Allylic Alkylation

Under an argon atmosphere phosphoramidite ligand (0.02 mmol,) and $(CuOTf)_2 \cdot C_6H_6$ (0.01 mmol CuOTf) were dissolved in 5 mL of THF and stirred for 10 min at room temperature. After cooling the solution to the appropriate temperature the allylic bromide (1 mmol) was added.[33] After 5 min R_2Zn (1 M in hexane, 1.2 mL, 1.2 mmol) was added and the reaction mixture was stirred at the reported temperature for 18 h. The reaction was quenched with 1 M aqueous H_2SO_4, and the separated aqueous layer was extracted twice with diethyl ether. The combined organic layers were treated with brine, dried over $MgSO_4$ and concentrated under vacuum.

(+)-(*S*)-3-Phenyl-1-pentene (2a)

Purification by column chromatography (SiO_2, ether/pentane, 1 : 50, R_f = 0.8) gave 118 mg (81%) of a mixture of **2a** and **3a** as a colorless oil. NMR experiments were performed on the mixture of products, but only data of the branched product **2a** are given. $[\alpha]_D^{22}$: + 40.4° (*c* 2.7, C_6H_6) with 58% ee (according to chiral GC). Proof of stereochemistry: literature value $[\alpha]_D^{22}$: + 35.0° (*c* 6, C_6H_6)[34] is assigned to the (*S*) enantiomer with 61% ee. ^{1}H NMR (200 MHz): δ = 7.32 – 7.18 (m, 5H), 5.95 (m, 1H), 5.02 (m, 2H), 3.14 (m, 1H), 1.70 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (200 MHz): δ = 144.4, 142.2, 128.3, 127.6, 126.1, 114.0, 51.7, 28.3, 12.1; MS (EI) for $C_{11}H_{14}$: *m/z* = 146 $(M)^+$. Determination of the ee of **2a** was performed

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by GC on a CP-Chiralsil-Dex CB, 25 m × 0.25 mm column, He flow 1.0 mL/min, isothermic 75 °C, $t_r = 39.8$ min for (*R*)-**2a**; $t_r = 40.5$ min for (*S*)-**2a**.

Supporting Information Available

General procedures and preparation of **2b**, **2c**, **2d**, **2e**, **2f**, **2 g**, **2 h** and **2i**; synthesis of allylic bromides **1b**, **1c**, **1d**, **1e**, **1f** and **1 g**; general procedure for preparation of phosphoramidite ligands **7**, **12**, **13** and **14**.

Acknowledgements

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References and Notes

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